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ORIGINAL ARTICLE

Comparison between patients under hemodialysis with community-onset bacteremia caused by community-associated and healthcare-associated methicillin-resistant *Staphylococcus aureus* strains

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Background/Purpose(s): Patients receiving hemodialysis infected with methicillin-resistant *Staphylococcus aureus* (MRSA) have been considered to have healthcare-associated (HA) infections, but strains with community-associated (CA) characteristics have also been identified in this population. The authors compared infections of the two strains among patients with end-stage renal disease.
Methods: From January 2004 to December 2008 the authors analyzed the demographic and microbiologic data of 57 patients with community-onset (defined as a positive culture obtained $\leq$ 48 hours after admission) MRSA bacteremia and end-stage renal disease at a 2900-bed tertiary medical center. MRSA isolate with staphylococcal cassette chromosome *mec* (SCC*mec*) type II/III was classified as HA strains, and SCC*mec* type IV/V as CA strains.
Results: Forty-seven patients (82%) had HA-MRSA strains and 10 patients (18%) had CA-MRSA strains. The major clones of HA-MRSA were sequence type (ST) 5 with SCC*mec* type II and staphylococcal protein A (*spa*) t002 as well as ST239 carrying SCC*mec* type III and *spa* t037. The CA-MRSA strains were predominantly ST59, more susceptible to non-β-lactam antimicrobial agents, and had a higher percentage of carrying the Panton-Valentine leukocidin gene

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in comparision with the HA-MRSA strains. Patients infected with HA-MRSA isolates had a higher overall mortality (57.4%, $p = 0.012$). In multivariate analysis, male patients were more likely to be infected with HA-MRSA isolates than CA-MRSA strains ($p = 0.037$), and a history of receiving urinary catheterization within 1 year prior to bacteremia onset ($p = 0.047$) is an independent risk factor to acquiring HA-MRSA strains.
Conclusion: Patients undergoing dialysis and infected with HA-MRSA strains had higher mortality rates and were more commonly associated with urinary catheterization within 1 year before bacteremia.

Introduction

After methicillin-resistant *Staphylococcus aureus* (MRSA) was first documented in Taiwan in the early 1980s, its prevalence has greatly increased and become an important nosocomial pathogen.[1,2] According to the definition advocated by the Centers for Disease Control and Prevention (CDC), MRSA infections can be classified as community-associated (CA) if cultured from patients without established risk factors,[3] and otherwise as healthcare-associated (HA). There are many differences between MRSA strains in these two groups, including pulsed-field gel electrophoresis (PFGE) patterns, staphylococcal cassette chromosome *mec* (SCC*mec*) type, susceptibility to non-β-lactam antimicrobial agents, and the presence of a pore-forming toxin, Panton-Valentine leukocidin (PVL).[4] Compared with HA-MRSA infections, CA infections are more likely to involve skin and soft tissues and less likely to involve the respiratory tract, urinary tract, or bloodstream.[5] HA-MRSA infections can be further divided into community- or hospital-onset infections according to the index culture obtained $\leq$ or $>$48 hours after hospital admission.[6]

Patients with end-stage renal disease (ESRD) undergoing dialysis are well known to have high rates of infection or colonization with MRSA,[7,8] and the mortality, length of hospital stay, and healthcare costs are higher among these patients infected with MRSA than those infected with methicillin-susceptible *S. aureus*.[9] The MRSA infections in dialysis-dependent patients were traditionally considered to be HA, typically with strains carrying SCC*mec* types II/III and lacking the gene for the PVL toxin.[7] However, this definition has recently been a matter of debate, because many HA-MRSA infections are caused by strains with the CA-MRSA phenotype and characteristics.[10] Several reports in the literature have demonstrated the increasing percentage of CA-MRSA genotypes among all MRSA isolates recovered from hospital or HA settings.[11–13] Therefore, the association with the healthcare environment has decreasing predictive value for distinguishing patients with infections involving HA-MRSA strains from those with CA-MRSA isolates.[4] Several studies have classified MRSA as HA or CA strains according to the definition of molecular phenotype.[12–14] In this study, we compared the demographic characteristics, clinical manifestations, outcomes, and microbiologic data between infections of CA- and HA-MRSA strains, classified based on SCC*mec* phenotype, in patients with community-onset (CO) MRSA bacteremia who were undergoing hemodialysis.

