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균혈증을 동반한 황색포도알균 폐렴의 미생물학적, 임상적 특성

Microbiological and clinical characteristics of

***Staphylococcus aureus* bacteremic pneumonia**

울산대학교 대학원

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Microbiological and clinical characteristics of *Staphylococcus aureus* bacteremic pneumonia

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ABSTRACT

Background: There have been limited efforts to evaluate the clinical, microbiological characteristics, and outcomes in patients with *Staphylococcus aureus* (*S. aureus*) bacteremic pneumonia (SABP), despite its high mortality.

Methods: A total of 164 patients with SABP from August 2008 to December 2020 at a tertiary hospital in South Korea were reviewed. Detailed clinical and microbiological data including genotyping for sequence type (ST), Staphylococcus protein A (*spa*), staphylococcal cassette chromosome *mec* (SCC*mec*), and virulence genes were evaluated. I compared the characteristics and outcomes of major ST versus other STs in methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteremic pneumonia, and analyzed the risk factors for 30-day mortality.

Results: I found that ST8 MRSA and ST6 MSSA were significantly more prevalent in SABP, compared to *S. aureus* bacteremia (SAB) with other primary sources ($P<0.001$ and $P=0.035$, respectively). The 30-day mortality was significantly higher in both MRSA (31.6%, $P<0.001$) and MSSA bacteremic pneumonia (30.3%, $P<0.001$) compared to SAB with other primary sources. ST5-SCC*mec* IIb-t2460 was the most predominant clone (25/98, 25.5%) in MRSA bacteremic pneumonia, and ST5 MRSA that frequently harbored virulence genes such as *sdrC*, *sec*, *sel*, and *tst*, was significant predictor for 30-day mortality in the multivariate analysis (adjusted OR [aOR], 5.479; 95% confidence interval [CI], 1.440–20.852; $P=0.013$). ST72-t126 was the most predominant clone (9/66, 13.6%) in MSSA bacteremic pneumonia, while no strain-specific clinical and microbiological characteristics were observed, compared to non-ST72 MSSA.

Conclusions: This study demonstrates the microbiological characteristics of SABP which provides a better understanding of clinical characteristics and outcomes of SABP, and active infection control strategy to prevent healthcare-associated SABP should be considered.

Keywords: *Staphylococcus aureus*, bacteremic pneumonia, sequence type, virulence genes, mortality

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INTRODUCTION

Staphylococcus aureus (*S. aureus*) is one of the most notorious pathogens that causes both community-acquired and nosocomial infections, such as osteomyelitis, arthritis, endocarditis, pneumonia, and bloodstream infections [1]. *S. aureus* is relatively common causative pathogen of community-acquired pneumonia (CAP) and nosocomial pneumonia, which accounts for 2.0–20.1% and 11.4–19.7% of cases, respectively [2–6].

The frequency of bacteremia in *S. aureus* pneumonia has been reported with the range of 12.2–26.9% [7–9], which indicates that bacteremic *S. aureus* pneumonia is relatively uncommon. Previous studies revealed that bacteremia on *S. aureus* pneumonia is associated with increased mortality and hospital length of stay [9,10], and the high related mortality rate of 46.9–84% in patients with *S. aureus* bacteremic pneumonia (SABP) has been reported [11–14].

While *S. aureus* pneumonia can be developed both via the airway and hematogenous spread, staphylococcal adherence and invasion to respiratory epithelium that leads to pneumonia from colonization has been well-recognized [15]. Although the mechanism and pathogenesis of SABP may differ from *S. aureus* bacteremia (SAB) with other primary source, little is known about microbiological characteristics including genotypes and virulence factors associated with SABP. In addition, there have been limited efforts to evaluate the clinical, microbiological characteristics, and outcomes in patients with SABP, simultaneously. Several recent studies evaluated the microbiological characteristics of *S. aureus* pneumonia, such as clonality and virulence genes, using *S. aureus* isolates from sputum specimen instead of blood [16,17]. One recent study with *S. aureus* blood isolates over 15 years suggested an associated between *S. aureus* genotype and the source of infections including endocarditis, skin and soft tissue infection, catheter-related bacteremia, osteoarticular infection, while no cases of SABP were evaluated [18].

Therefore, this study aims to investigate the clinical and microbiological characteristics of SABP, according to place of acquisition and methicillin resistance. In addition, risk factors associated with poor outcome were also evaluated, which can lead to active strategies for diagnosis and management given the high mortality of SABP.

METHODS

Study design and population

This study was conducted at Asan Medical Center, a 2700-bed tertiary care hospital in Seoul, South Korea. Adult patients (≥ 16 years of age) with SAB were prospectively enrolled and followed up in accordance with this study protocol over a period of 15 years (August 2008 and December 2020). In Asan Medical Center, routine infectious diseases consultation was conducted in patients with SAB with recommendations of follow-up blood cultures at 2-4 days interval until negative conversion. Clinical information, including demographics, the presence of metastatic infection, was reviewed for all patients with SAB a week after the first episode of SAB. The sources of primary infection in SAB other than SABP were categorized as catheter-related bloodstream infection (CRBSI), skin & soft tissue infection (SSTI), infective endocarditis (IE), bone & joint infection (BJI), arteriovenous fistula graft infection, surgical site infection, peripheral venous catheter-related infection, urinary tract infection, unknown primary bacteremia, and others.

Of the patients with SAB, those who had pneumonia as a primary site of infection, SABP, were analyzed in this study. SABP was considered when patients (1) had symptoms of lower respiratory tract infection, (2) imaging findings of pulmonary infiltrates, (3) isolation of *S. aureus* in blood culture with any other potential primary source of bacteremia, (4) mandatory isolation of *S. aureus* in respiratory specimens.

Data collection and definitions

The data obtained from all patients included demographics, presence of pre-existing underlying diseases or conditions, severity of the underlying diseases by the Charlson comorbidity score [19], mode of acquisition [20], the presence of indwelled device, sepsis severity, management, antibiotic therapy, and clinical outcomes. The system of McCabe and

Jackson was used to classify prognosis of the underlying disease; rapidly fatal (expected death within several months), ultimately fatal (expected death within 4 years), and nonfatal (life expectancy was > 4 years) [21]. The severity of bacteremia was identified based on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Pitt bacteremia score [22]. The presence of metastatic infection was defined as the newly developed infection in a new sterile site that was not clinically relevant at the time of the first blood culture and not identified at the initial diagnosis of SAB. Outcomes, including all-cause 30-day and 90-day mortality, SAB-related mortality, recurrence, were assessed during the 90 days after the first episode of SAB. Recurrence was defined as symptoms and signs of infection more than 7 days after clinical improvement with negative conversion of SAB. SAB-related mortality was defined as death occurring before the resolution of symptoms or signs within 7 days of SAB onset without other explanation.

Collection of *S. aureus* isolates

The *S. aureus* samples were plated on a blood agar plate. This sterile medium was streaked with a cotton swab and the plates were incubated overnight at 37℃. The isolate was grown to screen for and analyze *S. aureus.* The strains were stored in 20% glycerol-tryptic soy broth at −80℃ (Becton Dickinson, Sparks, MD). The methicillin resistance of *S. aureus* isolates was determined based on the oxacillin minimal inhibitory concentration (MIC) and the presence of the *mecA* gene.

Microbiological data and analysis

The antimicrobial susceptibility was determined using the standard criteria based on the MicroScan (Beckman Coulter, Brea, CA, USA) and the Clinical and Laboratory Standard Institute (CLSI) guidelines [23]. Vancomycin MIC was determined with the broth microdilution (BMD) according to the CLSI guideline and the Etest (AB Biodisk, Solna,

Sweden) according to the manufacturer's instructions. The heterogeneous vancomycin-intermediate *S. aureus* (hVISA) was detected using population analysis profiling of all methicillin-resistant *S. aureus* (MRSA) [24]. If the ratio of the area under the viable count-vancomycin curve (AUC) of *S. aureus* isolate versus that of the reference strain (Mu3; ATCC700698) was ≥ 0.9, the isolate was identified as hVISA.

