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Predominance of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Strains Carrying Staphylococcal Chromosome Cassette *mec* Type IVA in South Korea▽

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Studies on the molecular epidemiologic characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) strains have demonstrated their genetic and geographical diversity. In addition, it has been reported that there are genetic differences between community-associated (CA) and health care-associated (HA) MRSA strains. Therefore, we investigated the major epidemiologic characteristics of CA MRSA isolates in South Korea and compared them with those of HA MRSA strains. Distributions of staphylococcal chromosome cassette *mec* (SCC*mec*) types and other molecular features, including the Panton-Valentine leukocidin (PVL) gene, were studied in 138 invasive MRSA isolates. Multiplex type IVA SCC*mec* was identified as the major CA MRSA infection type (53.1%), with a significantly higher prevalence than in HA MRSA ($P < 0.001$). One major group of type IVA strains carried a larger atypical class B *mec* element and new subtypes of *ccrA2* (96% amino acid homology). The PVL gene was detected in one USA300-like isolate only. Seven major clone types determined by combinational grouping (genetic background SCC*mec* typing) showed representative patterns of antimicrobial susceptibilities. We concluded that less multi-drug-resistant strains of clone types B-I and D-1 (genetic background, B and D complexes; type IVA SCC*mec*) predominate in CA MRSA and that international PVL-positive strains have not spread in South Korea as yet.

Rates of methicillin-resistant *Staphylococcus aureus* (MRSA) infection have continuously increased in both communities and hospitals. The staphylococcal cassette chromosome *mec* element (SCC*mec*) has contributed to this phenomenon as an important epidemiologic factor and also as a determinant of antibiotic resistance patterns (16, 25). In parallel with the identification of various types and subtypes of SCC*mec* (14, 26, 30), a new nomenclature for the SCC*mec* element was proposed (5). In addition to antimicrobial resistance factors, a wide variety of virulent factors are also important for understanding *S. aureus* infection, which varies from mild to severe (2, 20). In particular, Panton-Valentine leukocidin (PVL) is a major concern with respect to MRSA infection, and community-associated MRSA (CA MRSA) has been isolated recently (13, 31, 32). There are some differences in the genetic and epidemiologic backgrounds of CA MRSA and health care-associated MRSA (HA MRSA). Some studies have suggested that the smaller SCC*mec* (type IV or V) and PVL are strongly associated with CA MRSA infection (21, 23, 32). Their features correspond to a non-multi-drug-resistant character, and such infections exhibit toxin-like risk factors, unlike HA MRSA infections. However, it has also been reported that type IV SCC*mec* isolates are rare in South Korea compared with type II and III SCC*mec* strains, which are isolated mainly from HA MRSA infections (4, 18). We noted that the number of SCC*mec* variants has increased recently in South Korea, and thus, we thought that the epidemiology of CA MRSA in South Korea could be different from that in other countries, because typical CA MRSA isolates characterized by PVL and type IV SCC*mec* have been rarely found in South Korea. Initially, we investigated the distribution of SCC*mec* types, genetic variations among invasive isolates, and other molecular epidemiologic characteristics. We then characterized the major epidemiologic features of CA MRSA isolates and compared them with HA MRSA by studying relationships between SCC*mec* diversity and molecular features or antimicrobial susceptibilities.

MATERIALS AND METHODS

Bacterial isolates and definitions. From April 2004 to October 2005, we collected a total of 138 invasive nonduplicate MRSA isolates from patients with bacteremia ($n = 74$) and skin and soft tissue infections ($n = 64$) at a tertiary-care hospital and five community hospitals in four regions of South Korea (two hospitals in Seoul, two in Incheon, one in Gyeongki, and one in Gyeongnam). Most of these isolates were recovered from blood, wounds, or pus. Possible colonizations and contaminants were excluded. Using medical records, CA MRSA was defined as described by Fridkin et al. (9) (CA isolates, $n = 81$; HA, $n = 57$). Briefly, CA MRSA isolates were recovered from a patient who had none of the following established risk factors; isolation of MRSA 48 h or more after hospitalization; a history of hospitalization, surgery, dialysis, or residence in a nursing home within the past year; the presence of a permanent indwelling catheter or percutaneous medical device at the time of culture; previous isolation of MRSA.