Materials and methods

Patient selection and data collection

We performed a retrospective study of all adult patients with ESRD and receiving hemodialysis who had blood cultures positive for MRSA within 48 hours after admission at a 2900-bed tertiary medical center in Taiwan from January 2004 to December 2008. The demographic characteristics, HA risk factors, comorbidities, Charlson comorbidity index,[15] empiric antibiotics therapy regimen, infection foci, type of vascular access for hemodialysis, length of hospitalization, and outcomes were reviewed. HA risk factors were defined as follows: hospitalization, surgery, colonization of MRSA, residency in a long-term care facility, and urinary catheterization within 1 year before bacteremia onset. Colonization was considered whenever MRSA was recovered from culture of any specimens in the previous year according to medical record. The probable focus of infection was assessed on the basis of microbiologic and clinical findings. Endovascular lesions included infection involving vessels such as mycotic aneurysm or endocarditis diagnosed according to Duke criteria.[16] Catheter-related bacteremia was defined by a semi-quantitative culture of the vascular catheter tip that yielded more than 15 MRSA colonies in the absence of other sources of bacteremia.[17] Deep-seated infections included empyema or abscess in the deep-seated organ. Antibiotic therapy was deemed appropriate if parenteral therapy to which the organism had documented susceptibility was initiated within the first 48 hours of obtaining the initial positive blood culture result.

Microbiologic and molecular characteristics of isolates

We classified an MRSA isolate as belonging to a CA-MRSA strain if the SCC*mec* type IV or V was present and to a HA-MRSA strain if the SCC*mec* type II or III was present. Identification of MRSA was performed using the Vitek II system (bioMérieux, Marcy l'Etoile, France). The bacteria were then stored at -70°C in trypticase soy broth (Difco Laboratories, Le Pont de Claix, France) supplemented with 15% glycerol before use. Antibiotic susceptibility tests included ciprofloxacin, clindamycin, daptomycin, gentamicin, levofloxacin, linezolid, rifampin, tigecycline, and vancomycin. Minimal inhibitory concentrations (MICs) were determined

by the broth dilution method for daptomycin and agar dilution methods for the other agents according to the Clinical and Laboratory Standards Institute guidelines.[18] The MIC of tigecycline was determined by the agar dilution method as approved by the Food and Drug Administration (Tygacil 2005, tigecycline package insert; Wyeth Pharmaceuticals, Philadelphia, PA, USA). Determination of SCC*mec* type, detection of the genes encoding PVL, and identification of specific accessory gene regulator (*agr*), staphylococcal protein A (*spa*) were performed using techniques described elsewhere.[19–22] Multilocus sequence typing was performed for the selected strains of representative PFGE patterns with 80% relatedness as described previously.[23]

Statistical analysis

Demographic data, risk factors, outcomes, and antibiotic susceptibility test results were compared. Categoric variables were compared using the χ^2 or Fisher exact test, and numeric variables were expressed as the mean ($\pm$ standard deviation) and analyzed by two-sample *t*-test or Mann-Whitney U test. Variables with $p < 0.1$ in the univariate analysis were entered into the multivariate analysis, carried out by logistic regression. All analyses were performed using SPSS software version 17.0 (SPSS, Chicago, IL, USA), and a *p* value of <0.05 was considered significant for two-tailed tests.

Results

From January 1, 2004 through December 1, 2008, 57 adult patients with CO-MRSA bacteremia and ESRD receiving hemodialysis were included in the study. The main demographic characteristics of the cohort are listed in Table 1. Each MRSA isolate was from a unique patient. Of the 57 isolates, 17 (29.8%) were SCC*mec* II, 30 (52.6%) were SCC*mec* III, 6 (10.5%) were SCC*mec* IV, and 4 (7.0%) were SCC*mec* V. The proportion of CA-MRSA isolates increased from 0% in 2003 to 30.8% in 2007, and decreased to 12.5% in 2008. Univariate analysis indicated that there were more male patients infected with HA-MRSA strains than with CA-MRSA strains (51.1% vs. 10%, $p = 0.032$). The patients who had a previous history of surgery within 90 days (68.1% vs. 30%, $p = 0.035$) and of receiving urinary catheterization within 1 year before onset of bacteremia (57.4% vs. 20%, $p = 0.041$) were more likely infected with HA-MRSA strain than with CA-MRSA strain. The other demographics, clinical characteristics, and comorbidities were similar in both groups. In multivariate logistic regression analysis, male sex (odds ratio = 11.57, $p = 0.037$, [95% confidence interval, 1.16–115.39]) and history of receiving urinary catheterization within 1 year before onset of bacteremia (odds ratio = 6.56, $p = 0.047$, [95% confidence interval, 1.03–42.12]) were independent factors associated with HA-MRSA strain infections (Table 2).