The delta-haemolysin activity was used to determine *agr* functionality by cross-streaking vertically to RN4220 and a test strain on a sheep blood agar plate (BAP). The beta-hemolysin produced by RN4220 enables detection of delta-hemolysin [25]. Delta-hemolytic activity was indicated by an enhanced area of hemolysis at the intersection of the streaks. Multilocus sequence typing (MLST) of the isolates was conducted by amplifying internal fragments of seven housekeeping genes of *S. aureus* as described previously [26]. The staphylococcal cassette chromosome *mec* (SCC*mec*) typing of MRSA isolates was performed using the multiplex polymerase chain reaction (PCR) method of Oliveira and de Lencastre [27]. The eight loci (A through H) and specific pairs of primers for SCC*mec* types and subtypes I, II, III and IV as described previously [28]. A multiplex PCR was performed to detect the presence of virulence genes and *agr* subgroups I–IV [29–32], and Staphylococcus protein A (spa) variable repeat region from each MRSA and MSSA isolate was amplified using simplex PCR oligonucleotide primers as described previously [27,33]. The purified spa PCR products were sequenced, and the typing of *spa* was performed using the public *spa* database website (http://spa.ridom.de/) for all *S. aureus* isolates.

Statistical analysis

All statistical analyses were performed using SPSS software, version 29 (IBM, Armonk, New York, USA). Student t test or the Mann-Whitney U test was used to compare differences between continuous variables, and the Pearson chi-square test or Fisher's exact test was used for the corresponding categorical variables, as appropriate. The variables with

P values < 0.10 in the univariate analysis were included in a multivariate logistic regression model to identify independent predictors for 30-day mortality of MRSA or methicillin-susceptible (MSSA) bacteremic pneumonia. Multicollinearity was considered to decide the variables. A two-tailed *P* value of less than 0.05 was considered statistically significant.

RESULTS

Molecular characteristics and outcomes of *S. aureus* bacteremic pneumonia

During the study period, a total of 1951 patients with *S. aureus* bacteremia (987 MRSA bacteremia and 964 MSSA bacteremia) were observed, and 164 patients with SABP were included and analyzed. Of the 164 patients, 98 had MRSA bacteremic pneumonia and 66 had MSSA bacteremic pneumonia.

Comparisons of the molecular characteristics and outcomes of SABP and SAB with other primary sources of infection are shown in Table 1 and Table 2. In MRSA bacteremic pneumonia (n = 98), sequence type 8 (ST8) was significantly more common in SABP (P<0.001) than in MRSA bacteremia with other primary sources of infection (n = 889). Between the two groups, there were no significant differences in rates of hVISA, *agr* dysfunction, and virulence factors, except that Panton-Valentine leucocidin (PVL) production associated with *lukSF-PV* gene was significantly more common in SABP (P<0.001). In MSSA bacteremia pneumonia (n = 66), ST6 was significantly more common in SABP (P=0.035) than in MSSA bacteremia with other primary sources of infection (n = 898). However, there were no significant differences in vancomycin MIC, prevalence of *agr* dysfunction, and *agr* types.

In the longitudinal change of MLST alleles and ST proportion in MRSA bacteremia (n = 987) and MRSA bacteremic pneumonia (n = 98) over the study period, ST5 showed a decreasing trend and ST72 showed an increasing trend (Figure 1). In MSSA bacteremia (n = 964) and MSSA bacteremic pneumonia (n = 66), ST188 showed a decreasing trend and ST72 showed an increasing trend (Figure 2).

The 30-day in MRSA and MSSA bacteremic pneumonia were 31.6% (31/98) and 30.3% (20/66), respectively, which were significantly higher than SAB with other primary sources of infection (P<0.001) (Table 1 and Table 2).

Table 1. Molecular characteristics and outcomes of MRSA bacteremic pneumonia (n = 98) and other primary source of infection (n = 889)[a]

Characteristic	SABP (n = 98)	Other source of infection (n = 889)	*P* value
ST[b]			
ST5	55 (56.1)	503 (56.6)	0.931
ST8	7 (7.1)	16 (1.8)	**<0.001**
ST72	30 (30.6)	298 (33.5)	0.562
ST188	0 (0)	7 (0.8)	>0.999
ST239	2 (2.0)	25 (2.8)	>0.999
Vancomycin MIC (mg/L) by Etest[c]			
0.5	1 (1.0)	10 (1.1)	>0.999
0.75	3 (3.1)	50 (5.6)	0.353
1	27 (27.6)	209 (23.5)	0.373
1.5	43 (43.9)	429 (48.3)	0.410
2	20 (20.4)	163 (18.3)	0.616
3	3 (3.1)	14 (1.6)	0.234
MIC > 1.5	24 (24.5)	177 (19.9)	0.285
Vancomycin MIC (mg/L) by BMD[c]			
0.5	2 (2.0)	16 (1.8)	0.697
0.75	37 (37.8)	298 (33.5)	0.401
1	36 (36.7)	371 (41.7)	0.340
1.25	10 (10.2)	138 (15.5)	0.162
1.5	7 (7.1)	45 (5.1)	0.381
1.75	4 (4.1)	10 (1.1)	**0.042**
2	2 (2.0)	9 (1.0)	0.300

MIC > 1.5	6 (6.1)	20 (2.2)	**0.023**
hVISA[d]	19/80 (23.8)	160/740 (21.6)	0.662
***agr* dysfunction**	61 (62.2)	542 (61.0)	0.806
***agr* type**			
I	43 (43.9)	366 (41.2)	0.606
II	55 (56.1)	488 (54.9)	0.816
III	0 (0)	16 (1.8)	0.392
IV	0 (0)	1 (0.1)	>0.999
SCC*mec*			
I	2 (2.0)	10 (1.1)	0.338
II	55 (56.1)	514 (57.8)	0.747
III	2 (2.0)	25 (2.8)	>0.999
IV	39 (39.8)	321 (36.1)	0.472
Virulence genes[e]			
Adhesin genes			
sdrC	39/41 (95.1)	370/436 (84.9)	0.099
map_eap	4/41 (9.8)	25/436 (5.7)	0.299
Toxin genes			
sea	3/41 (7.3)	24/436 (5.5)	0.497
sec	29/41 (70.7)	268/436 (61.5)	0.242
seg	36/41 (87.8)	403/436 (92.4)	0.296
sei	38/41 (92.7)	397/436 (91.1)	>0.999
sek	3/41 (7.3)	33/436 (7.6)	>0.999
sel	35/41 (85.4)	330/436 (75.7)	0.162
sem	37/41 (90.2)	404/436 (92.7)	0.536
sen	37/41 (90.2)	404/436 (92.7)	0.536

seo	36/38 (94.7)	337/365 (92.3)	>0.999
sep	4/38 (10.5)	13/364 (3.6)	0.066
tst	28/38 (73.7)	241/365 (66.0)	0.340
lukSF-PV	8/48 (16.7)	10/461 (2.2)	**<0.001**
Hemolysin genes			
hlb	30/41 (73.2)	349/436 (80.0)	0.298
hld	36/38 (94.7)	339/365 (92.9)	>0.999
Metastatic infection	4 (4.1)	170 (19.1)	**<0.001**
30-day mortality	31 (31.6)	137 (15.4)	**<0.001**
90-day mortality	41 (41.8)	245 (27.6)	**0.003**
90-day recurrence	5 (5.1)	64 (7.2)	0.440

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

MRSA, methicillin-resistant *Staphylococcus aureus*; SABP, *Staphylococcus aureus* bacteremic pneumonia; ST, sequence type; MIC, minimal inhibitory concentration; BMD, broth microdilution; hVISA, heteroresistant vancomycin-intermediate *Staphylococcus aureus*; SCC*mec*, staphylococcal cassette chromosome *mec*; *agr*, accessory gene regulator.

[a]This analysis included a total of 987 MRSA bacteremia with different primary sites of infection, including SABP (98), catheter-related bloodstream infection (CRBSI) (327), infective endocarditis (IE) (27), skin & soft tissue infection (SSTI) (60), bone & joint infection (BJI) (71), unknown primary bacteremia (139), and others (29 arteriovenous fistula graft infection, 70 surgical site infection, 37 peripheral venous catheter related, 14 urinary tract infection, and 115 other sites of infection).

[b]The major clones are shown. There were 42 isolates with STs not frequently detected, including ST89 (6), ST254 (6), ST509 (4), ST30 (3), ST1 (3), ST59 (2), and others.

[c]Etest and BMD to determine vancomycin MIC was used in 973 and 986 patients, respectively.

[d]Population analysing profiling (PAP) was performed in 820 MRSA isolates.

[e]MRSA isolates with performed gene tests were analyzed (41 SABP, 212 CRBSI, 9 IE, 23 SSTI, 28

BJI, 60 unknown primary bacteremia). 477 isolates (*sdrC, sea, sec, seg, sei, sek, sel, sem, sen, hlb*) and 403 isolates (*seo, tst, hld*) were analyzed. Genes found in > 95% or < 5% of the tested isolates were excluded in analysis; *fnbA* (100%, 403/403), *fnbB* (98.3%, 396/403), *bbp* (95.4%, 455/477), *ebps* (96.6%, 461/477), *sdrD* (100%, 477/477), *sdrE* (96.0%, 458/477), *clfA* (100%, 477/477), *clfB* (100%, 477/477), *can* (0.6%, 3/477), *icaA* (100%, 477/477), *seb* (100%, 477/477), *sed* (100%, 403/403), *see* (100%, 477/477), *seh* (100%, 403/403), *sej* (100%, 476/476), *sep* (4.2%, 17/402), *seq* (4.5%, 18/403), *eta* (0.4%, 2/477), *etb* (0.2%, 1/477), *lukD* and *E* (100%, 477/477), *hla* (99.6%, 475/477), *edin* (0.4%, 2/477).

