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Clinical predictors of methicillin-resistance and their impact on mortality associated with *Staphylococcus aureus* bacteraemia

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Abstract

We investigated the clinical predictors of methicillin-resistance and their impact on mortality in 371 patients with *Staphylococcus aureus* bacteraemia identified from two prospective multicentre studies. Methicillin resistant *S. aureus* (MRSA) accounted for 42.2% of community-onset and 74.5% of hospital-onset cases. No significant clinical difference was found between patients infected with MRSA *vs.* methicillin-sensitive *S. aureus* (MSSA), except that the former were more likely to have had hospital-onset bacteraemia and received antibiotics in the preceding 90 days. After stratifying according to the acquisition site, prior antibiotic use was the only independent predictor of having MRSA in both community-onset and hospital-onset cases. The frequency of inappropriate empirical antibiotic therapy was higher in patients with MRSA than in those with MSSA bacteraemia. However, methicillin resistance was not a predictor of mortality in patients and the clinical characteristics and outcomes of both MRSA and MSSA bacteraemia were similar. This study indicates that there are no definitive clinical or epidemiological risk factors which could distinguish MRSA from MSSA cases with the exception of the previous use of antibiotics for having MRSA bacteraemia, which emphasises the prudent use of glycopeptide treatment of patients at risk for invasive MRSA infections.

Introduction

Staphylococcus aureus is among the most common causes of bloodstream infection (BSI) and is widely recognised as the most important cause of BSI-associated death [1, 2] being associated with a high mortality rate, presentation of persistent bacteraemia and frequent spread to distant foci [3, 4]. Prior to the mid-1990s, methicillin-resistant *S. aureus* (MRSA) was almost exclusively a healthcare-associated pathogen (HA-MRSA) and infections in the community were nearly always caused by methicillin-susceptible strains (MSSA). However, the end of the twentieth century saw the emergence of community-associated MRSA (CA-MRSA) strains in patients without traditional epidemiological risk factors for MRSA infection and/or colonisation [5]. Subsequently, CA-MRSA has spread rapidly into hospital settings and has recently begun replacing pre-existing HA-MRSA strains in healthcare facilities [5–7]. This spread of several different CA-MRSA clones has complicated the epidemiological picture and posed a new challenge for infection prevention and control [8].

Previous studies have suggested that the delay in initiation of anti-MRSA therapy adversely affects the outcome of patients with MRSA bacteraemia, especially those with high Pitt Bacteraemia Scores [9, 10] and that vancomycin is inferior to beta-lactams for the treatment of MSSA bacteraemia [11]. As a result, risk factors associated with MRSA infection have been highlighted to optimise antibiotic use when initiating empirical antibiotics against *S. aureus* [12, 13]. A previous study showed that a patient history of MRSA infection or colonisation, recurrent skin infection and severe community-acquired pneumonia were independent predictors of community-acquired MRSA pneumonia [13]. However, a systematic review of 27 published studies showed that previous admission to hospital and antibiotic use were the only commonly examined risk factors associated with MRSA infection at admission, albeit with varying definitions [14]. The authors emphasised that clinicians and health system planners face many challenges in identifying individuals predisposed to MRSA infection [14]. Therefore, it is important to examine the predictors of MRSA infection and to determine whether the associated factors have changed in recent years.

We compared the clinical features of MSSA and MRSA bacteremia cases with a view to identify factors predictive of MRSA infection. In addition, we evaluated the impact of methicillin resistance on mortality in these patients.

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Methods

Patients and study design

The study data were obtained from databases for nationwide surveillance of bacteraemia. All patients with positive blood cultures for *S. aureus* were enrolled at 9 secondary- or tertiary-care hospitals through prospective surveillance studies during two periods from June to September 2011 and June to September 2012. Duplicate isolates were excluded from the analysis. For outcome measures, patients with polymicrobial bacteraemia were also excluded. We identified 371 consecutive patients with confirmed *S. aureus* bacteraemia and patient information was entered on a standardised case report form. The data collected included demographic information, co-morbid diseases and conditions, location of bacteraemia onset, shock at presentation, source of bacteraemia, antibiotic use and surgery within the preceding 90 days and appropriateness of antimicrobial treatment. Echocardiographs were performed for all patients with persistent *S. aureus* bacteraemia of more than 7 days duration. The study was approved by the Institutional Review Board of Samsung Medical Center and the local review boards.

All isolates were confirmed as *S. aureus* by standard methods and tested for antimicrobial susceptibility at each participating hospital using an automated system for the modified broth microdilution method (Vitek; bioMérieux, Durham, NC, USA, or Microscan; Microscan Systems, Renton, WA, USA) according to the recommendations of the Clinical and Laboratory Standards Institute (2010) [15].