SCC*mec* typing and genetic variation studies. We screened SCC*mec* isolates by multiplex PCR, as previously described (26). Single SCC*mec* PCR typing was then performed to further analyze variations in class *mec* complex and J region,

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TABLE 1. PCR primers used for sequencing analysis of class B *mec* element and *ccrA2*

Target	Primer	Sequence (5′→3′)	Location (nt)[a]	Reference
IS*1272*-*mecA*	IS5	AACGCCACTCATAACATATGGAA	11882–11904	23
	mA6	TATACCAAACCCGACAAC	13860–13877	17
mecA	mAnew1	TGGAATTAACGTGGAGACGA	13569–13588	This study
	mAnew2	AACGTTGTAACCACCCCAAG	15127–15146	This study
mecA-IS*431mec*	mA1	TGCTATCCACCCTCAAACAGG	14861–14881	11
	IS2	TGAGGTTATTCAGATATTTCGATGT	18911–18935	17
ccrA2	ccrA2-F	GGATAGGCCCTTCAGGAGTT	5785–5804	This study
	ccrA2-R	TGTGCTTTGCATTTCTGTTGA	7476–7496	This study

[a] Locus of AB245470.

as previously described (12, 23). SCC*mec* type was assigned using multiplex type nomenclature and the nomenclature recently proposed by Chongtrakool et al. (5). Atypical elements of the class B *mec* complex and of the *ccrA2* gene were sequenced with the primers listed in Table 1 in order to analyze genetic variations. Sequences homologous with class B *mec* complex and in the new *ccrA2* gene subtype were searched for with BLAST (BLASTP version 2.2.16; http://www.ncbi.nlm.nih.gov/BLAST).

MLST, *spa* and other molecular characterizations. Multilocus sequence typing (MLST) was performed as previously described (7). Alleles of each locus were compared, and sequence types (STs) were assigned based on the *S. aureus* MLST database (http://saureus.mlst.net/).

The typing of the polymorphic region of the protein A gene (*spa*) was performed as previously described (1, 29). The product was amplified using spa-1113f (5′-TAAAGACGATCCTTCGGTGAGC-3′) and spa-1514r primers (5′-CAGCAGTAGTGCCGTTTGCTT-3′), as previously described (1). Purified *spa* PCR products were sequenced, and short sequence repeats (SSRs) were assigned using the *spa* database web site (http://www.ridom.de/spaserver). The *spa* complex was defined by visual analysis whereby *spa* types with similar SSRs were clustered into the complexes previously described by Ruppitsch et al. (28).

The accessory gene regulator locus (*agr*) gene was amplified, and *agr* group was determined by DraI restriction fragment length polymorphism analysis, as previously described (27). The PVL, *hlg*, *hlg-2*, and *lukE-lukD* genes were detected, as previously described (15). *nuc* PCR was performed as the control for validation purposes, as previously described (3).

Antimicrobial susceptibilities. Antimicrobial susceptibilities were determined using the disc diffusion method, as recommended by the CLSI (6). BBL Sensi-Discs (Becton Dickinson, Sparks, MD) of arbekacin, ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin, penicillin, rifampin, tetracycline, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin were used. Multidrug resistance was defined as resistance to three or more classes of antimicrobials. *S. aureus* ATCC 29213 was used as a control strain.

Clone type definitions based on molecular characteristics and antimicrobial susceptibilities. MRSA isolates were clustered into representative groups based on genetic background as previously described by Oliveira et al. (24, 25), with some modifications. Briefly, genetic backgrounds were determined by MLST profile with one or two allelic variants corresponding to the *spa* complex. Based on genetic backgrounds, clone types were redefined according to SCC*mec* type and antimicrobial susceptibilities.

Statistical analysis. Comparisons were made using the χ^2 test or Fisher's exact test in Sigma Stat version 3.10 (Systat Software, San Jose, CA). All hypotheses were two-tailed and were considered significant at the $P < 0.05$ level.

Nucleotide sequence accession numbers. Nucleotide sequences determined during the present study were submitted to GenBank (http://www.ncbi.nlm.nih.gov/GenBank) under accession numbers EF584543 and EF596937.

