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Community-associated MRSA strain ST72-SCCmecIV causing bloodstream infections: clinical outcomes and bacterial virulence factors

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Objectives: Community-associated MRSA (CA-MRSA) has emerged in the community and has recently been spreading in healthcare settings. The objectives of this study were to evaluate the clinical outcomes and bacterial virulence factors of the Korean CA-MRSA (ST72-SCCmecIV) strain, which causes bloodstream infections.

Methods: All adult patients with MRSA bacteraemia were prospectively enrolled. Clinical outcomes, microbiological characteristics and 40 bacterial virulence factors were evaluated.

Results: Of the 352 typed MRSA isolates, 342 isolates (97.2%) belonged to three Panton–Valentine leucocidin-negative strains: ST5-SCCmecII (70.2%), ST72-SCCmecIV (22.4%) and ST239-SCCmecIII (4.6%). The remaining 10 (2.8%) isolates from minor strains were excluded from the final analysis. After controlling for several confounding factors, ST72-SCCmecIV was associated with the lowest mortality (compared with ST5-SCCmecII, adjusted OR=0.26; 95% CI=0.13–0.54). However, MRSA isolates with vancomycin MICs of $\geq$1.5 mg/L were more common in ST72-SCCmecIV compared with ST5-SCCmecII (84.8% versus 66.7%; P=0.002). Reduced vancomycin susceptibility and vancomycin heteroresistance were not associated with mortality. Compared with ST5-SCCmecII isolates, ST72-SCCmecIV isolates were less likely to harbour multiple virulence genes. Of these genes, three staphylococcal superantigen genes were associated with mortality: *sec* (OR=2.31; P=0.002), *sel* (OR=2.55; P=0.003) and *tst* (OR=2.76; P<0.001).

Conclusions: After controlling for confounding factors, ST72-SCCmecIV was independently associated with lower mortality compared with ST5-SCCmecII, suggesting this CA-MRSA strain to be of lower virulence. The lack of virulence genes, including staphylococcal superantigen genes, may play a role in the lower virulence of this strain.

Keywords: *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, bacteraemia, genotype, outcome

Introduction

In recent years, community-associated MRSA (CA-MRSA) has emerged as an important cause of infection with geographical differences among strains: ST1 (USA400) and ST8 (USA300) exist in North America, ST80 is found in Europe, ST59 is found in the Asia-Pacific region and ST30 is noted worldwide.[1,2] The major CA-MRSA clone in South Korea (ST72) is distinct from those that have spread throughout Asia (ST30, ST59 and ST338) or internationally.[2] The Korean CA-MRSA strain has emerged in the community and has recently been spreading in healthcare settings.[3–7]

The widespread existence of CA-MRSA in both community and healthcare settings has raised serious concerns that CA-MRSA causes more severe disease and has worse clinical outcomes than hospital-associated MRSA (HA-MRSA). However, the effect of CA-MRSA on the clinical outcome of MRSA infection remains unclear. Previous studies have reported conflicting results regarding the role of host factors, microbiological factors and CA-MRSA clonal type on MRSA infection outcomes.[3,5,8–19] Many of these studies were limited by small case numbers[5,10,14] or a failure to control for potential confounding factors.[5,8–10,14] Additionally, studies evaluating this association may be hampered by the differences among MRSA strains. Therefore, we conducted a prospective cohort study of the effect of Korean CA-MRSA, specifically ST72-SCCmecIV, on clinical outcomes in patients with MRSA bacteraemia. We explored the

virulence factors of this MRSA strain that are involved in blood-stream infections.

Methods

Study design and patients

This prospective cohort study was conducted at the Asan Medical Center, Seoul, Republic of Korea. This 2700 bed, university-affiliated teaching hospital provides both primary and tertiary care and has an average of ~124 000 patient discharges annually. From August 2008 through July 2011, patients aged ≥16 years with MRSA bacteraemia were included. The Asan Medical Center Institutional Review Board approved this study (IRB number: 2008–0274). Informed consent was waived given that no interventions were planned and the data collected were stored anonymously.