Definitions

Clinically significant bacteraemia was defined as at least one positive blood culture together with clinical features consistent with systemic inflammatory response syndrome. Catheter-related BSI was defined as growth of >15 colony-forming units from the catheter tip in a semiquantitative culture or growth of *S. aureus* from a blood sample drawn from a catheter hub at least 2 h before MRSA was obtained from a peripheral venous blood sample. Infective endocarditis was defined according to the modified Duke criteria [16]. Neutropaenia was defined as an absolute neutrophil count of $<500/mm^3$. Isolates defined as 'community-onset' were cultured in the outpatient setting and within 48 h of hospital admission while 'hospital-onset' isolates were classified as obtained 48 h after hospitalisation. Community-onset infections were further categorised as community-acquired (CA) or HA. HA infections were defined as previously described [17]. Antibiotic use in preceding 90 days was collected by chart review and through interview with patients and prescribers; prescribed antibiotics was further classified into four classes; glycopeptides, β-lactams, fluoroquinolones and others. A history of MRSA was determined through a review of each hospital's clinical microbiology record and included both asymptomatic MRSA colonisations and infections in the previous 90 days. The severity of underlying disease was classified according to the McCabe and Jackson criteria: rapidly fatal when death was expected within days or weeks; ultimately fatal when death was expected within months or years; and non-fatal when death was not expected [18]. In addition, Pitt Bacteraemia Scores were determined for all patients [19]. Appropriate antibiotic use was defined as the administration of antibiotics, to which the isolated organism was susceptible *in vitro*, within 24 h after the acquisition of blood culture samples. Persistent bacteraemia was defined as persisting for $\geqslant 3$ days after initiation of appropriate antibiotic treatment. The outcome measure was the 30-day all-cause mortality, beginning from the date of the index culture. Deaths occurring after discharge but within the 30-day interval were captured using the National Health Insurance system of the Republic of Korea, which records all deaths.

Statistical analysis

Discrete data are presented as frequencies and percentages and continuous variables are summarised as the mean±standard deviation after the normality of data was tested using the Shapiro–Wilk normality test. The chi-square (χ^2) test or Fisher's exact test was used to compare categorical variables as appropriate and two-sample *t*-test was used to compare continuous variables. To identify predictors of methicillin resistance in patients with *S. aureus* bacteraemia, a multivariate logistic regression analysis was used to control for the effects of confounding variables and to identify predictors of mortality, a multivariate Cox proportional hazards regression model was used to control for the effects of confounding variables. Variables with *P* value <0.05 were included in the multivariate analyses. The Hosmer–Lemeshow test was used for goodness of fit for logistic regression models. All *P* values were 2-tailed and $P < 0.05$ was considered significant. All analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients with S. aureus bacteraemia

A total of 371 patients met the case definition of *S. aureus* bacteraemia; MSSA was isolated from 155 patients (41.8%) and MRSA from 216 patients (58.2%). MRSA accounted for 42.2% of community-onset and 74.5% of hospital-onset cases. The clinical characteristics and outcomes of patients with *S. aureus* bacteraemia are summarised in Table 1. Significant differences in clinical and epidemiological characteristics between MRSA and MSSA were found for several variables; hospital-onset origin ($P < 0.001$), surgery in the preceding 90 days ($P < 0.001$), antibiotic use in the same period ($P < 0.001$), history of MRSA infection ($P = 0.002$), underlying cerebrovascular disease ($P = 0.005$) or haematologic malignancy ($P = 0.035$), undergoing immunosuppressive therapy ($P = 0.030$), presentation with central venous catheterisation ($P < 0.001$) or percutaneous drainage ($P = 0.001$), presentation with acute renal failure ($P < 0.001$), primary bacteraemia ($P = 0.049$) and catheter-related BSI ($P = 0.030$) were risk factors for having MRSA bacteraemia. The multivariate analysis showed that hospital-onset (odds ratio (OR) 2.82, 95% confidence interval (CI) 1.62–4.91, $P < 0.001$) and any antibiotic use in the preceding 90 days (OR 2.47, 95% CI 1.41–4.34, $P = 0.002$) were independent predictors for MRSA bacteraemia. The goodness of fit of the final logistic regression model appeared to be satisfactory (Hosmer-Lemeshow statistic, $\chi^2 = 5.627$, $P = 0.689$). The frequency of inappropriate empirical therapy was higher in patients with MRSA than MSSA bacteraemia (56.5% *vs.* 2.6%, $P < 0.001$), but 30-day mortality rates did not differ between the two groups (20.9% *vs.* 21.5%, $P = 0.828$).