For infection foci, catheter-related infections were the most common identified source, followed by pneumonia and skin and soft-tissue infections, with 34, 11, and 7 isolates, respectively; however, there was no statistically significant difference between the two groups (Table 3). The patients infected with HA-MRSA strains had a higher overall mortality (57.4% vs. 10%, $p = 0.012$), despite similar length of hospitalization and mortality within 7 days and 30 days after admission between the two groups (Table 3).

The molecular characteristics of the isolates are presented in Table 4, and the PFGE results of the MRSA isolates containing the four different SCC*mec* types are shown in Fig. 1. The major pulsotypes carrying SCC*mec* type II were ST5, *spa* t002 (65%), and *agr* II (94.1%). The main isolates with SCC*mec* type III were ST 239, *spa* t037 (77%), and *agr* I (100%). The 10 CA-MRSA strains harboring SCC*mec* type IV/V were heterogeneous in *spa* type and were predominantly ST59 and *agr* I (70%). No HA-MRSA isolates carried the *PVL* gene, and three CA-MRSA isolates (30%) carried the *PVL* gene ($p = 0.04$). For antimicrobial susceptibility (Table 5), the HA-MRSA strains were more resistant to clindamycin, ciprofloxacin, gentamicin, and levofloxacin (all $p < 0.05$). Although no significantly different vancomycin-susceptible rate (defined as MIC $\leq$ 1 mg/L) between the two groups ($p = 0.184$) was observed, a higher MIC was found in the HA-MRSA isolates.

Discussion

MRSA infections in dialysis-dependent patients have been considered to be HA according to epidemiologic classification, but recent research has found that MRSA strains harboring SCC*mec* types IV/V, which are predominantly present in CA infections, are also responsible for HA infections or colonization in these patients.[7,8,14,24] In our investigation, an increasing frequency of CA-MRSA strains infections is noted during the study period, similar to the results of other reports.[12–14,24] The acquisition of CA-MRSA strains may have occurred either at home or from healthcare contact, as there is a rising proportion of MRSA infections caused by CA-MRSA strains in the healthcare setting.[7]

The patients in our study infected with CA-MRSA strains were predominantly female (9 of 10, 90%). There were more female patients ($n = 12$, 75%) with ESRD colonized by MRSA carrying SCC*mec* type II in the study by Johnson et al.[7] but no significant difference in sex distribution in the report by Lin et al.[14] Few data are available about the relationship between the presence of MRSA strains with different SCC*mec* types and urinary catheterization within 1 year before MRSA bacteremia, which is a risk factor for acquisition of HA-MRSA strains in our study. In previous research of MRSA infection in critically ill patients,[25] patients receiving urinary catheterization within 7 days prior to acquisition of MRSA were more likely to acquire HA strains than CA strains with an insignificant difference. A recent study by Lin et al.[14] demonstrated that a longer duration of dialysis was an independent factor for infection with CA-MRSA strains. Nevertheless, there was no significant difference in duration of dialysis between the two groups in our study.

Previous studies have revealed infections with CA-MRSA strains are more likely to be skin and soft-tissue infections, osteomyelitis, and joint infections, whereas bloodstream infections are more common among HA-MRSA

Table 1 Demographic and clinical characteristics of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* strains in patients with community-onset bacteremia and end-stage renal disease

