

# Emergence of Community-Genotype Methicillin-Resistant *Staphylococcus aureus* in Korean Hospitals: Clinical Characteristics of Nosocomial Infections by Community-Genotype Strain

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**Background:** As community-genotype methicillin-resistant *Staphylococcus aureus* (MRSA) strains spread into hospitals, the genotypes of the MRSA strains causing hospital-acquired (HA) infections have become more diverse. We describe clinical characteristics of nosocomial MRSA infections by a community-genotype of sequence type (ST) 72.

**Materials and Methods:** A case-control study was designed among patients with HA-MRSA infections. Forty patients with infections caused by ST72-MRSA SCCmec type IV were selected as cases. Cases were matched to the controls with 106 patients infected with ST5/ST239 MRSA, which are representative hospital genotypes in Korea.

**Results:** Patients infected with ST72 isolates were younger than those with ST5/ST239 isolates. Female gender predominated among ST72 MRSA group compared to ST5/ST239 MRSA group. Solid tumor was a more frequent underlying disease in MRSA infections by ST72 isolates, whereas underlying renal, lung, heart, and neurologic diseases were more frequently found in those by ST5/ST239 isolates. The most common type of infection was pneumonia in both ST72 and ST5/ST239 groups (45.0% vs. 51.9%), followed by skin and soft tissue infection (SSTI). Female gender and underlying solid tumor were identified to be independent predictors for MRSA infections by ST72 isolates. All-cause mortality rates (20.0% vs. 30.2%) were not different between the groups.

**Conclusion:** A community-genotype MRSA, ST72 isolate has emerged as a nosocomial pathogen presenting as hospital-acquired pneumonia and SSTI. Although differences in underlying disorders were found, the distribution of infection type and mortality rate did not differ between the groups.

**Key Words:** Methicillin-resistant *Staphylococcus aureus*; Nosocomial infections; Genotyping

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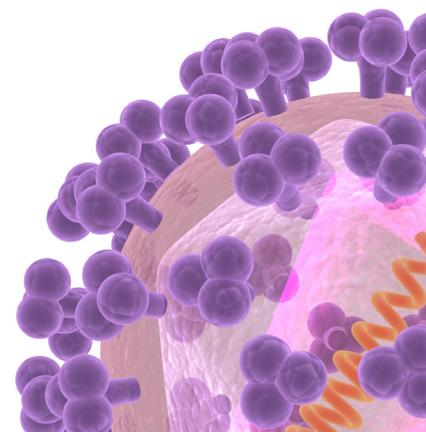
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## Introduction

The hospital epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) has changed in the past few years due to the emergence of community-associated MRSA (CA-MRSA) strains in healthcare settings [1, 2]. Recently, community-genotype strains carrying SCCmec type IV have emerged as a significant cause of healthcare-associated (HCA) and hospital-associated (HA) infection in the USA and European countries [2-6]. CA-MRSA strain, ST72 MRSA has also emerged as a major cause of bloodstream infection (BSI) in healthcare settings in Korea [7-9].

Despite increasing trends in the annual incidence of nosocomial MRSA infections by community-genotype strain worldwide, there are few reports regarding clinical characteristics in nosocomial MRSA infections by community-genotype strain [10, 11]. Furthermore, it is still questionable whether clinical outcomes in patients with nosocomial MRSA infections would be adversely affected by the community-genotype strain. This study was performed to identify clinical characteristics and outcomes in patients with nosocomial infections due to the community-genotype ST72 MRSA.

## Materials and Methods

### 1. Study design and patient selection

A case-control study was designed to identify clinical characteristics in patients with HA-MRSA infections by comparison of outcomes in those with community-genotype strain, ST72-MRSA-SCCmec type IV, and hospital genotype strains, ST5- and ST239-MRSA-SCCmec type II and III. Databases and electronic medical charts were reviewed in *S. aureus* isolates that had been collected at Samsung Medical Center (a 1,950-bed tertiary care university hospital, Seoul, Korea) and stored in the Asian Bacterial Bank (Asia Pacific Foundation for Infectious Diseases, Seoul, Korea) during the period of January 2007 through December 2009. The study patients were enrolled when they were clinically diagnosed with nosocomial MRSA infections by attending physicians, based on clinical presentation and manifestation with culture results of MRSA isolates. When the patients carried MRSA but showed no clinical signs or symptoms of infection, the isolates were determined to be colonizer and excluded from this study.