Clinical characteristics and outcomes of MRSA according to primary acquisition site

The clinical characteristics and outcomes of MRSA among *S. aureus* bacteraemia patients according to acquisition site are

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Table 1. Clinical predictors and outcomes of methicillin resistance bacteraemia in 371 patients with *Staphylococcus aureus bacteraemia*

	MSSA ($n = 155$)	MRSA ($n = 216$)	*P* value	Adjusted OR (95% CI)	*P* value
Age, year, mean ± S.D.	54.9 ± 21.4	57.6 ± 22.0	0.248		
Male	92 (59.4)	132 (61.1)	0.733		
Hospital onset infection	47 (30.3)	137 (63.4)	<0.001	2.82 (1.62–4.91)	<0.001
Surgery in previous 90 days	10 (6.5)	47 (21.8)	<0.001		
Antibiotics use in previous 90 days	39 (25.2)	128 (59.3)	<0.001	2.47 (1.41–4.34)	0.002
Glycopeptides	5 (3.2)	27 (12.5)	0.002		
β-lactams	30 (19.4)	111 (51.4)	<0.001		
Fluoroquinolones	4 (2.6)	27 (12.5)	0.001		
History of MRSA infection	5 (3.2)	27 (12.5)	0.002		
Underlying co-morbidities					
Diabetes mellitus	40 (25.8)	58 (26.9)	0.822		
Chronic renal failure	29 (18.7)	42 (19.4)	0.859		
Liver cirrhosis	16 (10.3)	32 (14.8)	0.206		
Chronic lung disease	15 (9.7)	24 (11.1)	0.657		
Congestive heart failure	39 (25.2)	65 (30.1)	0.297		
Cerebrovascular disease	9 (5.8)	34 (15.7)	0.005		
Haematologic malignancy	24 (15.5)	18 (8.3)	0.035		
Solid cancer	38 (24.5)	52 (24.1)	0.922		
Solid organ transplantation	5 (3.2)	6 (2.8)	0.802		
Neutropaenia	19 (12.3)	16 (7.4)	0.118		
Immunocompromised agents	28 (18.1)	22 (10.2)	0.030		
Corticosteroid use	19 (12.3)	28 (13.0)	0.840		
McCabe and Jackson Classification					
Rapid or ultimately fatal underlying disease	70 (45.2)	91 (42.1)	0.561		
Invasive medical devices at presentation					
Central venous catheter	49 (31.6)	108 (50.0)	<0.001		
Percutaneous drain	20 (12.9)	58 (26.9)	0.001		
Presentation with septic shock	22 (14.2)	44 (20.4)	0.127		
Presentation with acute renal failure	30 (19.4)	90 (44.4)	<0.001		
Pitt score, median (IQR)	1 (0–2)	1 (0–3)	0.090		
Primary site of infection					
Primary bacteraemia	47 (30.3)	46 (21.3)	0.049		
Catheter related blood stream	31 (20.0)	65 (30.1)	0.030		
Respiratory tract infection	21 (13.5)	41 (19.0)	0.168		
Urinary tract infection	4 (2.6)	4 (1.9)	0.635		
Intra-abdominal infection	14 (9.0)	10 (4.6)	0.095		
Skin and soft tissue infection	24 (15.5)	28 (13.0)	0.491		
Bone and joint infection	13 (8.4)	23 (10.6)	0.469		
Endocarditis	6 (3.9)	10 (4.6)	0.723		
Meningitis	3 (1.9)	3 (1.4)	0.682		
Treatment					
Inappropriate empirical antibiotics	4 (2.6)	122 (56.5)	<0.001		
Outcomes					

(*Continued*)

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Table 1. (*Continued.*)

	MSSA ($n = 155$)	MRSA ($n = 216$)	*P* value	Adjusted OR (95% CI)	*P* value
Persistent bacteraemia	39 (25.2)	80 (37.0)	0.326		
Mortality	32 (20.9)	47 (21.9)	0.828		

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; OR, odds ratio; CI, confidence interval; S.D., standard deviation; IQR, interquartile range.
Hosmer-Lemeshow goodness of fit statistic $\chi^2 = 5.627$, $P = 0.689$.
Data are *n* (%) unless otherwise stated.