TABLE 2. Genetic diversities of SCC*mec* types classified by multiplex and single PCR

SCC*mec* multiplex type[1]	Amplified locus or loci[a]	MLST sequence type(s) (*n*)	Proposed SCC*mec* type[b]	*mec* class[c]	*ccr* type[c]	J region[d]	No. of isolates (%)
II	B, C, D, G	ST5	II.1.1	A	2		9 (6.5)
II variant	B, C, D	ST5 (25), $ST5_{SLV}$ (1)	II.1.2	A	2	Does not carry pUB110	26 (18.9)
II NT1	C, D, G	ST89 (4), ST5 (1)	ND[e]	A	2	Does not carry *kdp* operon	5 (3.6)
II NT2	C, D	ST5	ND	A	2	Does not carry *kdp* and pUB110	5 (3.6)
III	C, E, F, H	ST239	III.1	A	3		13 (9.4)
IIIA	C, E, F	ST239	III.1.2	A	3	Does not carry pT181	12 (8.7)
III NT1	C, H	ST239	ND	A	3	Does not carry RIF	2 (1.5)
IV	D	ST8 (1), ST1 (2)	IV.1	B	2	IVA (1), IVC (2)	3 (2.2)
IV NT1	D, F	ST254	ND	B	2	Carries RIF5	1 (0.7)
IVA	D, G	ST72	IV.N.2	(B)[f]	(2)[g]	IVC, carries pUB110	32 (23.2)
		ST1 (19),[h] ST493 (1),[h] ST573 (1)[h]	ND	B	2	IVC, carries pUB110	21 (15.2)
		ST89	ND	(A)[i]	2	ND	3 (2.2)
NT	None amplified	ST188, ST72, ST1, ST89, ST30, ST239	ND	ND	ND	ND	6 (4.3)

[a] Multiplex PCR results described by Oliveira and de Lencastre (26).
[b] Proposed SCC*mec* type described by Chongtrakool et al. (5).
[c] Single PCR results described by Okuma et al. (23).
[d] Subtyping of J region was performed as described by Hisata et al. (12); other characteristics were determined from multiplex PCR results.
[e] ND, not determined.
[f] The increased size of class B *mec* was due to the presence of IS*1272-tnp20-*Δ*mecR1-mecA*-IS*431* (GenBank no. EF596937).
[g] *ccrA2* (GenBank no. EF584543) shared 96% homology with other *ccrA2* genes.
[h] Belongs to CC1 (ST1, 1-1-1-1-1-1-1; ST493, 62-1-1-1-1-1-1; ST573, 1-1-1-1-12-1-1).
[i] Class A *mec* complex variant, Δ*mecI-mecR1-mecA*.

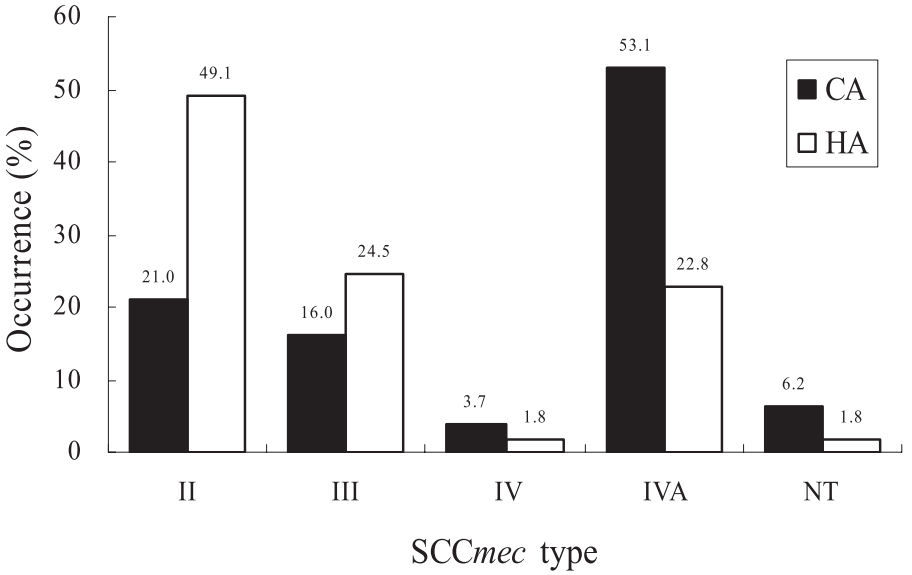

FIG. 1. Distribution of SCC*mec* types in invasive CA and HA MRSA isolates. Each type includes variants.

RESULTS

Genetic diversities of SCC*mec* types from CA and HA MRSA isolates. Screening by SCC*mec* multiplex- and single-PCR typing resulted in the typing of 132 of the 138 (95.7%) isolates; the remaining 6 (4.3%) could not be typed (Table 2). Multiplex type II (including variants) accounted for 32.6% (45/138), III for 19.6% (27/138), IV for 3.8% (4/138), and IVA for 40.6% (56/138). Investigations of the distribution of each SCC*mec* type in CA and HA MRSA showed that multiplex type IVA was significantly prevalent in CA MRSA ($P < 0.001$) (Fig. 1). On the other hand, type II was more prevalent in HA MRSA ($P < 0.001$) (Fig. 1). Also, the occurrence of type III was a little higher in HA than in CA MRSA, although the difference was statistically insignificant ($P = 0.276$) (Fig. 1).