Table 2. Molecular characteristics and outcomes of MSSA bacteremic pneumonia (n = 66) and other primary source of infection (n = 898)[a]

Characteristic	SABP (n = 66)	Other source of infection (n = 898)	*P* value
CC (ST)[b]			
CC1	11 (16.7)	195 (21.7)	0.334
ST1	3 (4.5)	59 (6.6)	0.793
ST188	8 (12.1)	137 (15.3)	0.506
CC5	11 (16.7)	95 (10.6)	0.127
ST5	3 (4.5)	44 (4.9)	>0.99
ST6	8 (12.1)	51 (5.7)	**0.035**
CC7 (ST7)	0 (0)	16 (1.8)	0.619
CC8	15 (22.7)	228 (25.4)	0.631
ST8	1 (1.5)	36 (4.0)	0.507
ST72	14 (21.2)	167 (18.6)	0.600
ST630	0 (0)	25 (2.8)	0.408
CC15 (ST15)	8 (12.1)	71 (7.9)	0.228
CC30 (ST30)	3 (4.5)	78 (8.7)	0.356
CC45 (ST45)	2 (3.0)	6 (0.7)	0.099
CC59 (ST59)	3 (4.5)	15 (1.7)	0.120
CC97 (ST97)	4 (6.1)	24 (2.7)	0.118
CC121 (ST121)	1 (1.5)	20 (2.2)	>0.99
CC398 (ST291)	0 (0)	15 (1.7)	0.617
Vancomycin MIC (mg/L) by Etest[c]			
0.5	0 (0)	28 (3.1)	0.252
0.75	6 (9.1)	122 (13.6)	0.299

1	25 (37.9)	329 (36.6)	0.840
1.5	29 (43.9)	343 (38.2)	0.355
2	4 (6.1)	52 (5.8)	0.789
Vancomycin MIC (mg/L) by BMD[c]			
0.5	0 (0)	26 (2.9)	0.250
0.75	50 (75.8)	649 (72.3)	0.668
1	15 (22.7)	206 (22.9)	0.968
1.25	1 (1.5)	12 (1.3)	0.605
1.5	0 (0)	5 (0.6)	>0.99
***agr* dysfunction**	18 (27.3)	282 (31.9)	0.435
***agr* type**			
I	44 (66.7)	603 (67.1)	0.936
II	13 (19.7)	119 (13.3)	0.142
III	4 (6.1)	125 (13.9)	0.089
IV	0 (0)	17 (1.9)	0.623
Metastatic infection	1 (1.5)	172 (19.2)	**<0.001**
30-day mortality	20 (30.3)	113 (12.6)	**<0.001**
90-day mortality	29 (43.9)	203 (22.6)	**<0.001**
90-day recurrence	0 (0)	28 (3.1)	0.252

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

MSSA, methicillin-susceptible *Staphylococcus aureus*; CC, cloncal complex.

[a]This analysis included a total of 964 MSSA bacteremia with different primary sources, including SABP (66), CRBSI (161), IE (48), SSTI (123), BJI (116), unknown primary bacteremia (185), and others (30 arteriovenous fistula graft infection, 1 central nervous system infection, 37 surgical site infection, 84 peripheral venous catheter related, 13 urinary tract infection, and 100 other sites of infection).

[b]The major clones are shown. There were 116 isolates with STs not frequently detected, including ST101 (14), ST96 (6), ST580 (5), ST586 (5), and others.

[c]Etest and BMD to determine vancomycin MIC was used in 939 and 964 patients, respectively.

Figure 1. Longitudinal change of multilocus sequence typing ST proportion in MRSA bacteremia (n = 987) and MRSA bacteremic pneumonia (n = 98) over the study period (2008-2020)

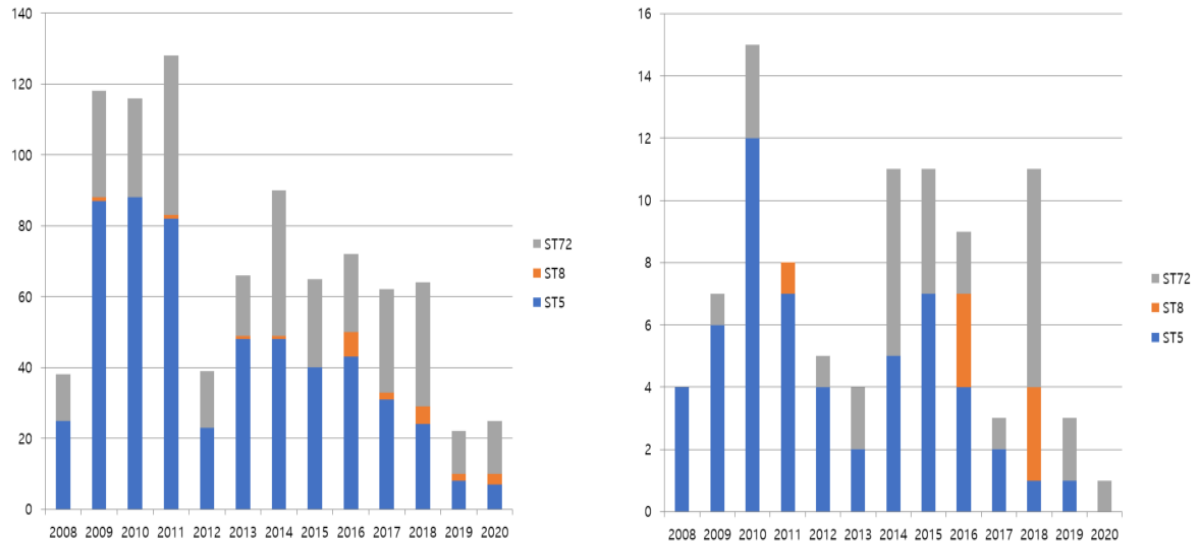
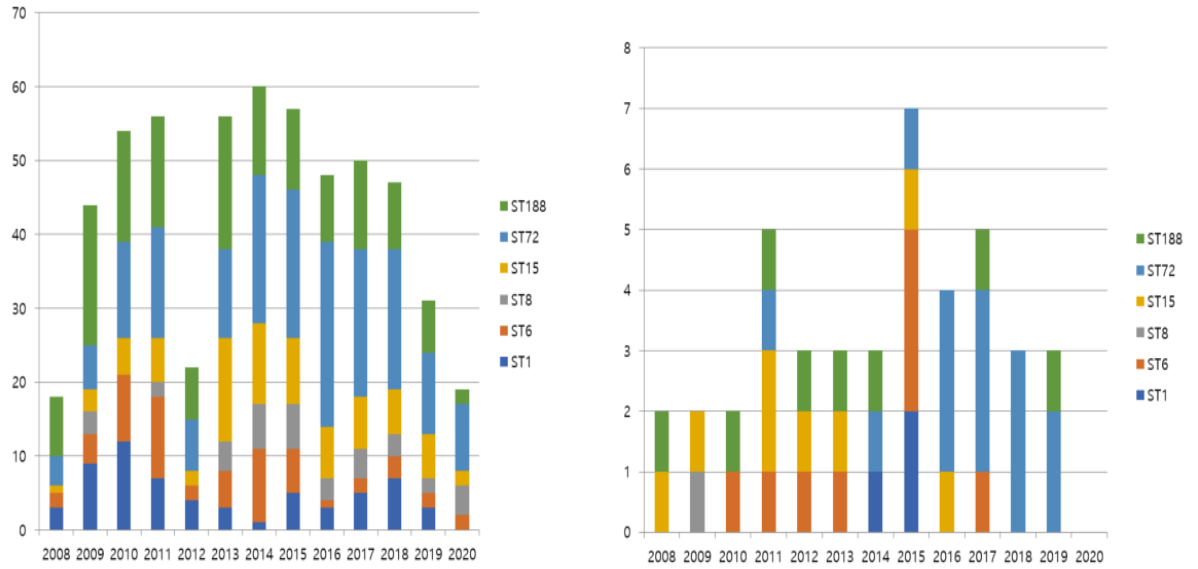


Figure 2. Longitudinal change of multilocus sequence typing ST proportion in MSSA bacteremia (n = 964) and MSSA bacteremic pneumonia (n = 66) over the study period (2008-2020)



Molecular characteristics of MRSA and MSSA isolates

According to place of acquisition, there were 5 and 93 MRSA isolates from CAP and healthcare-associated pneumonia (HCAP)/hospital-acquired pneumonia (HAP), respectively (Table 3). As shown in Table 3, ST5 was the most common MRSA clone (55/98, 56.1%) followed by ST72 (30/98, 30.6%), and the most common genotype was ST5-SCC*mec* typeIIb-*agr* typeII-t2460 followed by ST72-SCC*mec* typeIVa-*agr* type I-t324. *agr* type II and I correlated with ST5 (54/55) and ST72 (30/30), respectively. There were 6 isolates of PVL-positive ST8-SCC*mec* typeIV-t008 (2 in CAP and 4 in HCAP/HAP), which indicates USA300 or its genetically related ST8 genotype.