presented in Table 2. Surgery in the previous 90 days ($P = 0.007$), antibiotic use in the same period ($P = 0.005$) and bone and joint infection ($P = 0.032$) were risk factors for CA-MRSA bacteraemia. By multivariate analysis only prior antibiotic use (OR 2.04, 95% CI 1.01–4.14, $P = 0.047$) was an independent predictor of MRSA in community-onset cases. Prescribed β-lactams was the only antibiotic class associated with having MRSA bacteraemia among prior antibiotic uses in both the multivariate analysis and in bivariate testing. The goodness of fit of the final logistic regression model appeared to be satisfactory (Hosmer-Lemeshow statistic, $\chi^2 = 2.701$, $P = 0.259$). On the other hand, for hospital-onset cases, several risk factors were more prevalent in MRSA than MSSA bacteraemia including: surgery in previous 90 days ($P = 0.040$), antibiotic use in the same period ($P < 0.001$), underlying diabetes ($P = 0.017$), underlying cerebrovascular diseases ($P = 0.008$) or haematologic malignancy ($P = 0.006$), neutropaenia ($P = 0.035$), use of immunosuppressive agents ($P = 0.001$), central venous catheterisation ($P = 0.030$) and percutaneous drainage at presentation ($P = 0.021$), presentation with septic shock ($P = 0.040$) or acute renal failure ($P < 0.001$). Prior use of any antibiotic (OR 2.25, 95% CI 1.01–5.01, $P = 0.047$) was also the only independent predictor of HA-MRSA bacteremia in multivariate analysis. The goodness of fit of the final logistic regression model in hospital-onset population appeared to be satisfactory (Hosmer-Lemeshow statistic, $\chi^2 = 6.095$, $P = 0.637$).

Predictors of 30-day mortality in patients with S. aureus *bacteraemia*

The multivariate analysis of potential risk factors associated with 30-day mortality of cases is shown in Table 3. Variables with *P*-value of <0.05 in the univariate analysis (i.e. age, liver cirrhosis, solid cancer, rapidly or ultimately fatal disease, central venous catheterisation at presentation, septic shock, acute renal failure, Pitt Bacteraemia Score, respiratory, or skin and soft tissue infection, endocarditis and persistent bacteraemia) were included in the subsequent multivariate analysis. A Cox proportional hazards model revealed that of the above factors, age (hazard ratio (HR) = 1.03, 95% CI 1.01–1.04; $P = 0.001$), liver cirrhosis (HR = 2.21, 95% CI 1.24–3.97, $P = 0.008$), rapidly or ultimately fatal disease (HR = 2.38, 95% CI 1.46–3.89, $P = 0.001$), septic shock (HR = 2.14, 95% CI 1.22–3.78; $P = 0.008$), Pitt Bacteraemia Score (HR = 1.14, 95% CI 1.05–1.23, $P = 0.002$), skin and soft tissue infection (HR = 0.28, 95% CI 0.09–0.90, $P = 0.032$) and persistent bacteraemia (HR = 2.84, 95% CI 1.76–4.56; $P < 0.001$) were independent predictors of 30-day mortality. Methicillin resistance (HR = 1.01, 95% CI 0.66–1.53; $P = 0.972$) was not a predictor of mortality in these patients and remained non predictive of mortality after stratifying according to acquisition site in both community-onset (HR = 0.96, 95% CI 0.52–1.77; $P = 0.889$) and hospital-onset cases (HR = 1.06, 95% CI 0.54–2.07; $P = 0.862$) (Table 4).

Discussion

Our study found no significant differences in clinical outcome between bacteraemic patients infected with MRSA *vs.* MSSA. However, MRSA patients were more likely to have acquired the infection in hospital and received antibiotics in the preceding 90 days and this was the only marker predictive of methicillin-resistance. Inappropriate empirical therapy was more frequently prescribed for MRSA bacteraemia but the 30-day mortality did not differ between the two groups.

The epidemiology of *S. aureus* has undergone significant changes over the past three decades. Initially, HA-MRSA infection was thought to be primarily a HA disease; however, several CA-MRSA strains have emerged in the community some of which have recently spread into healthcare settings [5–7]. In addition, a recent study from Chicago, USA showed that a possible role reversal had occurred for MSSA and MRSA strains as the former were predominantly HA and many MRSA patients no longer had recent exposure to the healthcare setting [20]. Therefore, it is important to examine the factors that may be associated with MRSA infection. Miller *et al.* [21] showed from a prospective investigation of consecutive hospitalised patients with *S. aureus* infection in Los Angeles, that clinical and epidemiological risk factors did not reliably distinguish between MRSA and MSSA. Similar findings were reported from a study of *S. aureus* infections among military veterans except that methicillin resistance was higher in subjects who had a prior MRSA infection or stay in a long-term care facility [22]. Likewise, a cross-sectional study from Colombia found that most clinical and epidemiological factors evaluated did not allow discrimination of MRSA from MSSA infected patients with the exception of a history of MRSA infection, prior antibiotic therapy and stay in children's day care centres [23]. These factors are corroborated by the few clinical differences found in our study between MRSA and MSSA patients, with prior antibiotics being the only independent predictor of both CA- and HA-MRSA bacteraemia. In community-onset *S. aureus* cases, only prior β-lactam therapy was a risk factor for having MRSA, as opposed to all classes of antibiotics for hospital onset MRSA. In another study, prior exposure to the carbapenems appeared to have a gradient effect for the emergence of methicillin resistance [24].