Laboratory and molecular methods

The MIC of vancomycin was determined using the Etest (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. All MRSA isolates were assessed using the population analysis profiling–AUC method, using the technique of Wootton *et al.*[20] An isolate was identified as hetero-resistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) if the ratio of the AUC of the test isolate to that of the reference strain (Mu3; ATCC 700698) was ≥0.9. We used δ-haemolysin activity to determine *agr* functionality as described previously.[21]

The staphylococcal cassette chromosome *mec* (SCC*mec*) types were identified using a method described previously.[22] MLST was performed as described previously. The presence of 40 bacterial virulence factors and *agr* subgroups I–IV was determined using a multiplex PCR as described previously.[23–26]

Data collection and information on variables

The following data were obtained from all patients: age, gender, presence of pre-existing comorbidities, recent surgery history, history of immuno-suppressive therapy, mode of acquisition,[27] sepsis severity, primary site of infection, antibiotic treatment and clinical outcome. The severity of pre-existing comorbidities was measured using the Charlson comorbidity score.[28] Charlson comorbidity score was dichotomized by classification and regression tree (CART) for multivariate regression modelling. Effective empirical antibiotic treatment was defined as the initiation of anti-MRSA antibiotics within 24 h of obtaining the index blood culture. Inadequate vancomycin therapy was defined as a vancomycin trough level of <10 mg/L measured after ≥3 days of vancomycin therapy.[19]

The primary study outcome was crude mortality, which was defined as death from any cause during hospitalization. Secondary study outcomes included persistent bacteraemia, recurrent bacteraemia and length of hospital stay (LOS) after infection. Persistent bacteraemia was defined as a positive MRSA blood culture after >7 days of anti-MRSA antibiotic treatment during index hospitalization. Recurrent bacteraemia was defined as an occurrence of MRSA bacteraemia within 30 days of discontinuation of the anti-MRSA therapy. LOS after infection was determined in all surviving patients and was calculated from the date of first positive blood culture for MRSA until the date of discharge.

Statistical analysis

All statistical analyses were performed using SPSS for Windows®, version 19.0 (SPSS, Chicago, IL, USA). Clinical and microbiological characteristics as well as bacterial virulence determinants were compared between three groups of MRSA strains (ST5-SCC*mec*II, ST72-SCC*mec*IV and ST239-SCC*mec*III) rather than between two groups (CA-MRSA and HA-MRSA),

because outcomes and virulence determinants of ST5-SCC*mec*II differed from those of ST239-SCC*mec*III. Continuous and categorical variables were compared among the three groups using Kruskal–Wallis tests and Fisher's exact tests, respectively. *Post hoc* analyses with Mann–Whitney *U*-tests or Fisher's exact tests were conducted with Bonferroni correction applied, resulting in a significance level set at a P value of <0.017.

Univariate and multivariate analyses using logistic regression models were performed to identify independent risk factors for crude mortality. All variables with P values <0.10 upon univariate analysis were included in the multivariate logistic regression model. Because MRSA strains might exert their effect on mortality through acute bacteraemia severity, we elaborated two multivariate models, one with and the other without inclusion of sepsis severity, to estimate the impact of different MRSA strains on mortality. Multicollinearity was assessed using variance inflation factors. All tests of significance were two-tailed and P values <0.05 were considered to indicate significance.

Results

A total of 356 MRSA bacteraemia patients were prospectively enrolled during the study period. Four episodes were excluded because MRSA blood isolates were unable to be typed by molecular analysis. Of the 352 typed isolates, 342 (97.2%) comprised three MRSA strains: ST5-SCC*mec*II in 247 (70.2%), ST72-SCC*mec*IV in 79 (22.4%) and ST239-SCC*mec*III in 16 (4.6%). The remaining 10 (2.8%) isolates were as follows: ST254-SCC*mec*I ($n=4$), ST8-SCC*mec*I ($n=1$), ST1-SCC*mec*II ($n=1$), ST89-SCC*mec*II ($n=1$), ST1-SCC*mec*IV ($n=1$), ST8-SCC*mec*IV ($n=1$) and ST188-SCC*mec*IV ($n=1$). Excluding the 10 infections caused by the minor strains, 342 MRSA bacteraemia episodes were included in the final analyses.

Clinical features

The clinical characteristics of the 342 patients with MRSA bacteraemia are shown in Table 1. Patients with ST72-SCC*mec*IV were less likely to have a history of recent surgery ($P<0.001$), nosocomial infection ($P<0.001$) and intravascular catheter infections ($P=0.002$) compared with ST5-SCC*mec*II infection. ST72-SCC*mec*IV caused osteoarticular infection more frequently compared with ST5-SCC*mec*II ($P<0.001$). Vancomycin therapy was administered more frequently to patients with ST72-SCC*mec*IV compared with those with ST5-SCC*mec*II ($P=0.008$). There were no significant differences among patients infected with the three different MRSA strains with respect to age, comorbidity, Charlson score, prescription of immunosuppressive therapy and sepsis severity.