In table 4, the high genetic diversity between isolates was identified in 66 MSSA isolates, which included 17 distinct STs. ST72 was the most common clone (14/66, 21.2%), which accounted 17.4% (4/23) and 23.6% (10/43) in CAP and HCAP/HAP, respectively. *Spa* type t126 was most common in ST72 (9/14, 64.3%). ST188-t189 (6 isolates), ST15-t084 (4 isolates), and ST6-t304 (2 isolates) were found relatively common.

Table 3. Molecular characteristics of MRSA bloodstream isolates in SABP (n = 98) according to place of acquisition

	CAP (n = 5)					HCAP/HAP (n = 93)				
MLST	**n**	***spa* type (n)**	**SCC*mec* type (n)**	***agr* type (n)**	**PVL (+) /tested**	**n**	***spa* type (n)**	**SCC*mec* type (n)**	***agr* type (n)**	**PVL (+) /tested**
ST5	1	t002 (1)	IIb (1)	II (1)	0/0	54	t2460 (25), t9353 (8), t002 (7), t463 (3), t264 (2), t9363 (1), t148 (1), t688 (1), t535 (1), t439 (1), t769 (1), t17573 (1), t324 (1), unknwon (1)	IIb (50), II (4)	II (53), I (1)	0/32
ST72	1	unknown (1)	IVa (1)	I (1)	0/0	29	t324 (13), t664 (4), t148 (2), t2431 (2), t664 (1), t8578 (1), t9602 (1), t15957 (1), unknown (4)	IVa (25), IV (4)	I (29)	0/5

ST8	2	t008 (2)	IV (2)	I (2)	2/2	5	t008 (4), t211 (1)	IV (4), Ic (1)	I (5)	5/5
ST239	0					2	t037 (1), t148 (1)	IIIa (2)	I (2)	0/2
ST97	0					1	t121 (1)	IV (1)	1 (1)	0/0
ST254	1	T664 (1)	I (1)	I (1)	1/1	0				
Unknown	0					2	t002 (1), t586 (1)	IV (2)	I (1), II (1)	0/1

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; MLST, multilocus sequence typing; ST, sequence type; spa, staphylococcus protein A; PVL, Panton-Valentine leucocidin; SCC*mec*, staphylococcal cassette chromosome *mec*; *agr*, accessory gene regulator.

Table 4. Molecular characteristics of MSSA bloodstream isolates in SABP (n = 66) according to place of acquisition

	CAP (n = 23)			HCAP/HAP (n = 43)		
MLST	**n**	***spa* type (n)**	***agr* type (n)**	**n**	***spa* type (n)**	***agr* type (n)**
ST72	4	t126 (3), t967 (1)	I (4)	10	t126 (6), t18240 (1), t2703 (1), t012 (1), unknown (1)	I (9), unknown (1)
ST188	3	t189 (2), t11978 (1)	I (2), unknown (1)	5	t189 (4), t002 (1)	I (4), unknown (1)
ST15	3	t084 (1), t085 (1), unknown (1)	II (3)	5	t084 (3), t7200 (1), unknown (1)	II (4), I (1)
ST6	5	t304 (1), t701 (1), t008 (1), t091 (1), t18173 (1)	I (5)	3	t304 (1), t4298 (1), unknown (1)	I (3)
ST97	1	t1200 (1)	I (1)	3	t359 (1), t2802 (1), t12229 (1)	I (3)
ST5	0			3	t002 (1), t179 (1). t062 (t)	II (3)
ST1	1	t12303 (1)	III (1)	2	t127 (1), t189 (1)	II (1), III (1)
ST30	1	t8185 (1)	III (1)	2	t338 (1), t127 (1)	III (1), Unknown (1)
ST59	2	t1151 (1), unknown (1)	I (2)	1	t3093 (1)	I (1)
ST45	1	t1460 (1)	I (1)	1	t11967 (1)	I (1)

ST513	1	t164 (1)	I (1)	1	t164 (1)	I (1)
ST199	1	t774 (1)	II (1)	0		
ST8	0			1	t008 (1)	I (1)
ST96	0			1	t164 (1)	Unknown (1)
ST101	0			1	t2078 (1)	I (1)
ST121	0			1	t012 (1)	Unknown (1)
ST2990	0			1	t091 (1)	II (1)
Unknown	0			2	t571 (1), unknown (1)	I (2)

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; MLST, multilocus sequence typing; ST, sequence type; spa, staphylococcus protein A; *agr*, accessory gene regulator.

Characteristics and outcomes of MRSA and MSSA bacteremic pneumonia

In table 5, I compared the characteristics and outcomes of MRSA ST5 versus ST72 and non-ST5 in SABP patients. Previous colonization (*P*<0.001) and nosocomial acquisition (*P*<0.001) were more common in ST5 MRSA bacteremic pneumonia was more common. Other factors associated with hospital exposure were more common in ST5 than in ST72 and non-ST5, such as central venous catheter (*P*=0.030 and *P*=0.004), previous antibiotic exposure (*P*<0.001 and *P*<0.001), and previous glycopeptide exposure (*P*<0.001 and *P*<0.001). Bacteremia without sepsis was less common in ST5 than in ST72 (*P*=0.022), and Pitt bacteremia score was significantly higher in ST5 than in ST72 (*P*<0.001) accompanied with more frequent intensive care unit treatment (*P*<0.001) and mechanical ventilation (*P*<0.001). The hVISA phenotype and *agr* dysfunction were significantly more prevalent in ST5 compared with ST72 (*P*=0.007 and *P*<0.001) and non-ST5 (*P*= 0.025 and *P*<0.001). The distribution of virulence genes was different according to the clonality. *sdrC* (*P*=0.016), *sec* (*P*<0.001), *sel* (*P*=0.005), and tst (*P*<0.001) were significantly more common in ST5 than in ST72, while map/eap (*P*=0.002), sek (*P*=0.011), and *lukSF-PV* (*P*<0.001) were less common in ST5 than in non-ST5. The 30-day mortality and 90-day mortality were significantly higher in ST5 than in non-ST5 (*P*= 0.044 and *P*= 0.004, respectively).

In the multivariate analysis for 30-day mortality in MRSA bacteremic pneumonia, ST5 was the independent risk factor (adjusted OR [aOR], 5.479; 95% confidence interval [CI], 1.440–20.852; *P*=0.013). In addition, in multivariate analysis, independent risk factors for 30-day mortality in MRSA bacteremic pneumonia included rapidly or ultimately fatal disease in McCabe and Jackson criteria (aOR, 5.348; 95% CI, 1.485–19.258; *P*=0.010) and severe sepsis or septic shock (aOR, 3.640; 95% CI, 1.049–12.629; *P*=0.042), days to negative conversion of blood culture (aOR, 1.458; 95% CI, 1.027–2.071; *P*=0.035), while vancomycin therapy (aOR, 0.027; 95% CI, 0.080–0.938; *P*=0.039) was protective against 30-day mortality (Table 6).