Variable, *n* (%)	HA-MRSA	CA-MRSA	*p*
No.	47 (82.5%)	10 (17.5%)	
Age, mean ± SD, years	70.9 ± 13.2	72.6 ± 10.3	0.712
Male	24 (51.1)	1 (10)	0.032
Underlying diseases			
Alcoholism	5 (10.6)	0 (0)	0.574
Cerebrovascular disease	9 (19.1)	2 (20)	>0.999
Congestive heart failure	10 (21.3)	3 (30)	0.680
Coronary artery disease	10 (21.3)	0 (0)	0.182
Chronic obstructive pulmonary disease	10 (21.3)	0 (0)	0.182
Charlson comorbidity index, mean ± SD	5.9 ± 2.6	5.4 ± 3.1	0.578
Diabetes mellitus	30 (63.8)	5 (50)	0.485
Hypertension	31 (66.0)	7 (70)	>0.999
Liver cirrhosis	1 (2.1)	0 (0)	>0.999
Malignancy	10 (21.3)	2 (20)	>0.999
Operation within 90 days before bacteremia	32 (68.1)	3 (30)	0.035
Current smoker	10 (21.3)	0 (0)	0.182
Duration of hemodialysis before bacteremia, months			
Mean ± SD	24.96 ± 33.76	12.19 ± 15.71	0.250
Median (interquartile range)	13 (2.2-3.6)	9 (3.35-12.75)	0.367
Vascular access at the time of admission[a]			
Graft (synthetic conduit)	2 (4.3)	1 (10)	0.446
Tunneled catheter	23 (48.9)	4 (40)	0.734
Fistula (natural vessel)	15 (31.9)	4 (40)	0.717
Temporary catheter	14 (29.8)	2 (20)	0.708
Year of isolation			
2004	10 (100)	0 (0)	
2005	14 (87.5)	2 (12.5)	
2006	7 (70)	3 (30)	
2007	9 (69.2)	4 (30.8)	
2008	7 (87.5)	1 (12.5)	
HA risk factor within 1 year before bacteremia			
Colonization of MRSA[b]	20 (42.6)	1 (10)	0.074
Hospitalization	46 (97.9)	9 (90)	0.323
Residency in a long-term care facility	10 (21.3)	2 (20)	>0.999
Surgery	39 (80.9)	7 (70)	0.424
Urinary catheterization	27 (57.4)	2 (20)	0.041

[a] Numbers may sum to more than 100% because patients could have multiple hemodialysis access sites.
[b] Colonization was considered whenever MRSA was recovered from culture of any specimens in the previous year.
CA = community-associated; HA = healthcare-associated; MRSA = methicillin-resistant *Staphylococcus aureus*; SD = standard deviation.

strains.[3,5,11,26,27] This distribution pattern did not appear in our study, and catheter-related infections were the most common infection focus, probably because our patients all receive dialysis.

In the previous two reports of MRSA infection among dialysis population,[8,14] the groups with CA-MRSA infections and with HA-MRSA infections had similar mortality rates. Nevertheless, the patients with CA-MRSA infections in our investigation had a significant lower overall mortality than those with HA-MRSA infections, despite no significant difference in 7- and 30-day mortality.

In Taiwan, the most prevalent HA-MRSA strains are ST239 carrying SCC*mec* type III, and these account for approximately half of the HA infections.[11,28,29] MRSA ST5 with SCC*mec* type II is an epidemic clone, spreading through Japan, the United States, and Europe, and has demonstrated an increased prevalence in Taiwan.[1,2,11] The two strains were also the predominant clones in our investigation, which was comparable with a previous study.[11] The ST59 strain with SCC*mec* type IV/*PVL*-negative or with SCC*mec* type V/*PVL*-positive is the major CA-MRSA clone in Taiwan and the second most common MRSA clone.[1,14,28,30] This clone primarily causes CA infections in Taiwan, but HA infections have also been reported.[2,29] MRSA ST59 accounted for 10% (6 of 57) of the infections in our investigation, much lower than the rate of 76% reported

Table 2 Results of multivariate logistic regression analyses of factors associated with hospital-associated methicillin-resistant *Staphylococcus aureus* strains in patients with community-onset bacteremia and end-stage renal disease

Variable	Odds ratio	95% confidence interval	*p*
Colonization within 1 year before admission	2.57	0.24–27.10	0.432
Operation within 90 days before admission	2.98	0.53–16.68	0.214
Male	11.57	1.16–115.39	0.037
Urinary catheter within 1 year before admission	6.56	1.03–42.12	0.047

Table 3 Infection foci and outcome for healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* strains in patients with community-onset bacteremia and end-stage renal disease