Microbiological characteristics

The microbiological characteristics and antibiotic susceptibilities of the three MRSA strains are shown in Table 2. *agr* dysfunction was more common in ST5-SCC*mec*II (96.4%) compared with ST72-SCC*mec*IV (8.9%; $P<0.001$) and ST239-SCC*mec*III (68.8%; $P=0.001$). The hVISA phenotype frequency differed among ST5-SCC*mec*II (33.6%), ST72-SCC*mec*IV (13.9%) and ST239-SCC*mec*III (81.3%) ($P<0.001$). Compared with ST5-SCC*mec*II, ST72-SCC*mec*IV isolates were more likely to have vancomycin MICs ≥1.5 mg/L ($P=0.002$). Compared with ST5-SCC*mec*II isolates, ST72-SCC*mec*IV isolates were less likely to be resistant to several non-β-lactam antibiotics, including clindamycin, ciprofloxacin, erythromycin, fusidic acid, gentamicin and rifampicin.

Table 1. Clinical characteristics of 342 adult patients with MRSA bacteraemia

Characteristic	ST5-SCC*mec*II (n=247)	ST72-SCC*mec*IV (n=79)	ST239-SCC*mec*III (n=16)	overall	ST5-SCC*mec*II versus ST72-SCC*mec*IV	ST5-SCC*mec*II versus ST239-SCC*mec*III
Age (years), median (IQR)	66 (56–72)	64 (55–71)	59 (49–68)	0.13		
Male	168 (68.0)	44 (55.7)	14 (87.5)	0.02	0.06	0.16
Comorbidity						
cancer	123 (49.8)	37 (46.8)	4 (25.0)	0.15		
diabetes mellitus	72 (29.1)	26 (32.9)	3 (18.8)	0.55		
liver cirrhosis	30 (12.1)	7 (8.9)	2 (12.5)	0.73		
end-stage renal disease	26 (10.5)	10 (12.7)	1 (6.3)	0.81		
chronic pulmonary disease	13 (5.3)	2 (2.5)	0 (0)	0.60		
Charlson score, median (IQR)	3 (2–5)	2 (1–4)	3 (0–4)	0.18		
Charlson score (>4)	63 (25.5)	15 (19.0)	2 (12.5)	0.33		
Recent surgery[a]	100 (40.5)	15 (19.0)	6 (37.5)	0.001	<0.001	>0.99
Prescription of immunosuppressive therapy[a]	54 (21.9)	12 (15.2)	6 (37.5)	0.12		
Mode of acquisition						
community associated	2 (0.8)	11 (13.9)	0 (0)	<0.001	<0.001	>0.99
healthcare associated	32 (13.0)	26 (32.9)	5 (31.2)	<0.001	<0.001	0.06
nosocomial onset	213 (86.2)	42 (53.2)	11 (68.8)	<0.001	<0.001	0.07
Sepsis severity						
sepsis/no SIRS	170 (68.8)	60 (75.9)	14 (87.5)	0.19		
severe sepsis	27 (10.9)	7 (8.9)	2 (12.5)	0.76		
septic shock	50 (20.2)	12 (15.2)	0 (0)	0.08		
Primary site of infection						
intravascular catheter-related	134 (54.3)	27 (34.2)	9 (56.1)	0.007	0.002	>0.99
pneumonia	27 (10.9)	5 (6.3)	1 (6.3)	0.55		
surgical site infection	18 (7.3)	4 (5.1)	1 (6.3)	0.85		
endovascular infection	11 (4.5)	9 (11.4)	1 (6.3)	0.08		
osteoarticular infection	6 (2.4)	11 (13.9)	2 (12.5)	<0.001	<0.001	0.08
skin and soft tissue infection	9 (3.6)	6 (7.6)	2 (12.5)	0.10		
other	22 (8.9)	8 (10.1)	0 (0)	0.52		
unknown	20 (8.1)	9 (11.4)	0 (0)	0.38		
Effective empirical antibiotic treatment	151 (61.1)	51 (64.6)	10 (62.5)	0.90		
Definite antibiotic treatment						
no treatment	0 (0)	1 (1.3)	0 (0)	0.28		
vancomycin	221 (89.5)	78 (98.7)	14 (87.5)	0.01	0.008	0.68
other anti-MRSA agents[b]	26 (10.5)	0 (0)	2 (12.5)	0.002	0.001	0.68
Inadequate vancomycin therapy[c]	34/198 (17.2)	17/66 (25.8)	0/12 (0)	0.07		

Data are no. (%) of patients unless otherwise indicated. SIRS, systemic inflammatory response syndrome.
[a]During the previous month.
[b]Teicoplanin was used in 18 patients and linezolid in 10 patients.
[c]Determined in 276 patients in whom vancomycin trough levels were measured after ≥3 days of vancomycin therapy.