Table 5. Comparison of characteristics and outcomes of MRSA ST5 versus ST72 and non-ST5 in SABP patients (n = 98)

Characteristic	ST5 (n = 55)	ST72 (n = 30)	non-ST5 (n = 43)	*P* value[a]	*P* value[b]
Age (years), median (IQR)	67.0 (58.0–73.0)	71.5 (59.8–78.0)	68.0 (60.0–77.0)	0.161	0.309
Male	38 (69.1)	21 (70.0)	31 (72.1)	0.931	0.747
Previous colonization of MRSA	29 (52.7)	4 (13.3)	8 (18.6)	**<0.001**	<0.001
Mode of acquisition					
Nosocomial	48 (87.3)	14 (46.7)	20 (46.5)	**<0.001**	**<0.001**
Healthcare-associated	6 (10.9)	15 (50.0)	19 (44.2)	**<0.001**	**<0.001**
Community-acquired	1 (1.8)	1 (3.3)	4 (9.3)	>0.999	0.165
Charlson comorbidity index, median (IQR)	3.0 (1.0–5.0)	3.0 (2.0–4.0)	2.0 (1.0–6.0)	0.345	0.553
McCabe and Jackson criteria					
Rapidly or ultimately fatal disease	26 (47.3)	19 (63.3)	22 (51.2)	0.156	0.702
Underlying disease/condition					
Solid cancer	19 (34.5)	17 (56.7)	20 (46.5)	**0.049**	0.230
Hematologic malignancy	3 (5.5)	4 (13.3)	4 (9.3)	0.237	0.696
Diabetes mellitus	14 (25.5)	11 (36.7)	17 (39.5)	0.278	0.137

End-stage renal disease	1 (1.8)	0 (0)	1 (2.3)	>0.999	>0.999
Liver cirrhosis	6 (10.9)	2 (6.7)	2 (4.7)	0.707	0.460
Solid organ transplantation	5 (9.1)	1 (3.3)	1 (2.3)	0.417	0.226
Hematopoietic cell transplantation	2 (3.6)	1 (3.3)	1 (2.3)	>0.999	>0.999
Chronic lung disease	3 (5.5)	3 (10.0)	4 (9.3)	0.661	0.696
Rheumatologic disease	3 (5.5)	2 (6.7)	2 (4.7)	>0.999	>0.999
Ischemic heart disease	10 (18.2)	2 (6.7)	4 (9.3)	0.200	0.256
Heart failure	4 (7.3)	1 (3.3)	3 (7.0)	0.652	>0.999
Neutropenia	1 (1.8)	3 (10.0)	3 (7.0)	0.124	0.316
Recent surgery[c]	13 (23.6)	3 (10.0)	5 (11.6)	0.155	0.128
Chemotherapy[c]	1 (1.8)	14 (46.7)	15 (34.9)	**<0.001**	**<0.001**
Immunosuppressive therapy[c]	32 (58.2)	13 (43.3)	15 (34.9)	0.190	**0.022**
Indwelling device					
Central venous catheter	30 (54.5)	9 (30.0)	11 (25.6)	**0.030**	**0.004**
Pacemaker or defibrillator	3 (5.5)	0 (0)	0 (0)	0.549	0.254
Prosthetic valve	2 (3.6)	2 (6.7)	2 (4.7)	0.611	>0.999
Orthopedic device	1 (1.8)	0 (0)	1 (2.3)	>0.999	>0.999

Sepsis grade					
No sepsis	4 (7.3)	8 (26.7)	8 (18.6)	**0.022**	0.122
Sepsis	28 (50.9)	11 (36.7)	18 (41.9)	0.208	0.373
Severe sepsis	9 (16.4)	7 (23.3)	11 (25.6)	0.432	0.261
Septic shock	14 (25.5)	4 (13.3)	6 (14.0)	0.269	0.161
Pitt bacteremia score, median (IQR)	3.0 (0–5.0)	0 (0–2.0)	0 (0–2.0)	**<0.001**	**<0.001**
APACHE II score, median (IQR)	20.0 (15.0–29.0)	17.5 (14.0–22.0)	18.0 (14.0–22.0)	0.060	0.066
Management					
First blood culture follow up interval, median days (IQR)	3.0 (2.0–3.3)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.554	0.340
Days to negative conversion, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.623	0.750
Intensive care unit treatment	30 (54.5)	4 (13.3)	6 (14.0)	**<0.001**	**<0.001**
Mechanical ventilation	26 (47.3)	3 (10.0)	4 (9.3)	**<0.001**	**<0.001**
Antibiotic therapy					
Previous antibiotic exposure[c]	47 (85.5)	14 (46.7)	19 (44.2)	**<0.001**	**<0.001**
Previous glycopeptide exposure[c]	25 (45.5)	2 (6.7)	4 (9.3)	**<0.001**	**<0.001**
Days to appropriate antibiotic therapy, median (IQR)	0 (0–1.0)	0 (0–1.0)	0 (0–0)	0.346	0.159
Vancomycin therapy	36 (65.5)	22 (73.3)	31 (72.1)	0.456	0.483

Vancomycin TDM[d]	34 (61.8)	22 (73.3)	30 (69.8)	0.285	0.412
Trough concentration, median mg/L (IQR)	16.1 (7.7–20.1)	11.2 (8.5–16.9)	11.1 (7.7–15.2)	0.306	0.105
Microbiological characteristics					
Vancomycin MIC (mg/L) by Etest					
0.5	3 (5.5)	0 (0)	0 (0)	0.549	0.254
0.75	2 (3.6)	0 (0)	1 (2.3)	0.538	>0.999
1	14 (25.5)	7 (23.3)	14 (32.6)	0.828	0.440
1.5	24 (43.6)	20 (66.7)	23 (53.5)	**0.042**	0.333
2	12 (21.8)	2 (6.7)	3 (7.0)	0.124	0.051
3	0 (0)	1 (3.3)	2 (4.7)	0.353	0.190
Vancomycin MIC (mg/L) by BMD					
0.5	2 (3.6)	0 (0)	0 (0)	0.538	0.502
0.75	21 (38.2)	10 (33.3)	17 (39.5)	0.657	0.891
1	19 (34.5)	18 (60.0)	23 (53.5)	**0.024**	0.060
1.25	5 (9.1)	1 (3.3)	1 (2.3)	0.417	0.226
1.5	8 (14.5)	0 (0)	1 (2.3)	**0.046**	0.073
2	0 (0)	1 (3.3)	1 (2.3)	**0.353**	0.439

hVISA[e]	15 (28.8)	0 (0)	2 (7.1)	**0.007**	**0.025**
***agr* dysfunction**	54 (98.2)	4 (13.3)	7 (16.3)	**<0.001**	**<0.001**
***agr* type**					
I	2 (3.6)	30 (100.0)	42 (97.7)	**<0.001**	**<0.001**
II	53 (96.4)	0 (0)	1 (2.3)	**<0.001**	**<0.001**
SCC*mec* type					
I	0 (0)	0 (0)	2 (4.7)	NA	0.190
II	55 (100)	0 (0)	0 (0)	**<0.001**	**<0.001**
III	0 (0)	0 (0)	2 (4.7)	NA	0.190
IV	0 (0)	30 (100)	39 (90.7)	**<0.001**	**<0.001**
Virulence genes[f]					
Adhesin genes					
sdrC	31/31 (100)	3/5 (60.0)	8/10 (80.0)	**0.016**	0.055
map/eap	0/31 (0)	0/5 (20)	4/10 (40.0)	NA	**0.002**
cna	0/31 (0)	0/5 (20)	2/10 (20.0)	NA	0.055
Toxin genes					
sea	0/31 (0)	0/5 (0)	3/10 (30.0)	NA	**0.011**

sec	29/31 (93.5)	0/5 (0)	0/10 (0)	**<0.001**	**<0.001**
sel	30/31 (96.8)	2/5 (40.0)	5/10 (50.0)	**0.005**	**0.002**
seg	30/31 (96.8)	0/5 (0)	6/10 (60.0)	NA	**0.009**
sei	31/31 (100)	0/5 (0)	7/10 (70.0)	NA	**0.011**
sek	0/31 (0)	0/5 (0)	3/10 (30.0)	NA	**0.011**
sem	30/31 (96.8)	0/5 (0)	7/10 (70.0)	NA	**0.039**
sen	30/31 (96.8)	0/5 (0)	7/10 (70.0)	NA	**0.039**
seo	29/29 (100)	0/5 (0)	7/9 (77.8)	NA	0.051
sep	4/29 (13.8)	0/5 (0)	0/9 (0)	>0.999	0.554
seq	0/29 (0)	0/5 (0)	2/9 (22.2)	NA	0.051
tst	27/29 (93.1)	0/5 (0)	1/9 (11.1)	**<0.001**	**<0.001**
Leucodicin genes					
lukSF-PV	0/32 (0)	0/5 (0)	8/16 (50.0)	NA	**<0.001**
Hemolysin genes					
hlb	25/31 (80.6)	3/5 (60.0)	5/10 (50.0)	0.305	0.057
hld	28/29 (96.6)	4/5 (80.0)	8/9 (88.9)	0.276	0.422
Metastatic infection	3 (5.5)	0 (0)	1 (2.3)	0.549	0.629

30-day mortality	22 (40.0)	9 (30.0)	9 (20.9)	0.360	**0.044**
90-day mortality	30 (54.5)	11 (36.7)	11 (25.6)	0.115	**0.004**
SAB-related mortality	16 (29.1)	9 (30.0)	9 (20.9)	0.930	0.358
90-day recurrence	4 (7.3)	1 (3.3)	1 (2.3)	0.652	0.381

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

MRSA, methicillin-resistant *Staphylococcus aureus*; SABP, *Staphylococcus aureus* bacteremic pneumonia; IQR, interquartile range; ST, sequence type; MIC, minimal inhibitory concentration; BMD, broth microdilution; hVISA, heteroresistant vancomycin-intermediate *Staphylococcus aureus*; SCC*mec*, staphylococcal cassette chromosome *mec*; *agr*, accessory gene regulator; APACHE II, Acute Physiology and Chronic Health Evaluation II; TDM, therapeutic drug montoring; SAB, *Staphylococcus aureus* bacteremia; NA, not applicable

[a]The number of patients in ST5 (55) was compared with those in ST72 (30).