Other established risk factors [25, 26], including history of MRSA infection, residing in a long-term care facility with MRSA infections, recent surgery and indwelling percutaneous medical devices and catheters, failed to differentiate MRSA from MSSA infection in our study. Taken together with other studies, these results support the view that MRSA and MSSA bacteraemic infection share most clinical characteristics. This might be explained by the striking increase of CA-MRSA infections in many countries and their dissemination in to healthcare settings.

Consistent with previous studies [27, 28], the clinical spectrum of disease caused by MRSA appears to be similar to that of MSSA

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Table 2. Clinical predictors and outcomes of patients with *Staphylococcus aureus bacteraemia* stratified by acquisition site

	Community-onset infection					Hospital-onset infection				
	MSSA (*n* = 108)	MRSA (*n* = 79)	*P* value	Adjusted OR (95% CI)	*P* value	MSSA (*n* = 47)	MRSA (*n* = 137)	*P* value	Adjusted OR (95% CI)	*P* value
Age, year, mean ± S.D.	55.9 ± 21.1	57.7 ± 21.2	0.573			52.7 ± 22.2	57.6 ± 22.6	0.204		
Male	68 (63.0)	53 (67.1)	0.560			24 (51.1)	79 (57.7)	0.432		
Healthcare risk factor	54 (50.0)	50 (63.3)	0.071			NA	NA	NA		
Surgery in previous 90 days	5 (4.6)	13 (16.5)	0.007			5 (10.6)	34 (24.8)	0.040		
Antibiotics use in previous 90 days	20 (18.5)	29 (36.7)	0.005	2.01 (1.01–4.14)	0.047	19 (40.4)	99 (72.3)	<0.001	2.25 (1.01–5.01)	0.047
Glycopeptides	2 (1.9)	0	0.497			3 (6.4)	27 (19.7)	0.010		
β-lactams	15 (13.9)	27 (34.2)	0.004			15 (31.9)	84 (61.3)	<0.001		
Fluoroquinolones	3 (2.8)	6 (7.6)	0.157			1 (2.1)	21 (15.3)	0.012		
History of MRSA infection	5 (4.6)	2 (2.5)	0.701			3 (6.4)	22 (16.1)	0.095		
Underlying co-morbidities										
Diabetes mellitus	35 (32.4)	20 (25.3)	0.293			5 (10.6)	38 (27.7)	0.017		
Chronic renal failure	21 (19.4)	21 (26.6)	0.248			8 (17.0)	21 (15.3)	0.783		
Liver cirrhosis	14 (13.0)	12 (15.2)	0.664			2 (4.3)	20 (14.6)	0.059		
Chronic lung disease	9 (8.3)	4 (5.1)	0.385			6 (12.8)	20 (14.6)	0.756		
Congestive heart failure	26 (24.1)	23 (29.1)	0.439			13 (27.7)	42 (30.7)	0.699		
Cerebrovascular disease	7 (6.5)	5 (6.3)	0.967			2 (4.3)	29 (21.2)	0.008		
Haematologic malignancy	12 (11.1)	5 (6.3)	0.261			12 (25.5)	13 (9.5)	0.006		
Solid cancer	22 (20.4)	14 (17.7)	0.650			16 (34.0)	38 (27.7)	0.413		
Neutropaenia	9 (8.3)	3 (3.8)	0.211			10 (21.3)	13 (9.5)	0.035		
Immunocompromised agents	11 (10.2)	4 (5.1)	0.203			17 (36.2)	18 (13.1)	0.001		
Corticosteroid use	7 (6.5)	5 (6.3)	0.967			12 (25.5)	23 (16.8)	0.188		
McCabe and Jackson classification										
Rapid or ultimately fatal underlying disease	44 (40.7)	34 (43.0)	0.753			26 (55.3)	57 (41.6)	0.103		
Invasive medical devices at presentation										
Central venous catheter	25 (23.1)	14 (17.7)	0.367			24 (51.1)	94 (68.6)	0.030		
Percutaneous drain	12 (11.1)	10 (12.7)	0.746			8 (17.0)	48 (35.0)	0.021		
Presentation with septic shock	17 (15.7)	10 (12.7)	0.554			5 (10.6)	34 (24.8)	0.040		
Presentation with acute renal failure	18 (16.7)	11 (13.9)	0.609			12 (25.5)	85 (62.0)	<0.001		
Pitt score, median (IQR)	1 (0–1.8)	1 (0–2.0)	0.342			0 (0–2.0)	1 (0–3.5)	0.185		
Primary site of infection										