Diverse genetic variants or subtypes were observed within each multiplex type (Table 2). In particular, multiplex type IVA was subdivided into two major groups and one minor group carrying a class A *mec* complex variant (Δ*mecI-mecR1-mecA*) (Table 2). The class B *mec* complex of the first group was different from that of type IV due to increased size of the element and new subtypes of *ccrA2* (GenBank no. EF584543; 96% homology), while the other major group carried typical class B *mec* and *ccrA2* (Table 2). Atypical class B *mec* was composed of IS*1272-tnp20* (pfam02371)-Δ*mecR1-mecA*-IS*431* (GenBank no. EF596937).

MLST, *spa* complex, and other molecular epidemiologic factors. MLST analysis showed that some STs (ST1, -5, -72, and -239) were prevalent in MRSA infections and also that there should be an epidemiological relationship among STs, SCC*mec* types, and *spa* types (Tables 2 and 3). A total 22 of *spa* types were analyzed in 137 of the 138 MRSA isolates, and 5 of them (t2457 to t2461) were assigned as new types in the *spa* database (http://www.ridom.de/spaserver). The *spa* gene of isolate ST254 (SSR profile, 3-32-1-1-4-4-3) could not be amplified by PCR.

Visual analysis of the SSR profile was used to group *spa* types with similar repeat profiles into five *spa* complexes with two singletons (Table 3). *spa* class A (type II SCC*mec* including variants, *agr* group II) and C (type III and IIIA SCC*mec*, *agr* group I) complexes were associated mainly with HA MRSA infection, and their major STs were, respectively, ST5 and ST239 (Table 3). CA MRSA strains were strongly associated with *spa* class B and D complexes, which mainly exhibited ST72 and CC1 (ST1, ST493, and ST573) (Table 3). ST72 isolates exhibited type IVA SCC*mec* (IV.N.2) and *agr* group I, and isolates of the *spa* class D complex were associated with SCC*mec* type IVA with typical class B *mec* complexes and *agr* group III. Isolates of the *spa* class E complex (ST89) were infrequently found in CA MRSA infections (type II; NT1 and IVA SCC*mec* carrying a class A *mec* variant). The PVL gene was detected in only one USA300-like strain exhibiting ST8, *spa* t008, type IVA SCC*mec*, and *agr* group I. Most strains carried *hlg-2*, except for isolates of the *spa* class E complex and an ST30 isolate, which carried *hlg* (Table 3).

Clone types of MRSA isolates by molecular characteristics and antimicrobial susceptibilities. All isolates showed resistance against oxacillin, penicillin, and tobramycin but no resistance against vancomycin. Antimicrobial resistance patterns were dependent mainly on genetic background and SCC*mec* type. Thus, we could group 131 of the 138 isolates into clone types, which are expected to represent antimicrobial susceptibility patterns (Table 4) In the same *spa* complex, isolates with three more allelic variants in the MLST profile were considered to have a different genetic background and were classified as singletons (ST580, 3-35-48-19-20-26-39, compared to ST239 in the *spa* class C complex). Also, a single isolate with no *spa* type (ST254 isolate) and six with nonamplified SCC*mec* were excluded from the analysis. Isolates with genetic background A were divided into two clone types (A-I and A-II), and these exhibited different antimicrobial susceptibilities, especially with respect to tetracycline ($P < 0.001$) (Table 4). Isolates with