Variable, *n* (%)	SCC*mec* types		*p*
	HA-MRSA (*n*=47)	CA-MRSA (*n*=10)	
Infection foci[a]			
Primary bacteremia	5 (10.6)	0 (0)	0.574
Skin and soft tissue infection	6 (12.8)	1 (10)	>0.999
Catheter-related infection	26 (55.3)	8 (80)	0.178
Bone and joint infection	2 (4.3)	0 (0)	>0.999
Pneumonia	10 (21.3)	1 (10)	0.668
Infective endocarditis	3 (6.4)	0 (0)	>0.999
Surgical site infection	1 (2.1)	2 (20)	>0.999
Urinary tract infection	1 (2.1)	1(10)	0.323
Deep seated abscess	5 (10.6)	0 (0)	0.574
Appropriate empirical antibiotics	24 (51.1)	6 (60)	0.869
Intravascular catheter/device removal after bacteremia onset	20 (42.6)	5 (50)	0.936
Outcome			
Length of hospital stay, mean ± SD	29.7 ± 30.3	38.4 ± 49.5	0.467
7-day mortality	10 (21.3)	0 (0)	0.182
30-day mortality	19 (40.4)	1 (10)	0.082
Overall mortality	27 (57.4)	1 (10)	0.012

[a] Patients may have more than one focus.
CA = community-associated; HA = healthcare-associated; MRSA = methicillin-resistant *Staphylococcus aureus*; SCC*mec* = staphylococcal cassette chromosome *mec*; SD = standard deviation.

by Huang et al.[29] Different study populations and periods might explain this discrepancy, whereas both reports have revealed the spread of CA-MRSA strains into the hospital setting. In the current study, CA-MRSA strains were more susceptible to non-β-lactam antimicrobial agents, similar to the results of previous reports.[5,8,11] Despite both groups being susceptible to vancomycin, the proportion of the HA-MRSA strains displaying a vancomycin MIC >1 mg/L is slightly higher than that of CA-MRSA clones without a significant difference. It has been reported that CA-MRSA isolates possess lower MICs to vancomycin than HA strains.[11] Although CA-MRSA strains were more susceptible to clindamycin than HA strains with statistical significance, the resistant rates of both strains were high.

Table 4 Molecular typing and virulence genes of methicillin-resistant *Staphylococcus aureus* with different SCC*mec* types

Characteristic	SCC*mec* types			
	II	III	IV	V
No.	17	30	6	4
MLST of major pulsotype	ST5	ST239	ST59	ST59
spa (%)	T002 (65)	t037 (77)	t437(50), t3525(50)	NA[a]
Major *agr* type (%)	agr2 (94.1)	agr1 (100)	agr1 (66)	agr1 (75)
PVL (%)	0 (0)	0 (0)	0 (0)	3 (75)

[a] The *spa* types of the four isolates were different to each other and were t3525, t2755, t441, and t437 respectively.
agr = accessory gene regulator; MLST = multilocus sequence typing; PVL = Panton-Valentine leukocidin; SCC*mec* = staphylococcal cassette chromosome *mec; spa* = staphylococcal protein A.