Primary bacteraemia	33 (30.6)	20 (25.3)	0.432	14 (29.8)	26 (19.0)	0.121
Catheter related blood stream	15 (13.9)	7 (8.9)	0.292	16 (34.0)	58 (42.3)	0.317
Respiratory tract infection	14 (13.0)	9 (11.4)	0.747	7 (14.9)	32 (23.4)	0.221
Urinary tract infection	4 (3.7)	2 (2.5)	1.000	0	2 (1.5)	1.000
Intra-abdominal infection	12 (11.1)	4 (5.1)	0.144	2 (4.3)	6 (4.4)	1.000
Skin and soft tissue infection	17 (15.7)	14 (17.7)	0.719	7 (14.9)	14 (10.2)	0.384
Bone and joint infection	12 (11.1)	18 (22.8)	0.032	1 (2.1)	5 (3.6)	1.000
Endocarditis	6 (5.6)	6 (7.6)	0.574	0	4 (2.9)	0.574
Meningitis	3 (2.8)	2 (2.5)	1.000	0	1 (0.7)	1.000
Treatment						
Inappropriate empirical antibiotics	4 (3.7)	43 (54.4)	<0.001	0	79 (57.7)	<0.001
Outcomes						
Persistent bacteremia	27 (25.0)	26 (32.9)	0.236	12 (25.5)	54 (39.4)	0.087
Mortality	22 (20.5)	16 (20.5)	0.968	10 (21.3)	31 (22.6)	0.848

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; S.D., standard deviation; IQR, interquartile range.
Hosmer-Lemeshow goodness of fit statistic for community-onset infection $\chi^2 = 2.701$, $P = 0.259$.
Hosmer-Lemeshow goodness of fit statistic for hospital-onset infection $\chi^2 = 6.095$, $P = 0.637$.
Data are *n* (%) unless otherwise stated.

Table 3. Variables associated with 30-day mortality in 371 patients with *Staphylococcus aureus bacteraemia*

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age	1.03 (1.01–1.04)	<0.001	1.03 (1.01–1.04)	0.001
Male	1.11 (0.71–1.73)	0.662		
Hospital onset infection	1.14 (0.67–1.95)	0.632		
Methicillin resistance	1.01 (0.66–1.53)	0.972		
Surgery in previous 90 days	0.84 (0.45–1.59)	0.597		
Antibiotics use in previous 90 days	1.06 (0.68–1.65)	0.785		
History of MRSA infection	1.00 (0.52–1.94)	0.991		
Underlying co-morbidities				
Diabetes mellitus	0.92 (0.56–1.51)	0.728		
Chronic renal failure	1.15 (0.67–2.00)	0.609		
Liver cirrhosis	1.84 (1.07–3.19)	0.029	2.21 (1.24–3.97)	0.008
Chronic lung disease	1.29 (0.68–2.45)	0.430		
Congestive heart failure	1.07 (0.66–1.73)	0.796		
Cerebrovascular disease				
Haematologic malignancy	0.70 (0.32–1.52)	0.363		
Solid cancer	1.98 (1.25–3.12)	0.004		
Neutropaenia	1.30 (0.67–2.52)	0.443		
Immunocompromised agents	0.56 (0.26–1.22)	0.145		
Corticosteroid use	0.75 (0.38–1.51)	0.424		
McCabe and Jackson classification				
Rapid or ultimately fatal underlying disease	3.19 (1.98–5.12)	<0.001	2.38 (1.46–3.89)	0.001
Invasive medical devices at presentation				
Central venous catheter	1.67 (1.07–2.61)	0.023		
Percutaneous drain	0.98 (0.57–1.68)	0.939		
Presentation with septic shock	3.80 (2.42–5.95)	<0.001	2.14 (1.22–3.78)	0.008
Presentation with acute renal failure	2.15 (1.38–3.34)	0.001		
Pitt score	1.25 (1.18–1.33)	<0.001	1.14 (1.05–1.23)	0.002
Primary site of infection				
Primary bacteraemia	1.19 (0.70–2.04)	0.527		
Catheter related blood stream	0.73 (0.43–1.25)	0.248		
Respiratory tract infection	2.19 (1.36–3.54)	0.001		
Urinary tract infection	1.06 (0.39–2.90)	0.913		
Intra-abdominal infection	0.61 (0.19–1.94)	0.402		
Skin and soft tissue infection	0.20 (0.06–0.64)	0.006	0.28 (0.09–0.90)	0.032
Bone and joint infection	0.57 (0.25–1.32)	0.192		
Endocarditis	2.64 (1.32–5.29)	0.006		
Meningitis	0.63 (0.09–4.55)	0.649		
Inappropriateness of initial empirical agents	1.22 (0.77–1.91)	0.402		
Persistent bacteremia	4.10 (2.60–6.44)	<0.001	2.84 (1.76–4.56)	<0.001