TABLE 3. The *spa* complex of MRSA isolates as determined by visual analysis

MLST sequence type	*spa* complex (*n*)[a]	*spa* type	SSR profile	No. of Isolates	Other characteristics	Genetic background[b] (*n*)[a]
ST5 (1-4-1-4-12-1-10)[c]	*spa* class A (41)	t002	26-23-17-34-17-20-17-12-17-16	15	CA (13/81, 16.0%)	A (41)
		t601	26-23-17-34-34-17-20-17-12-17-16	13	HA (28/57, 49.1%)	
		t2458[d]	26-16-34-34-17-20-17-12-17-16	8	*agr* group II, *hlg-2*	
		t2460[d]	26-17-34-34-17-20-17-17-17-16	3		
		t010	26-17-34-17-20-17-12-17-16	1		
		t306	26-23-17-34-17-20-17-12-17-17-16	1		
ST72 (1-4-1-8-4-4-3)	*spa* class B (33)	t324	07-23-12-12-17-20-17-12-12-17	25	CA (22, 27.2%),	B (33)
		t664	07-23-12-12-17-20-17-12-17	4	HA (11, 19.3%)	
		t148	07-23-12-21-12-17-20-17-12-12-17	2	*agr* group I, *hlg-2*	
		t901	07-23-12-17-20-17-12-12-17	1		
		t2461[d]	07-23-12-12-12-17-20-17-12-12-17	1		
ST239 (2-3-1-1-4-4-3)	*spa* class C (29)	t037	15-12-16-02-25-17-24	27	CA (15, 18.5%)	C (27)[e]
ST580 (3-35-48-19-20-26-39)		t021	15-12-16-02-16-02-25-17-24	1	HA (14, 24.6%)	
ST30 (2-2-2-2-6-3-2)		t138	08-16-02-25-17-24	1	*hlg*-2, *agr* group I (1)	
ST1 (1-1-1-1-1-1-1)	*spa* class D (24)	t286	07-23-13-34-16-34-33-13	21	CA (22, 27.2%)	D (24)
ST493 (62-1-1-1-1-1-1)		t1533	07-23-13-13-16-34-33-13	1	HA (2, 3.5%)	
ST573 (1-1-1-1-12-1-1)		t2457[d]	07-23-13-34-34-16-34-33-13	1	*agr* group III, *hlg-2*	
		t2459[d]	07-23-34-34-16-34-33-13	1		
ST89 (1-26-28-18-18-33-50)	*spa* class E (8)	t375	49-13-23-05-17-34-33-34	7	CA (8, 9.9%)	E (8)
		t1728	49-20-13-23-05-17-34-33-34	1	*agr* group III, *hlg*	
ST8 (3-3-1-1-4-4-3)	Singleton	t008	11-19-12-21-17-34-24-34-22-25	1	ST8 (PVL, *agr* group I)	
ST188 (3-1-1-8-1-1-1)	Singleton	t189	07-23-12-21-17-34	1	ST188 (*agr* group I)	

[a] Defined by visual analysis as described by Ruppitsch et al. (28); 137 of 138 isolates were analyzed, as 1 HA isolate was not amplified by *spa* PCR.
[b] Determined by MLST profile with one or two allelic variants corresponding to the *spa* complex.
[c] Includes the ST5 single locus variant.
[d] Newly reported in this study.
[e] ST580 and ST30 were excluded because of an MLST profile with three or more allelic variants.

genetic background C were also subgrouped into two clone types (C-I and C-II), and there were some differences in antimicrobial susceptibility patterns between them, especially with respect to trimethoprim-sulfamethoxazole ($P < 0.001$) (Table 4). Major CA MRSA isolates (clone types B-I, D-I, and E-I) were less multi-drug resistant than HA MRSA isolates (A-I, II, C-I, and II). Isolates of clone type B-I were much less resistant than those of clone type D-I, especially against erythromycin ($P = 0.0014$), gentamicin ($P < 0.001$), and tetracycline ($P < 0.001$).

DISCUSSION

It has been reported that ST5 and ST239 strains predominate in HA MRSA infections in South Korea (4, 18). However, few reports on the molecular characteristics of CA MRSA strains in South Korea have been issued. Thus, we tried to characterize CA MRSA strains in South Korea and compare them with HA MRSA strains. Oliveira et al. (25) have described the characterization of MRSA pandemic clones, in which major clones were classified according to genetic back-

TABLE 4. Antibiotic susceptibilities of major MRSA clone types according to genetic background and SCC*mec* type[a]

Clone type	Genetic background	SCC*mec* type	% of isolates resistant to[b]:								No. of CA isolates/total isolates
			GEN	ABK	CIP	CLI	ERY	TET	RIF	SXT	
A-I	A (ST5-*spa* A)	II, II NT1, or II NT2	86.7	0	100	66.7	100	100	0	6.7	6/15
A-II	A	II variant	100	0	100	100	100	19.2	0	0	7/26
B-I	B (ST72, *spa* B)	IVA (IV.N.2)	3.1	0	0	3.1	50.0	0	0	0	21/32
C-I	C (ST239, *spa* C)	III or III NT1	100	0	100	73.3	100	100	0	100	7/15
C-II	C	IIIA	100	18.2	81.8	90.9	100	81.8	18.2	0	5/11
D-I	D (CC1, *spa* D)	IVA or IV (IVC)	100	0	0	0	91.3	56.5	0	0	21/23
E-I	E (ST89, *spa* E)	IVA minor or II NT1	85.7	0	0	71.4	100	0	0	0	7/7
Minor 1	USA300-like (ST8, *spa* t008)	IVA	0	0	0	0	100	0	0	0	1/1
Minor 2	ST580, *spa* C	IIIA	0	0	0	0	100	0	0	0	1/1