[b]The number of patients in ST5 (55) was compared with those in non-ST5 (43).

[c]Within 30 days prior to the first day of *Staphylococcus aureus* bacteremia

[d]Vancomycin TDM performed within 5 days of vancomycin therapy.

[e]Population analysing profiling (PAP) was performed in 80 MRSA isolates.

[f]43 isolates (*lukSF-PV*), 41 isolates (*bbp, ebps, map_eap, sdrC, sdrD, sdrE, clfA, clfB, cna, icaA, sea, seb, sec, see, sei, sej, seg, sek, sel, sem, sen, eta, etb, edin, lukDE, lukM, lukE, hla, hlb*) and 38 isolates (*fnbA, fnbB, sed, seg, seo, sep, seh, tst, hld, hlg*) were analyzed. Genes found in > 95% or < 5% of the tested isolates were excluded in analysis.

Table 6. Independent predictors for 30-day mortality (n = 31) in MRSA SABP patients (n = 98)

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Rapidly or ultimately fatal disease	4.830 (1.878–12.422)	<0.001	5.348 (1.485–19.258)	0.010
Severe sepsis or septic shock	3.468 (1.427–8.430)	0.005	3.640 (1.049–12.629)	0.042
Days to negative conversion, median (IQR)	1.333 (1.052–1.687)	0.017	1.458 (1.027–2.071)	0.035
Vancomycin therapy	0.218 (0.087–0.546)	<0.001	0.274 (0.080–0.938)	0.039
Vancomycin TDM[a]	0.309 (0.128–0.748)	0.008		
ST5	2.519 (1.012–6.266)	0.044	5.479 (1.440–20.852)	0.013

CI, confidence interval; OR, Odds ratio.

[a]Vancomycin TDM performed within 5 days of vancomycin therapy.

In table 7, I compared the characteristics and outcomes of MSSA ST72 versus non-ST72 in SABP patients. There were no significant differences in clinical characteristics such as mode of acquisition, severity of comorbidity, severity of sepsis. In addition, microbiological characteristics such as vancomycin MIC and *agr* dysfunction were not different significantly. The 30-day and 90-day mortality were not significantly different between the 2 groups, while SAB-related mortality was significantly higher in ST72 than in non-ST72 (*P*=0.043).

In multivariate analysis, independent risk factors for 30-day mortality in MSSA bacteremic pneumonia included age (aOR, 1.052; 95% CI, 1.001–1.107; *P*=0.046) and underlying neurological disease (aOR, 6.848; 95% CI, 1.556–30.141; *P*=0.011) (Table 8).

Table 7. Comparison of characteristics and outcomes of MSSA ST72 versus non-ST72 in SABP patients (n = 66)

Characteristic	ST72 (n = 14)	non-ST72 (n = 42)	*P* value
Age (years), median (IQR)	53.0 (41.5–75.5)	64.0 (54.5–74.5)	0.239
Male	8 (57.1)	29 (55.8)	0.927
Mode of acquisition			
Nosocomial	4 (28.6)	11 (21.2)	0.720
Healthcare-associated	6 (42.9)	22 (42.3)	0.971
Community-acquired	4 (28.6)	19 (36.5)	0.755
Charlson comorbidity index, median (IQR)	3.5 (0.8–5.3)	3.0 (2.0–6.0)	0.472
McCabe and Jackson criteria			
Rapidly or ultimately fatal disease	9 (64.3)	32 (61.5)	0.851
Underlying disease/condition			
Solid cancer	5 (35.7)	22 (42.3)	0.656
Hematologic malignancy	1 (7.1)	4 (7.7)	>0.999
Diabetes mellitus	5 (35.7)	18 (34.6)	0.939
End-stage renal disease	1 (7.1)	4 (7.7)	>0.999
Liver cirrhosis	2 (14.3)	0 (0)	**0.042**
Solid organ transplantation	0 (0)	3 (5.8)	>0.999
Hematopoietic cell transplantation	0 (0)	1 (1.9)	>0.999
Chronic lung disease	0 (0)	3 (5.8)	>0.999
Rheumatologic disease	0 (0)	2 (3.8)	>0.999
Ischemic heart disease	0 (0)	5 (9.6)	0.576

Heart failure	2 (14.3)	4 (7.7)	0.600
Neutropenia	1 (7.1)	3 (5.8)	>0.999
Recent surgery[a]	1 (7.1)	4 (7.7)	>0.999
Chemotherapy[a]	1 (7.1)	16 (30.8)	0.093
Immunosuppressive therapy[a]	3 (21.4)	17 (32.7)	0.524
Indwelling device			
Central venous catheter	2 (14.3)	6 (11.5)	0.674
Prosthetic valve	1 (7.1)	3 (3.8)	0.517
Vascular graft	0 (0)	3 (5.8)	>0.999
Sepsis grade			
No sepsis	0 (0)	12 (23.1)	0.056
Sepsis	8 (57.1)	25 (48.1)	0.547
Severe sepsis	1 (7.1)	4 (7.7)	>0.999
Septic shock	5 (35.7)	11 (21.2)	0.259
Pitt bacteremia score, median (IQR)	2.0 (0.8–3.0)	1.0 (0–3.0)	0.298
APACHE II score, median (IQR)	20.5 (14.5–25.5)	18.0 (12.3–25.8)	0.428
Metastatic infection	1 (7.1)	0 (0)	0.212
Management			
First blood culture follow up interval, median days (IQR)	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.273
Days to negative conversion, median (IQR)	4.0 (3.0–8.5)	4.0 (3.0–5.0)	0.533
Intensive care unit treatment	2 (14.3)	3 (5.8)	0.285
Mechanical ventilation	2 (14.3)	3 (5.8)	0.285
Antibiotic therapy			

Previous antibiotic exposure[a]	1 (7.1)	8 (15.4)	0.671
Previous glycopeptide exposure[a]	1 (7.1)	0 (0)	0.212
Days to appropriate antibiotic therapy, median (IQR)	0 (0–0)	0 (0–1.0)	0.170
Vancomycin therapy	4 (28.6)	13 (25.0)	0.744
Microbiological characteristics			
Vancomycin MIC (mg/L) by Etest method			
0.5	0 (0)	0 (0)	NA
0.75	2 (14.3)	4 (7.7)	0.600
1	5 (35.7)	20 (38.5)	0.851
1.5	5 (35.7)	24 (46.2)	0.485
2	2 (14.3)	2 (3.8)	0.195
Vancomycin MIC (mg/L) by BMD method			
0.5	0 (0)	0 (0)	NA
0.75	11 (78.6)	39 (75.0)	>0.999
1	3 (21.4)	12 (23.1)	>0.999
1.25	0 (0)	1 (1.9)	>0.999
1.5	0 (0)	0 (0)	NA
***agr* dysfunction**	3 (21.4)	15 (28.8)	0.741
***agr* type**			
agr type I	13 (92.9)	31 (59.6)	**0.024**
agr type II	0 (0)	13 (25.0)	0.055
agr type III	0 (0)	4 (7.7)	0.571

30-day mortality	5 (35.7)	15 (28.8)	0.620
90-day mortality	7 (50.0)	22 (42.3)	0.607
SAB-related mortality	6 (42.9)	9 (17.3)	**0.043**
90-day recurrence	0 (0)	0 (0)	NA

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

MSSA, methicillin-susceptible *Staphylococcus aureus*; SABP, *Staphylococcus aureus* bacteremic pneumonia; IQR, interquartile range; SAB, *Staphylococcus aureus* bacteremia; NA, not applicable.