HR, hazard ratio; MRSA, methicillin-resistant *S. aureus.*

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Table 4. Variables associated with 30-day mortality in 371 patients with *Staphylococcus aureus bacteraemia* stratified by acquisition site

	Community onset infection				Hospital onset infection			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age	1.03 (1.01–1.06)	0.001	1.04 (1.01–1.06)	0.004	1.02 (1.01–1.03)	0.033	1.03 (1.01–1.06)	0.003
Male, *n* (%)	1.26 (0.68–2.33)	0.466			0.85 (0.49–1.48)	0.563		
Methicillin resistance	0.96 (0.52–1.77)	0.889			1.06 (0.54–2.07)	0.862		
Surgery in previous 90 days	0.18 (0.03–1.32)	0.092			1.04 (0.54–2.03)	0.904		
Antibiotics use in previous 90 days	1.17 (0.61–2.25)	0.640			1.71 (0.90–3.27)	0.103		
History of MRSA infection	1.94 (0.60–6.27)	0.271			1.34 (0.67–2.68)	0.402		
Underlying co-morbidities								
Diabetes mellitus	1.24 (0.67–2.31)	0.498			0.81 (0.42–1.57)	0.523		
Chronic renal failure	1.72 (0.87–3.38)	0.118			0.77 (0.35–1.71)	0.517		
Liver cirrhosis	2.05 (1.01–4.17)	0.049	3.36 (1.34–8.38)	0.010	1.57 (0.74–3.33)	0.243		
Chronic lung disease	2.62 (1.10–6.22)	0.029			0.98 (0.46–2.08)	0.953		
Congestive heart failure	1.29 (0.67–2.48)	0.448			0.87 (0.47–1.60)	0.649		
Cerebrovascular disease	0.87 (0.21–3.61)	0.848			0.85 (0.40–1.80)	0.669		
Haematologic malignancy	1.15 (0.41–3.22)	0.793			0.86 (0.39–1.91)	0.709		
Solid cancer	1.91 (0.97–3.73)	0.060			1.71 (0.99–3.05)	0.053		
Neutropaenia	1.89 (0.67–5.32)	0.226			1.30 (0.63–2.67)	0.475		
Immunocompromised agents	0.88 (0.27–2.85)	0.832			0.60 (0.27–1.34)	0.212		
Corticosteroid use	1.55 (0.55–4.36)	0.404			0.75 (0.37–1.54)	0.433		
McCabe and Jackson classification								
Rapid or ultimately fatal underlying disease	4.58 (2.33–8.99)	<0.001	2.63 (1.22–5.67)	0.014	2.18 (1.25–3.81)	0.006	3.80 (1.83–7.90)	<0.001
Invasive medical devices at presentation								
Central venous catheter	3.12 (1.68–5.78)	<0.001			1.15 (0.65–2.06)	0.634		
Percutaneous drain	0.66 (0.20–2.13)	0.485			1.23 (0.70–2.16)	0.478		
Presentation with septic shock	3.59 (1.89–6.83)	<0.001			3.08 (1.77–5.37)	<0.001		
Presentation with acute renal failure	4.28 (2.26–8.09)	<0.001			1.71 (0.97–3.00)	0.064		
Pitt score	1.28 (1.19–1.38)	<0.001			1.21 (1.12–1.31)	<0.001		
Primary site of infection								
Primary bacteraemia	0.95 (0.45–1.99)	0.892			1.13 (0.58–2.20)	0.719		
Catheter related blood stream	1.12 (0.44–2.84)	0.817			0.63 (0.35–1.13)	0.123		

(*Continued*)

Table 4. (*Continued.*)

	Community onset infection				Hospital onset infection			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Respiratory tract infection	2.29 (1.09–4.80)	0.028			2.47 (1.42–4.29)	0.001		
Urinary tract infection	NA	0.556			8.32 (2.00–34.69)	0.004		
Intra-abdominal infection	0.58 (0.14–2.41)	0.457			0.45 (0.06–3.25)	0.428		
Skin and soft tissue infection	0.25 (0.08–0.81)	0.021			0.46 (0.14–1.46)	0.187		
Bone and joint infection	0.64 (0.28–1.45)	0.280			NA	0.305		
Endocarditis	3.73 (1.78–7.79)	<0.001			NA	0.391		
Meningitis	0.64 (0.09–4.62)	0.654			NA	0.670		
Inappropriateness of initial empirical agents	1.56 (0.81–3.01)	0.181			1.10 (0.64–1.91)	0.722		
Persistent bacteremia	3.99 (2.14–7.44)	<0.001	2.60 (1.21–5.59)	0.015	2.79 (1.61–4.83)	<0.001	3.63 (1.90–6.93)	<0.001