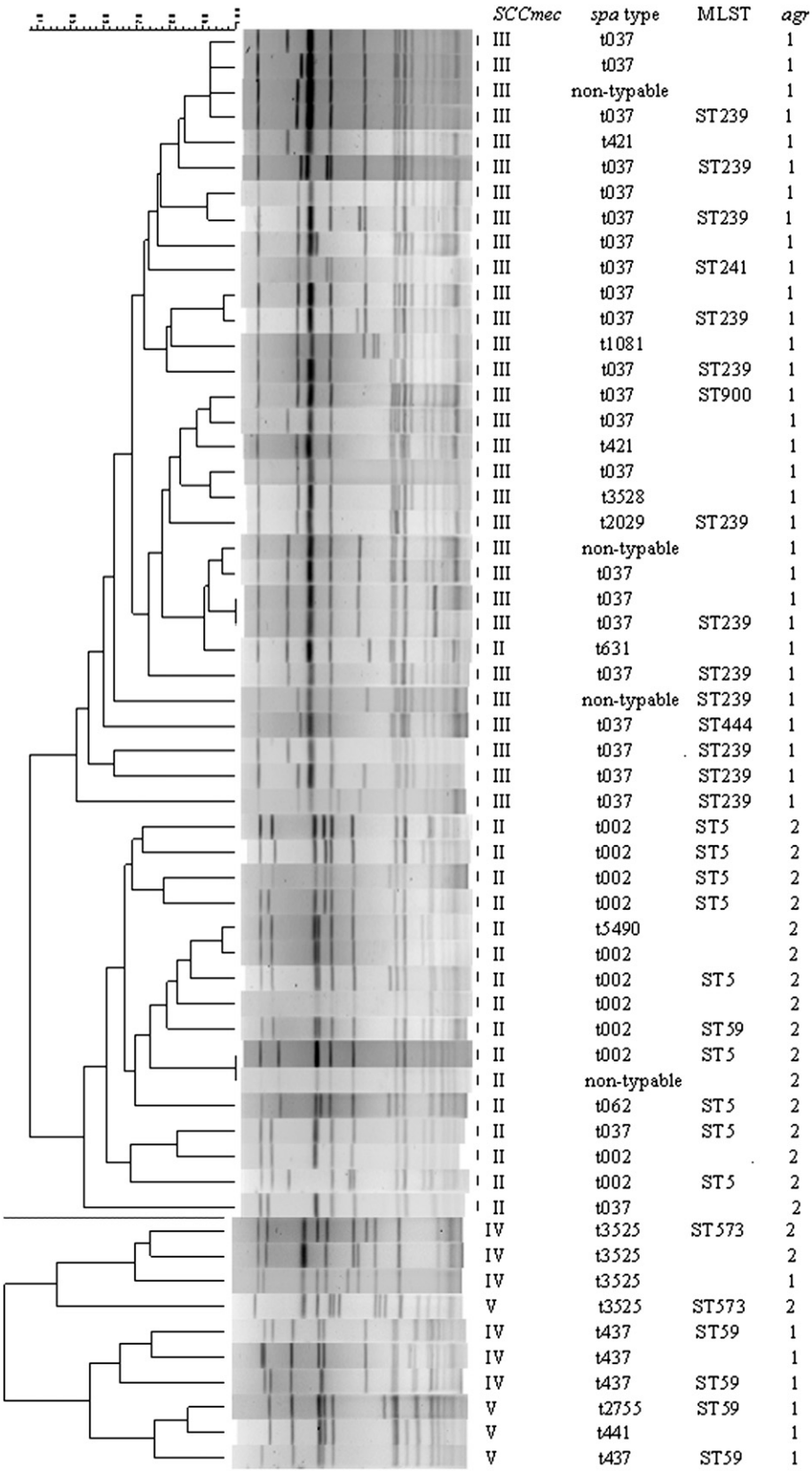

Figure 1. Pulsed-field gel electrophoresis of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* strains. SCCmec = staphylococcal cassette chromosome mec; spa = staphylococcal protein A; MLST = multilocus sequence typing; agr = accessory gene regulator.

Table 5 Antimicrobial susceptibility of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* strains

	HA-MRSA	CA-MRSA	*p*
Antimicrobial susceptible rate (%)			
Ciprofloxacin	0 (0)	10 (100)	<0.01
Clindamycin	1 (2.1)	3 (30)	0.015
Daptomycin	47 (100)	10 (100)	
Gentamicin	1 (2.1)	6 (60)	<0.01
Levofloxacin	0 (0)	10 (100)	<0.01
Linezolid	47 (100)	10 (100)	
Rifampin	45 (95.7)	10 (100)	>0.999
Tigecycline	47 (100)	10 (100)	
Vancomycin	47 (100)	10 (100)	
Vancomycin (MIC $\leq$ 1)	38 (80.9)	10 (100)	0.336

CA = community-associated; HA = healthcare-associated; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*.

Our investigation had certain limitations. First, the study was retrospective, based on chart review, and information bias might have been introduced. Second, the comprehensive medical managements were not recorded in our studies. Thus, the difference in outcome might be influenced by factors other than SCC*mec* phenotype.

With the encroachment of CA-MRSA strains into the healthcare setting, the creation of a category of patients who have CA-strain-related CO-MRSA bacteremia with standard definitions would allow improved categorization of the patients with ESRD in future studies. There were more females infected with MRSA carrying SCC*mec* type IV/V, and MRSA harboring type II/III was found more frequently in patients with previous urinary catheterization, surgery, and associated higher mortality. Further prospective studies with larger samples might be needed to confirm these results.

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The authors declare that they have no conflicts of interest related to the material in this manuscript.

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