Table 2. Microbiological characteristics of 342 MRSA isolates causing bloodstream infections

| | ST5-SCC*mec*II (*n*=247) | ST72-SCC*mec*IV (*n*=79) | ST239-SCC*mec*III (*n*=16) | P | | |
| | | | | | | |
Characteristic				overall	ST5-SCC*mec*II versus ST72-SCC*mec*IV	ST5-SCC*mec*II versus ST239-SCC*mec*III
agr subgroup	II	I	I	NA		
agr dysfunction	238 (96.4)	7 (8.9)	11 (68.8)	<0.001	<0.001	0.001
hVISA	83 (33.6)	11 (13.9)	13 (81.3)	<0.001	0.001	<0.001
Vancomycin MIC by Etest						
≤1.0 mg/L	82 (33.2)	12 (15.2)	4 (25.0)	0.005	0.002	0.59
1.5 mg/L	109 (44.1)	48 (60.8)	8 (50.0)	0.04	0.01	0.80
≥2.0 mg/L	56 (22.6)	19 (24.0)	4 (25.0)	0.92		
Resistance to						
clindamycin	244 (98.8)	18 (22.8)	15 (93.8)	<0.001	<0.001	0.22
ciprofloxacin	245 (99.2)	5 (6.3)	16 (100)	<0.001	<0.001	>0.99
erythromycin	237 (96.0)	28 (35.4)	16 (100)	<0.001	<0.001	>0.99
fusidic acid	218 (88.3)	0 (0)	2 (12.5)	<0.001	<0.001	<0.001
gentamicin	197 (79.8)	12 (15.2)	16 (100)	<0.001	<0.001	0.048
rifampicin	21 (8.5)	0 (0)	1 (6.3)	0.009	0.003	>0.99
trimethoprim/ sulfamethoxazole	2 (0.8)	0 (0)	16 (100)	<0.001	>0.99	<0.001

Data are no. (%) of patients unless otherwise indicated. NA, not applicable.
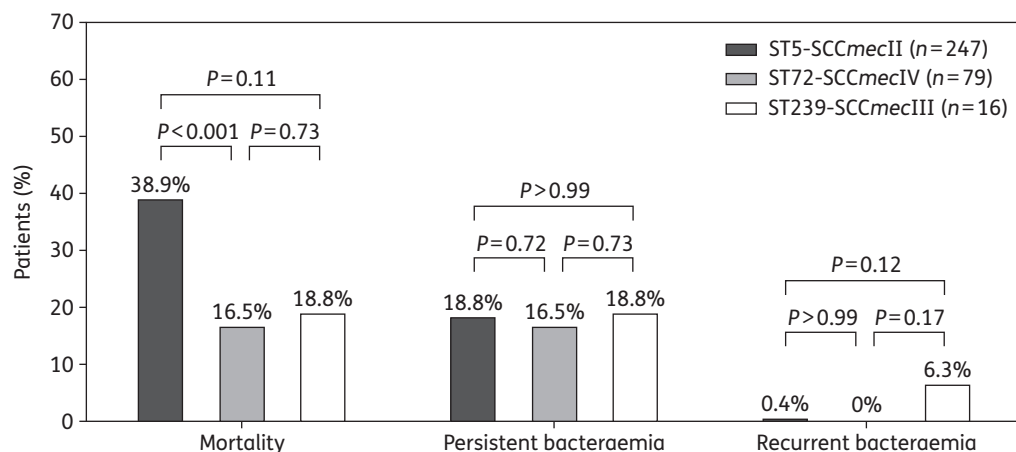
Figure 1. Treatment outcomes of 342 patients with MRSA bacteraemia according to MRSA genotype.

Outcomes

The treatment outcomes of 342 patients with MRSA bacteraemia are shown in Figure 1. A total of 112 patients died, resulting in a crude mortality rate of 32.7%. The highest rate was 38.9% (96/247) for patients with ST5-SCC*mec*II isolates, followed by 18.8% (3/16) for those with ST239-SCC*mec*III isolates and 16.5% (13/79) for patients with ST72-SCC*mec*IV isolates. The rates of persistent and recurrent bacteraemia were comparable among the three groups. LOS after bacteraemia onset was determined in 230 surviving patients. The median LOS after the onset of bacteraemia was 37, 28 and 35 days for patients with ST5-SCC*mec*II, ST72-SCC*mec*IV and ST239-SCC*mec*III, respectively (*P*=0.07).

Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for mortality (Table 3). In univariate analyses, underlying malignancy, liver cirrhosis, Charlson score (>4), septic shock, pneumonia, endovascular infection and *agr* dysfunction were associated with increased mortality, whereas ST72-SCC*mec*IV was associated with decreased mortality. Increased vancomycin MICs and hVISA phenotype were not associated with mortality.

In multivariate analyses, after controlling for several confounders, ST72-SCC*mec*IV (compared with ST5-SCC*mec*II, adjusted OR=0.26; 95% CI=0.13–0.54) was independently associated with lower mortality. When analysis was repeated after excluding the sepsis severity in the multivariate model, ST72-SCC*mec*IV was

Table 3. Univariate and multivariate analyses of risk factors associated with mortality in patients with MRSA bacteraemia

Risk factor	Univariate analysis		Multivariate analysis (model 1)[a]		Multivariate analysis (model 2)[b]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age ≥65 years	1.23 (0.79–1.94)	0.36				
Male	1.20 (0.74–1.94)	0.47				
Underlying malignancy	1.93 (1.22–3.06)	0.005				
Diabetes mellitus	0.72 (0.43–1.19)	0.20				
Liver cirrhosis	2.15 (1.09–4.21)	0.03				
End-stage renal disease	1.13 (0.55–2.31)	0.74				
Charlson score (>4)	3.25 (1.94–5.46)	<0.001	3.93 (2.24–6.92)	<0.001	3.71 (2.14–6.46)	<0.001
Mode of acquisition						
community acquired	1	NA				
healthcare associated	1.67 (0.41–6.71)	0.47				
nosocomial	1.65 (0.44–6.14)	0.46				
Sepsis severity						
sepsis/no SIRS	1	NA	1	NA	NE	NA
severe sepsis	1.75 (0.85–3.63)	0.13	1.92 (0.89–4.15)	0.10	NE	NA
septic shock	3.13 (1.77–5.56)	<0.001	3.31 (1.77–6.21)	<0.001	NE	NA
Intravascular catheter-related infection	0.74 (0.47–1.16)	0.19				
Pneumonia	2.09 (1.01–4.31)	0.046			2.30 (1.05–5.04)	0.04
Endovascular infection	2.95 (1.20–7.22)	0.02	6.15 (2.22–17.06)	<0.001	6.53 (2.40–17.78)	<0.001
Osteoarticular infection	0.23 (0.05–1.004)	0.051				
Effective empirical antibiotic therapy	1.30 (0.81–2.08)	0.28				
Inadequate vancomycin therapy	0.76 (0.38–1.51)	0.43				
MRSA genotype						
ST5-SCCmecII	1	NA	1	NA	1	NA
ST72-SCCmecIV	0.31 (0.16–0.59)	<0.001	0.26 (0.13–0.54)	<0.001	0.27 (0.13–0.54)	<0.001
ST239-SCCmecIII	0.36 (0.10–1.31)	0.12	0.31 (0.13–1.90)	0.50	0.40 (0.11–1.52)	0.18
agr dysfunction	2.89 (1.57–5.32)	0.001				
Vancomycin MIC by Etest						
≤1.0 mg/L	1	NA				
1.5 mg/L	0.98 (0.57–1.67)	0.93				
≥2.0 mg/L	1.07 (0.57–2.01)	0.83				
hVISA phenotype	1.20 (0.74–1.94)	0.46				

NA, not applicable; NE, not entered.
[a]First multivariate model adjusted all clinical variables that might confound the result of mortality in MRSA bacteraemia.
[b]Second multivariate model adjusted variables in the first model except variables of acute severity of bacteraemia.

still independently associated with the lower mortality compared with ST5-SCCmecII (Table 3). When analysis was repeated after combining ST5-SCCmecII and ST239-SCCmecIII into HA-MRSA strain, this analysis did not modify the results (Table S1, available as Supplementary data at JAC Online).

Bacterial virulence factors

We explored the virulence factor profiles in the three MRSA genotypes (Table 4). Compared with ST5-SCCmecII isolates, ST72-SCCmecIV isolates were less likely to harbour virulence-related genes including hlb (26.6% versus 78.5%; P<0.001), sdrC (39.2% versus 96.0%; P<0.001), sec (3.8% versus 92.7%; P<0.001), sel (20.3% versus 98.4%; P<0.001), seo (96.2% versus 100%; P=0.01) and tst genes (3.8% versus 96.0%; P<0.001). Among the 40 virulence genes, those associated with mortality were the three staphylococcal superantigen genes: sec (OR=2.31; 95% CI=1.36–3.93; P=0.002), sel (OR=2.55; 95% CI=1.38–4.71; P=0.003) and tst (OR=2.76; 95% CI=1.58–4.85; P<0.001) (detailed data are not shown). These three