[a]Within 30 days prior to the first day of *Staphylococcus aureus* bacteremia

Table 8. Independent predictors of 30-day mortality (n = 20) in MSSA SABP patients (n = 66)

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Age (years), median (IQR)	1.066 (1.018–1.117)	0.007	1.052 (1.001–1.107)	0.046
Neutropenia	7.941 (0.772–81.696)	0.079		
APACHE II score, median (IQR)	1.068 (1.004–1.135)	0.036		
Neurologic disease	7.000 (1.795–27.299)	0.005	6.848 (1.556–30.141)	0.011

CI, confidence interval; OR, Odds ratio.

Antimicrobial susceptibilities of MRSA isolates

Out of 98 MRSA bacteremic pneumonia, the susceptibility profiles were evaluated in 96 isolates (Table 9). ST72 (n = 30) showed relatively low resistance rates to non-ß-lactam antimicrobial agents, such as clindamycin (13.3%), ciprofloxacin (16.7%), tetracycline (3.3%), while ST5 had high resistance rates to clindamycin (94.5%), ciprofloxacin (96.4%), and tetracycline (90.1%). In addition, ST5 had resistance rate of 12.7% to rifampin (7/55). There were 15 and 2 isolates of ST5 and ST239 hVISA, respectively. Most hVISA isolates had high resistance rates to both ß-lactam and non-ß-lactam antimicrobial agents, and resistance rates to trimethoprim/sulfamethoxazole and rifampin were 11.8% (2/17) and 17.6% (3/17), respectively. ST8 isolates had high resistance rate to ciprofloxacin (100%, 7/7).

Table 9. Susceptibility profiles of 96 tested MRSA bloodstream isolates in patients with SABP

MLST	No. of isolates	No. of resistant isolates (resistance rate, %)									
		AMP	CLI	CIP	TMP/SMX	ERY	FA	GEN	Q/D	RIF	TET
ST5	55	54 (98.2)	52 (94.5)	53 (96.4)	0 (0)	53 (96.3)	46 (83.6)	39 (70.9)	1 (1.8)	7 (12.7)	50 (90.1)
hVISA[a]	15	14 (93.3)	14 (93.3)	14 (93.3)	0 (0)	14 (93.3)	15 (100)	9 (60.0)	0 (0)	3 (20.0)	14 (93.3)
ST72	30	27 (90.0)	4 (13.3)	5 (16.7)	0 (0)	6 (20.0)	0 (0)	5 (16.7)	0 (0)	1 (3.3)	1 (3.3)
ST8	7	7 (100)	0 (0)	7 (100)	0 (0)	6 (85.7)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)
ST239[a]	2	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)
ST97	1	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ST254	1	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	96	92 (95.8)	58 (60.4)	69 (71.9)	2 (2.1)	68 (70.8)	46 (47.9)	47 (48.9)	1 (1.0)	8 (8.3)	53 (55.2)

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

AMP, ampicillin; ERY, erythromycin; CLI, clindamycin; CIP, ciprofloxacin; TET, tetracycline; GEN, gentamicin; RIF, rifampin; TMP/SMX, trimethoprim-sulfamethoxazole; Q/D, quinupristin/dalfopristin; FA, fusidic acid.

[a]Among 17 isolated of hVISA, 15 isolates were ST5 and 2 isolates were ST239.

Bacterial virulence genes of MRSA isolates

Out of 98 MRSA bacteremic pneumonia, the virulence gene profiles were analyzed in 41 isolates (Table 10). Some virulence genes were found in 100% of the tested isolates, such as *fnbA* (100%, 38/38), *fnbB* (100%, 38/38), *clfA* (100%, 41/41), *clfB* (100%, 41/41), *icaA* (100%, 41/41). ST5 isolates commonly harbour virulence genes including *sdrC* (100%, 31/31), *sdrE* (96.8%, 30/31), *sec* (93.5%, 29/31), *sel* (96.8%, 30/31), tst (93.1%, 27/29), and *hlb* (80.6%, 25/31), while relatively low rates of virulence genes detections were found in ST72, such as *sdrC* (60.0%, 3/5), *sec* (0%, 0/5) and *sel* (40.0 %, 2/5).

Table 10. Virulence genes profile of 41 tested MRSA bloodstream isolates in patients with SABP

	Frequency of virulence genes according to different sequence types (%)						
Virulence gene	**ST5 (n = 31)**	**ST72 (n = 5)**	**ST239 (n = 2)**	**ST254 (n = 1)**	**ST8 (n = 1)**	**Unknown (n = 1)**	**Total (n = 41)**
Adhesin genes							
sdrC	31/31 (100)	3/5 (60.0)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	39/41 (95.1)
sdrE	30/31 (96.8)	3/5 (60.0)	2/2 (100)	1/1 (100)	1/1 (100)	0/1 (0)	39/41 (95.1)
map/eap	0/31 (0)	0/5 (0)	2/2 (100)	1/1 (100)	1/1 (100)	0/1 (0)	4/41 (9.6)
clfA	31/31 (100)	5/5 (100)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	41/41 (100)
clfB	31/31 (100)	5/5 (100)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	41/41 (100)
fnbA	29/29 (100)	5/5 (100)	2/2 (100)	1/1 (100)	N/A	1/1 (100)	38/38 (100)
fnbB	29/29 (100)	5/5 (100)	2/2 (100)	1/1 (100)	N/A	1/1 (100)	38/38 (100)
icaA	31/31 (100)	5/5 (100)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	41/41 (100)
cna	0/31 (0)	0/5 (0)	0/2 (0)	1/1 (100)	1/1 (100)	0/1 (0)	2/41 (4.9)
Toxin genes							
sea	0/31 (0)	0/5 (0)	2/2 (100)	0/1 (0)	0/1 (0)	1/1 (100)	3/41 (7.3)
sec	29/31 (93.5)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	29/41 (70.7)

sed	0/31 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/41 (0)
see	0/31 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/41 (0)
seg	30/31 (96.8)	5/5 (100)	0/2 (0)	0/1 (0)	0/1 (0)	1/1 (100)	36/41 (87.8)
sei	31/31 (100)	5/5 (100)	1/2 (50.0)	0/1 (0)	0/1 (0)	1/1 (100)	38/41 (92.7)
sej	0/31 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/41 (0)
sek	0/31 (0)	0/5 (0)	2/2 (100)	1/1 (100)	0/1 (0)	0/1 (0)	3/41 (7.3)
sel	30/31 (96.8)	2/5 (40.0)	1/2 (50.0)	0/1 (0)	1/1 (100)	1/1 (100)	35/41 (85.4)
sep	4/29 (13.8)	0/5 (0)	0/2 (0)	0/1 (0)	NA	0/1 (0)	4/38 (10.5)
tst	27/29 (93.1)	0/5 (0)	1/2 (50.0)	0/1 (0)	NA	0/1 (0)	28/38 (73.7)
Leucocidin genes							
lukDE	31/31 (100)	5/5 (100)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	41/41 (100)
lukSF-PV	0/32 (0)	0/5 (0)	0/2 (0)	1/1 (100)	7/7 (100)	0/1 (0)	8/48 (16.7)
Hemolysin genes							
hla	30/31 (96.8)	5/5 (100)	2/2 (100)	1/1 (100)	1/1 (100)	1/1 (100)	40/41 (97.6)
hlb	25/31 (80.6)	3/5 (60.0)	1/2 (50.0)	0/1 (0)	1/1 (100)	0/1 (0)	30/41 (73.2)

hld	28/29 (96.6)	4/5 (80.0)	2/2 (100)	1/1 (100)	N/A	1/1 (100)	36/38 (94.7)
hlg	0/29 (0)	0/5 (0)	0/2 (0)	0/1 (0)	N/A	0/1 (0)	0/38 (0)
Others							
eta	0/41 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/41 (0)
etb	0/41 (0)	0/5 (0)	0/2 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/41 (0)

Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified.

NA, not applicable.

DISCUSSION

In the present study, ST8 MRSA and ST6 MSSA were significantly more prevalent in SABP, compared to SAB with other primary sources. The 30-day mortality rates of MRSA and MSSA bacteremic pneumonia were 31.6% and 30.3%, respectively, which was significantly higher than SAB with other primary sources. Notably, ST5-MRSA, the most prevalent strain in MRSA bacteremic pneumonia, was significant microbiological risk factor for poor outcome, while some virulence genes including *sdrC, sec, sel* were closely related to ST5-MRSA. In MSSA bacteremic pneumonia, ST72 was the most predominant strain, while no strain-specific clinical and microbiological characteristics were observed, compared to non-ST72 MSSA.