HR, hazard ratio; MRSA, methicillin-resistant *S. aureus*.

in the community. However, Lee *et al.* [29] suggested that bone and joint infection was a predictor of CA-MRSA bacteraemia in Korea and identified a specific clone, ST72-SCCmec IV/IVA, which predominated in primary bone and joint infections that progressed to bacteraemia. In our study, bone and joint infections were significantly more prevalent in patients with MRSA than those with community-onset MSSA but statistical significance was lost after adjusting for prior surgery and antibiotic use. The predominance of bone and joint infections in patients with CA-MRSA bacteraemia warrants further investigation.

Many previous studies evaluating the outcomes of MRSA bacteraemia have shown conflicting results [30–33]. Some have reported significant association of MRSA with mortality [30, 32], while others have not [31, 33–35]. In the Cox regression model, we could not link MRSA bacteraemia with higher mortality than that with MSSA and after stratifying by acquisition site, methicillin resistance was still not a significant predictor of mortality. Outcomes of MRSA infections could also be made worse due to confounding associations with other prognostic factors. Almost all relevant studies have shown that infections due to MRSA occur in sicker patients [35, 36], suggesting that differences in mortality may, at least in part, be attributable to the patients' underlying illnesses. Our study population showed few significant clinical differences between MRSA and MSSA bacteraemia and this was reflected in their similar mortality rates. Indeed, previous studies of patient outcomes with MRSA bacteraemia also linked this to a longer hospital stay and not with mortality [37, 38].

We have shown that patients with MRSA bacteraemia were more likely to receive inappropriate empirical antibiotic therapy but this was not an independent predictor of mortality. Others have reported conflicting findings on this issue [39–44]. Interestingly, three studies conducted in Asia found that this factor did not have a detrimental effect on mortality in MRSA bacteraemic patients [43, 45, 46]. Yoon *et al.* [46] in Korea considered that an initial delay in the use of definitive antibiotics did not necessarily prejudice the clinical outcomes of patients with HA-MRSA bacteraemia and recommended the prudent use of glycopeptides as empirical therapy in the context of increasing antibiotic resistance. Similarly, in Taiwan, Fang *et al.* [45] did not support the view that earlier empirical use of glycopeptide therapy reduces mortality in patients with HA-MRSA bacteraemia and, likewise, no significant difference in MRSA-related mortality was evident between patients who had received an appropriate or inappropriate empirical regimen [43].

Some limitations of this study are noted. First, only measured variables were controlled and some additional confounding factors were not accounted for such as prior residence in a long-term care facility, or receipt of hemodialysis and hospitalisation, which are often cited in similar studies as contributory factors differentiating between MRSA and MSSA patients. Second, the failure to show a significant difference in mortality according to empirical antibiotic therapy may be a consequence of the limited sample size; third, and we chose to define appropriate antibiotic use based on in vitro susceptibility of the recovered isolate and did not take account of the fact that different agents differ in clinical outcomes such as the reported inferiority of vancomycin to beta-lactams for the treatment of MSSA bacteraemia [11, 44]. Finally, the absence of molecular analysis did not allow investigation of the clonal background which might have impacted on mortality given the reported associations of, for example, strain lineages CC22 and endocarditis, [47], CC8 and vancomycin resistance [48] and CC5 or CC30 and haematogenous complications [49].

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The predominant CA-MRSA clone in Korea, ST72-SCCmecIV, was shown to be independently associated with lower mortality compared with ST5-SCCmecII [50]; furthermore, the lack of virulence markers including staphylococcal superantigen genes, may play a role in the lower virulence of ST72-SCCmecIV strain [50]. Further clonal analysis of both MRSA and MSSA strains is therefore necessary to explore further any associations of strain type with mortality.

In conclusion, we found no definitive clinical or epidemiological risk factors which could distinguish MRSA from MSSA in bacteraemic patients with the exception of the previous use of antibiotics for having MRSA bacteraemia in such patients regardless of its acquisition site. MRSA bacteraemia was not associated with higher risks of mortality. Finally, the prudent use of glycopeptide treatment of patients at risk for invasive MRSA infections should be emphasised in order to stem the tide of increasing resistance to these highly effective agents.

Conflict of interest. None.

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