Table 4. MRSA virulence gene profiles according to isolate genotype

Characteristic	ST5-SCC*mec*II (n=247)	ST72-SCC*mec*IV (n=79)	ST239-SCC*mec*III (n=16)	overall	ST5-SCC*mec*II versus ST72-SCC*mec*IV	ST5-SCC*mec*II versus ST239-SCC*mec*III
Leucocidin genes						
lukDE	247 (100)	77 (97.5)	16 (100)	0.08		
lukM	0 (0)	0 (0)	0 (0)	NA		
lukSF-PV	0 (0)	0 (0)	0 (0)	NA		
Haemolysin genes						
hla	240 (97.2)	77 (97.5)	16 (100)	>0.99		
hlb	194 (78.5)	21 (26.6)	2 (12.5)	<0.001	<0.001	<0.001
hld	232 (93.9)	74 (93.7)	15 (93.8)	>0.99		
hlg	0 (0)	0 (0)	0 (0)	NA		
hlg-2	242 (98.0)	78 (98.7)	16 (100)	>0.99		
Adhesin genes						
bbp	243 (98.4)	76 (96.2)	16 (100)	0.55		
clfA	247 (100.0)	79 (100)	16 (100)	NA		
clfB	247 (100.0)	79 (100)	16 (100)	NA		
cna	0 (0)	0 (0)	0 (0)	NA		
ebps	243 (98.4)	75 (94.9)	15 (93.8)	0.12		
fnbA	247 (100.0)	79 (100)	16 (100)	NA		
fnbB	243 (98.4)	77 (97.5)	16 (100)	0.73		
icaA	247 (100.0)	79 (100)	16 (100)	NA		
map/eap	0 (0)	2 (2.5)	12 (75.0)	<0.001	0.06	<0.001
sdrC	237 (96.0)	31 (39.2)	16 (100.0)	<0.001	<0.001	>0.99
sdrD	237 (96.0)	75 (94.9)	16 (100.0)	0.87		
sdrE	243 (98.4)	74 (93.7)	15 (93.8)	0.04	0.04	0.27
Superantigenic toxin genes						
sea	3 (1.2)	1 (1.3)	15 (93.8)	<0.001	>0.99	<0.001
seb	0 (0)	0 (0)	0 (0)	NA		
sec	229 (92.7)	3 (3.8)	1 (6.3)	<0.001	<0.001	<0.001
sed	0 (0)	0 (0)	0 (0)	NA		
see	0 (0)	0 (0)	0 (0)	NA		
seg	246 (99.6)	77 (97.5)	2 (12.5)	<0.001	0.15	<0.001
seh	0 (0)	0 (0)	0 (0)	NA		
sei	244 (98.8)	75 (94.9)	0 (0)	<0.001	0.06	<0.001
sej	0 (0)	0 (0)	0 (0)	NA		
sek	2 (0.8)	2 (2.5)	14 (87.5)	<0.001	0.25	<0.001
sel	243 (98.4)	16 (20.3)	3 (18.8)	<0.001	<0.001	<0.001
sem	240 (97.2)	78 (98.7)	2 (12.5)	<0.001	0.69	<0.001
sen	244 (98.8)	78 (98.7)	2 (12.5)	<0.001	>0.99	<0.001
seo	247 (100)	76 (96.2)	2 (12.5)	<0.001	0.01	<0.001
sep	13 (5.3)	0 (0)	0 (0)	0.08		
seq	0 (0)	0 (0)	14 (87.5)	<0.001	NA	<0.001
tst	237 (96.0)	3 (3.8)	0 (0)	<0.001	<0.001	<0.001
Other toxin genes						
edin	0 (0)	0 (0)	0 (0)	NA		
eta	0 (0)	0 (0)	0 (0)	NA		
etb	0 (0)	0 (0)	0 (0)	NA		

Data are no. (%) of isolates unless otherwise indicated. NA, not applicable.

staphylococcal superantigen genes were not incorporated into the multivariate analysis because they were assessed to be multicollinear with MRSA strain type.