[a] In the same *spa* complex, the isolate with three more allelic variants of MLST profile was considered to carry another genetic background and was classified as a singleton (ST580, 3-35-48-19-20-26-39, compared to ST239 in the *spa* C complex). Isolates with no *spa* type (ST254 isolate) or nonamplified SCC*mec* ($n = 6$; CA $n = 5$) were excluded from the analysis.

[b] All isolates showed resistance against oxacillin, tobramycin, and penicillin, but no isolate showed resistance against vancomycin. Abbreviations: ABK, arbekacin; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; GEN, gentamicin; RIF, rifampin; TET, tetracycline; SXT, trimethoprim-sulfamethoxazole; and VAN, vancomycin.

ground and SCC*mec* type as an evolutionary marker (25). As *spa* types were very diverse in isolates of the same ST, we needed to group them into complexes which could represent the diversity as well as common motifs. *spa* complexes as well as MLST STs were meaningful for analyzing genetic backgrounds and relationships among isolates. In addition, as it could be difficult to define SCC*mec* types by previous nomenclature (12, 23, 26) due to increasing numbers of variants, we classified our results according to a new nomenclature which is able to represent the variants of each types. Along with genetic background, this nomenclature was very helpful for classifying isolates into clone types corresponding to antibiotic susceptibility as well as molecular epidemiological features of the isolates (Table 4).

In our study, the ST5 strains (clone types A-I and A-II) seemed to belong to the NY/Japan clone, and the ST239 strains (clone types C-I and C-II) seemed to be consistent, respectively, with Hungarian (type III SCC*mec*) and Brazilian (type IIIA SCC*mec*) clones, although there were some variants (Table 4) (25). This suggested that HA MRSA clones in South Korea were consistent with a pandemic clone.

While HA MRSA clones in South Korea are expected to have some features in common with pandemic HA clones, genetic features of major CA MRSA strains in South Korea may be unique compared with those of clones that have spread internationally. In particular, type IVA SCC*mec* is common in South Korea, whereas type IV is not (Fig. 1; Table 2). Moreover, the genetic background of CA MRSA strains in the present study was mainly associated with clone types B-I, D-I, and E-I, which may differ from prevalent CA MRSA strains in other countries (Table 4). Multiplex type IVA SCC*mec* was firstly mentioned by Oliveira and de Lencastre (26), and Shore et al. (30) reported that multiplex type IVA SCC*mec* carried the class A *mec* complex with some variants (30). However, our study showed that the upstream vicinity of type IVA of major groups could have been derived from type IVC and that it carries the class B *mec* complex, except for a minor group (*spa* E-type IVA) carrying a class A *mec* complex variant (Table 2). Chongtrakool et al. (5) proposed that type IVA be described as IV.N.2 (5). But we found three subtypes in type IVA SCC*mec*, and each subtype was found to represent a different antimicrobial susceptibility pattern (clone types B-I, D-I, and E-I).

It was interesting to find that representative HA MRSA strains have been spread in CA infections and CA MRSA strains have also been detected in HA infections (Tables 3 and 4). We do not know what epidemiologic factors have contributed to this spread, but these findings emphasize the need for continuous monitoring.

PVL-positive CA MRSA strains have recently spread globally (8, 10, 31, 32). However, no PVL-positive strain had been isolated from humans in South Korea, although it had been isolated from bovine milk (type IVG SCC*mec*, ST5) (19). In the present study, we detected just one PVL-positive isolate, which seemed to be a USA300-like strain exhibiting PVL, t008, ST8, and SCC*mec* IVA (22). This strain was recovered from a patient that had recently returned from Hawaii and subsequently developed an invasive MRSA infection.

In summary, we concluded that non-multi-drug-resistant strains of clone types B-I and D-I predominate in CA MRSA in South Korea. Moreover, the prevalence of type IVA SCC*mec* among CA MRSA strains contrasted with its prevalence in strains found in other countries. In addition, the international PVL-positive CA MRSA clone has not been frequently found in South Korea. Future studies are required to determine other factors that might contribute to the high occurrence of invasive MRSA infection in South Korea.

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