The mechanism that *S. aureus* causes pneumonia has been evaluated, which includes invasion to the lung epithelium and virulence factors associated with host defense escape [15]. There have been studies that some virulence factors such as *hla, clfA/clfB, tst*, and PVL promoted *S. aureus* pneumonia [34–37], and pathogen-specific characteristics might be associated with outcomes of *S. aureus* bacteremic pneumonia [38]. However, little is known which genotype of *S. aureus* isolates is the most prevalent to affect SABP, which hinders better understanding of clonal differences in SABP and the development of new therapeutic and preventive strategies to SABP.

One of the important findings of the present study is that ST8 MRSA was significantly more common in SABP, compared with SAB with other primary sources. ST8 has been increasing in the longitudinal change of MLST in MRSA bacteremia in South Korea [39], and several reports regarding the emergence of not only community-acquired but nosocomial PVL-positive ST8 MRSA infections in South Korea [40–42]. In addition, it is notable that the rapid clonal shifts of prior endemic clones to ST8/USA300 was recently observed in Taiwan [43], although the different epidemiology of PVL-positive ST8 strain has been

reported in Asian countries [44]. Because PVL can promote host defense escape and cytokine induction in *S. aureus* pneumonia [36,45], I posit that the continuous surveillance and active strategies to prevent the spread of ST8 are essential, given the high mortality of SABP.

Interestingly, ST6 MSSA caused SABP more frequently than SAB with other primary soureces compared to other sequence types and accounted for 12.1% (8/66) of MSSA bacteremic pneumonia in this study. ST6 was prevalent clone among *S. aureus* isolates from food [46,47], and ST6-t304 MRSA is a successful emerging clone in northern Europe after the Syrian Civil War [48]. Notably, PVL-positive ST6 clones has been also described [48,49], which may be associated with poor outcomes in patients with SABP. Although limited data is available about the association with ST6 clone and SABP, the present study suggests that the epidemiology of ST6 *S. aureus* infection should be evaluated vigorously.

Another important finding of this study was ST5-SCC*mec* typeIIb MRSA as the microbiological predictors for 30-day mortality in MRSA bacteremic pneumonia. I posit that bacterial strain-specific virulence factors of clonal differences in *S. aureus* may play an important role for this finding. Different clonality can affect the mortality in SAB [50], molecular determinants of virulence have an impact on outcomes in SAB [51]. ST5 MRSA clone have been reported to be potential pathogen factor associated with poor outcomes in SAB and MRSA pneumonia [52,53], and several previous studies suggested that virulence factors commonly harboured by ST5, such as *sdrC*, *sec*, *sel*, *fnbB*, contributed to poor outcomes of MRSA bacteremia [52,54,55]. The staphylococcal superantigen genes, such as *sdrC* and *sec*, can cause T-cell activation that can led to cytokine induction and shock [56], while adhesin genes *fnbB* and *sdrC* can be associated with expression of biofilms and persistent SAB, respectively [55,57]. In this study, the 30-day mortality of patients with ST5-hVISA infection was 80.0% (12/15), which suggests that ST5-hVISA-specific virulence rather than vancomycin heteroresistance itself was predictive, given the conflicting results

whether hVISA in MRSA bacteremia result in increased mortality [58]. From the point of view in different antimicrobial resistance patterns between sequence types, ST5 clone had high rates of resistance to non-beta-lactam agents, compared to ST72. Of note, high resistance rate to rifampin of 12.7% was observed in ST5, given only 0.4% (57/1615) of *S. aureus* isolates from SAB between 2008-2017 was found in one recent study conducted in this hospital [59]. Further study will be needed regarding the rifampin resistance in ST5 that caused *S. aureus* bacteremic pneumonia, because rifampin resistance in SAB may be associated with infection recurrence [60]. This study has strengths that provides evidence to determine the association between ST5-specific microbiological characteristics and increased mortality in MRSA bacteremic pneumonia. In addition, to the best of my knowledge, this is the first study to evaluate an association between *S. aureus* virulence factors and bacteremic pneumonia, especially for better understanding of its relationship with mortality.

The widespread existence of ST72 and ST8, regardless of methicillin resistance, to cause SABP in healthcare settings is noteworthy in this study, although they have been the predominant clones for CA-MRSA infections in South Korea. This study had strength to evaluate the distribution of genetic background of MRSA and MSSA isolates according to place of acquisition (CA vs. HCAP/HAP). The proportion of ST72 has been gradually increasing in the longitudinal change of MLST in MRSA bacteremia in South Korea [39], and ST72 has been already reported as a hospital genotype in South Korea [39,54,61]. Although the significant differences in clinical and microbiological characteristics as well as mortality were not observed in ST72 MSSA compared to other sequence types in this study, the strategies which can ascertain to prevent nosocomial dissemination and infections of ST72 clones.

This study has certain limitations. First, the observational nature in a single-center cohort study may limit generalizability. Second, I did not analyze the radiological findings of *S.*

aureus bacteremic pneumonia that may have affected the outcomes and had associations with microbiological characteristics. Third, I analyzed only 41 isolates of MRSA to assess the virulence factors according to sequence types. Despite the several limitations, the present results are valuable because of the scarcity of studies to date that have specifically evaluated the clinical, microbiological characteristics and outcomes in patients with *S. aureus* bacteremic pneumonia. Therefore, this study has important clinical implications and provides useful information for preventive infection control measures based on the molecular epidemiology of SABP in South Korea.

CONCLUSION

In conclusion, this study suggests that ST8 MRSA and ST6 MSSA affect SABP more frequently among the different clonality in *S. aureus* bacteremia, although ST5 MRSA and ST72 MSSA were the most prevalent clones in SABP. The 30-day mortality was significantly higher in SABP than SAB with other primary sources, and ST5-specific microbiological characteristics that frequently harbored virulence factors such as *sdrC*, *sec*, *sel*, *fnbB* may have contributed to poor outcomes of MRSA bacteremic pneumonia. This study results emphasize that microbiological characteristics can help better understanding of clinical characteristics and outcomes of SABP, and active infection control strategy to prevent healthcare-associated SABP should be considered.

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ABSTRACT (KOREAN)

배경: 균혈증을 동반한 황색포도알균(*Staphylococcus aureus*) 폐렴은 높은 사망률에도 불구하고 아직까지 임상적, 미생물학적 특징과 예후에 대해 분석하고자 한 노력이 그동안 부족하였다.

방법: 2008년 8월부터 2020년 12월까지의 연구기간 동안 균혈증을 동반한 황색포도알균 폐렴환자 164명을 분석하였다. 임상적 특성 자료와 함께, 균주의 sequence typing (ST), protein A 유전자 형별분석(*spa* typing), SCC*mec* typing, 병원성 인자를 포함한 미생물학적 특성 자료를 분석하였다. 또한, 균혈증을 동반한 메티실린 내성 황색포도알균(Methicillin-resistant *S. aureus*)와 메티실린 감수성 황색포도알균(Methicillin-susceptible *S. aureus*) 환자에서, 주된 sequence type과 그 외 간의 특징 및 예후에 대해 비교하였고, 30일 사망의 위험인자를 분석하였다.

결과: 균혈증을 동반한 황색포도알균 폐렴에서는, 다른 원발부위의 황색포도알균 균혈증 감염에 비해 ST8 MRSA (P<0.001)와 ST6 MSSA (P=0.035)가 통계적으로 유의하게 많이 관찰되었다. MRSA 및 MSSA 균혈증을 동반한 폐렴에서 30일 사망은 다른 원발부위를 가진 황색포도알균 균혈증보다 유의하게 높았다(MRSA, 31.6%, P<0.001; MSSA, 30.3%, P<0.001). MRSA 균혈증 폐렴에서 ST5-SCC*mec* IIb-t2460 MRSA가 가장 흔한 유전형이었고(25/98, 25.5%), *sdrC*, *sec*, *sel*, *tst*와 같은 병원성 인자를 빈번하게 보유하는 ST5가 다변량분석에서 30일 사망의 유의한 위험인자였다(adjusted OR [aOR], 5.479; 95% confidence interval [CI], 1.44020.852; P=0.013). ST72-t126이 MSSA 균혈증을 동반한 폐렴에서 가장 흔한 유전형이었지만, ST72와 그 외 ST간에 임상적 또는 미생물학적으로 유의한 특징 차이는 보이지 않았다.

결론: 본 연구에서는 균혈증을 동반한 황색포도알균 폐렴의 미생물학적 특징을 분석함과 동시에, 그와 관련된 임상적 특징과 예후에 대해 더 깊은 이해를 제공해준다. 이를 바탕

으로 균혈증을 동반한 황색포도알균 폐렴의 병원내전파 예방과 같은 전략이 필요하겠다.

중심단어: 황색포도알균, 균혈증을 동반한 폐렴, Sequence type, 병원성 인자, 사망