Discussion

In this prospective cohort study, we strictly controlled for potential confounding factors and identified lower mortality in patients with ST72-SCC*mec*IV compared with patients with ST5-SCC*mec*II. Two previous studies found that USA300 MRSA infections were associated with worse clinical outcomes than non-USA300 MRSA infections.[8,9] However, other studies reported a better outcome in USA300 MRSA infections compared with non-USA300 MRSA infections.[10–13] In studies conducted in Australia,[14] Taiwan[15–17] and South Korea,[3,5] there were no significant differences in outcomes between CA-MRSA and HA-MRSA infection. In contrast, a recent Taiwanese study found a lower risk of treatment failure in patients with CA-MRSA infection compared with HA-MRSA-infected patients.[19]

Reduced vancomycin susceptibility has been associated with a higher mortality rate in MRSA bacteraemia.[29] Notably, in this study, ST72-SCC*mec*IV isolates were more frequently associated with vancomycin MICs $\geq$1.5 mg/L, but were independently associated with lower mortality. Although the reason for this paradoxical finding remains unclear, some authors have related the lower pathogenic activity of vancomycin-resistant strains to impaired growth during the first hours of incubation[30] or to increased cell wall thickness.[31] Our data suggest that strain-specific virulence factors, rather than vancomycin susceptibility, may contribute to the outcome of MRSA bacteraemia.

To identify the intrinsic virulence factors that contribute to differences in strain-dependent mortality, we further explored the virulence factor profiles of our MRSA isolates. In these analyses, we found that three staphylococcal superantigen genes, *sel*, *sec* and *tst*, were associated with higher mortality. Moreover, these genes were less common in ST72-SCC*mec*IV isolates compared with ST5-SCC*mec*II isolates. Staphylococcal superantigens are known to cause immune system dysregulation and toxic shock syndrome.[32] A recent experimental study showed that staphylococcal superantigens also play a critical role in the development and progression of *S. aureus* infection.[33] Therefore, our data suggest that CA-MRSA strains lacking staphylococcal superantigens may be less virulent.

Our study had several limitations. First, this was a large, single-centre study conducted in South Korea and our findings cannot be generalized to other countries with different circulating CA-MRSA strains. Second, because of the potential for multicollinearity, three staphylococcal superantigen genes associated with mortality in univariate analyses could not be included with MRSA strain type in the multivariate analyses. Third, we selected 40 potential virulence factors and evaluated their associations with outcome. Therefore, it is possible that the differences in strain-dependent mortality are a result of other virulence factors that we did not examine.

In summary, after adjustment for potential confounders, CA-MRSA ST72-SCC*mec*IV was independently associated with lower mortality compared with ST5-SCC*mec*II. Our data suggest that strain-specific virulence factors, rather than vancomycin susceptibility, may contribute to the outcome of MRSA bacteraemia.

The lack of staphylococcal superantigen toxin genes might be associated with lower virulence of ST72-SCC*mec*IV. Further genome-wide studies and detailed functional analyses should be performed to clarify the role of virulence factors in the outcome of MRSA bacteraemia.

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Deleo FR, Otto M, Kreiswirth BN *et al*. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet* 2010; **375**: 1557–68.

2 Chuang YY, Huang YC. Molecular epidemiology of community-associated meticillin-resistant *Staphylococcus aureus* in Asia. *Lancet Infect Dis* 2013; **13**: 698–708.

3 Jang HC, Kang SJ, Choi SM *et al*. Difference in *agr* dysfunction and reduced vancomycin susceptibility between MRSA bacteremia involving SCC*mec* types IV/IVa and I–III. *PLoS One* 2012; **7**: e49136.

4 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.

5 Park SH, Park C, Yoo JH *et al*. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* strains as a cause of healthcare-associated bloodstream infections in Korea. *Infect Control Hosp Epidemiol* 2009; **30**: 146–55.

6 Park C, Lee DG, Kim SW *et al*. Predominance of community-associated methicillin-resistant *Staphylococcus aureus* strains carrying staphylococcal chromosome cassette *mec* type IVA in South Korea. *J Clin Microbiol* 2007; **45**: 4021–6.

7 Park KH, Kim ES, Kim HS *et al*. Comparison of the clinical features, bacterial genotypes and outcomes of patients with bacteraemia due to heteroresistant vancomycin-intermediate *Staphylococcus aureus* and vancomycin-susceptible *S. aureus*. *J Antimicrob Chemother* 2012; **67**: 1843–9.

8 Kempker RR, Farley MM, Ladson JL *et al*. Association of methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 genotype with mortality in MRSA bacteremia. *J Infect* 2010; **61**: 372–81.

9 Kreisel KM, Stine OC, Johnson JK *et al*. USA300 methicillin-resistant *Staphylococcus aureus* bacteremia and the risk of severe sepsis: is USA300 methicillin-resistant *Staphylococcus aureus* associated with more severe infections? *Diagn Microbiol Infect Dis* 2011; **70**: 285–90.

10 Lalani T, Federspiel JJ, Boucher HW *et al*. Associations between the genotypes of *Staphylococcus aureus* bloodstream isolates and clinical characteristics and outcomes of bacteremic patients. *J Clin Microbiol* 2008; **46**: 2890–6.

11 Ganga R, Riederer K, Sharma M *et al*. Role of SCC*mec* type in outcome of *Staphylococcus aureus* bacteremia in a single medical center. *J Clin Microbiol* 2009; **47**: 590–5.

12 Hota B, Lyles R, Rim J *et al*. Predictors of clinical virulence in community-onset methicillin-resistant *Staphylococcus aureus* infections: the importance of USA300 and pneumonia. *Clin Infect Dis* 2011; **53**: 757–65.

13 Lessa FC, Mu Y, Ray SM *et al*. Impact of USA300 methicillin-resistant *Staphylococcus aureus* on clinical outcomes of patients with pneumonia or central line-associated bloodstream infections. *Clin Infect Dis* 2012; **55**: 232–41.

14 Robinson JO, Pearson JC, Christiansen KJ *et al*. Community-associated versus healthcare-associated methicillin-resistant *Staphylococcus aureus* bacteraemia: a 10-year retrospective review. *Eur J Clin Microbiol Infect Dis* 2009; **28**: 353–61.

15 Chen SY, Wang JT, Chen TH *et al*. Impact of traditional hospital strain of methicillin-resistant *Staphylococcus aureus* (MRSA) and community strain of MRSA on mortality in patients with community-onset *S. aureus* bacteremia. *Medicine (Baltimore)* 2010; **89**: 285–94.

16 Kuo SC, Chiang MC, Lee WS *et al*. Comparison of microbiological and clinical characteristics based on SCC*mec* typing in patients with community-onset meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia. *Int J Antimicrob Agents* 2012; **39**: 22–6.

17 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.

18 Wu HS, Kuo SC, Chen LY *et al*. Comparison between patients under hemodialysis with community-onset bacteremia caused by community-associated and healthcare-associated methicillin-resistant *Staphylococcus aureus* strains. *J Microbiol Immunol Infect* 2013; **46**: 96–103.

19 Chen SY, Liao CH, Wang JL *et al*. Methicillin-resistant *Staphylococcus aureus* (MRSA) staphylococcal cassette chromosome *mec* genotype effects outcomes of patients with healthcare-associated MRSA bacteremia independently of vancomycin minimum inhibitory concentration. *Clin Infect Dis* 2012; **55**: 1329–37.

20 Wootton M, Howe RA, Hillman R *et al*. A modified population analysis profile (PAP) method to detect hetero-resistance to vancomycin in *Staphylococcus aureus* in a UK hospital. *J Antimicrob Chemother* 2001; **47**: 399–403.

21 Sakoulas G, Eliopoulos GM, Moellering RC Jr *et al*. Accessory gene regulator (*agr*) locus in geographically diverse *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin. *Antimicrob Agents Chemother* 2002; **46**: 1492–502.

22 Oliveira DC, de Lencastre H. Multiplex PCR strategy for rapid identification of structural types and variants of the *mec* element in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2002; **46**: 2155–61.

23 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.

24 Diep BA, Carleton HA, Chang RF *et al*. Roles of 34 virulence genes in the evolution of hospital- and community-associated strains of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 2006; **193**: 1495–503.

25 Peacock SJ, Moore CE, Justice A *et al*. Virulent combinations of adhesin and toxin genes in natural populations of *Staphylococcus aureus*. *Infect Immun* 2002; **70**: 4987–96.

26 Campbell SJ, Deshmukh HS, Nelson CL *et al*. Genotypic characteristics of *Staphylococcus aureus* isolates from a multinational trial of complicated skin and skin structure infections. *J Clin Microbiol* 2008; **46**: 678–84.

27 Klevens RM, Morrison MA, Nadle J *et al*. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007; **298**: 1763–71.

28 Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.

29 van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012; **54**: 755–71.

30 Peleg AY, Monga D, Pillai S *et al*. Reduced susceptibility to vancomycin influences pathogenicity in *Staphylococcus aureus* infection. *J Infect Dis* 2009; **199**: 532–6.

31 Walsh TR, Bolmstrom A, Qwarnstrom A *et al*. Evaluation of current methods for detection of staphylococci with reduced susceptibility to glycopeptides. *J Clin Microbiol* 2001; **39**: 2439–44.

32 McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. *Ann Rev Microbiol* 2001; **55**: 77–104.

33 Salgado-Pabon W, Breshears L, Spaulding AR *et al*. Superantigens are critical for *Staphylococcus aureus* infective endocarditis, sepsis, and acute kidney injury. *MBio* 2013; **4**: e00494–13.