To analyze clinical characteristics of nosocomial infection cases by community-genotype MRSA strain, ST72 isolates, we selected cases in a previous study [10], in which a total of 40

cases were finally identified to have nosocomial infections due to ST72 isolates. During the study period, a total of 675 patients were identified to carry MRSA isolates in Asian Bacterial Bank (157 in 2007, 227 in 2008, and 291 in 2009). MRSA isolates were matched to ST72 at a 4-5 times ratio, based on the date of acquisition of ST72 isolates. For the selection of a candidate for ST5/ST239 MRSA, antibiotic susceptibility patterns were reviewed in MRSA isolates to determine whether these are multidrug-resistant (MDR) or not. MDR were defined as resistant to at least 3 antibiotics of fluoroquinolone, gentamicin (GEN), rifampicin (RIF), trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin (CLI) and erythromycin (ERY). The electronic medical records of the patients were also reviewed in order to discern true pathogens from colonizers. After reviewing antimicrobial susceptibility test results and medical chart, a total 145 patients were identified to have MDR-MRSA infections. Multilocus sequence typing (MLST) was performed in 145 MRSA isolates, which revealed 106 isolates were ST5 and ST239 (94 and 12, respectively). Further molecular analysis was not performed in remaining 39 MRSA isolates when at least one allele profile of housekeeping genes in those isolates was not compatible to that in ST5 and ST239.

### 2. Definition and data collection

HA, nosocomial *S. aureus* infection was defined as infection occurring in the 48 hours after hospital admission. Appropriateness of empiric therapy was defined in cases that initial empiric antimicrobial agents, given during the first 48-72 hours after the onset of infection, were active against MRSA. As site of infection, skin and soft tissue infection (SSTI), surgical site infection (SSI) were defined according to the previous report [10]. Pneumonia was defined as cases meeting the following criteria. (1) "New or progressive" consolidation or cavitation. (2) At least one of the following: fever; leukocytosis; or leucopenia; for adults greater than or equal to 70 years, altered mental status with no other recognized cause. (3) New onset of purulent sputum or change in character of sputum or increased respiratory secretions; new-onset or worsening cough, dyspnea, or tachycardia; rales or bronchial breath sounds; or worsening gas exchange [12]. Relapse was evaluated until one year after hospital discharge.

We collected the following demographic data from electronic medical records: age, gender, underlying disease, comorbid conditions, severity of illness, and conditions prone to MRSA acquisition. Clinical data included type of infection, well-defined healthcare-associated risk factors, in-hospital mortality, and length of hospital stay. All-cause mortality was defined to

all causes of death. Attributable mortality was defined to deaths secondary to MRSA infection. This study was approved by the Institute Review Board of Samsung Medical Center.

### 3. Microbiological identification, antimicrobial susceptibility, and molecular testing

The VITEK II automated system (bioMérieux, Marcy l'Etoile, France) was used for microbiological identification and antimicrobial susceptibility testing using a standard identification card and the modified broth microdilution method. Minimum inhibitory concentration breakpoints and quality-control protocols were used according to standards established by the Clinical and Laboratory Standards Institute [13]. SCC $mec$  typing was performed for the controls, which had been verified to have MRSA infection. Multiplex polymerase chain reaction strategies for the rapid assignment of SCC $mec$  types were applied in selected isolates [14, 15]. Molecular typing of all MRSA isolates was performed by MLST [16]. Alleles of each locus were compared, and sequence types were assigned based on the *S. aureus* MLST database [16, 17].

### 4. Statistical analysis

Student's *t*-test and the Mann-Whitney test were used to compare continuous variables, and the  $\chi^2$  test or Fisher's exact test was used to compare categorical variables. To identify the independent risk factors for mortality, a stepwise backward multivariable logistic regression analysis model was used to control for the effects of confounding variables. Variables with  $P < 0.1$  in the univariate analyses were candidates for inclusion in the multivariate analysis and variables for which  $P < 0.05$  in the multivariate analysis were retained in the final model. Interactions between variables were not introduced in the models. Odds ratios (ORs) and their 95% confidential intervals (CIs) were calculated. All *P*-values were two-tailed, and *P*-values  $< 0.05$  were considered statistically significant. SPSS for Windows, PASW version 19.0 (SPSS Inc., Chicago, IL, USA) was used for these analyses.

## Results

### 1. Comparison of clinical outcome by community- and hospital genotype strains

Clinical characteristics of nosocomial MRSA infections in cases and controls are shown in Table 1. Patients with ST72 MRSA infections were younger than those with ST5/ST239 MRSA (mean age  $\pm$  SD;  $51 \pm 20$  vs.  $58 \pm 19$ ;  $P = 0.039$ ). ST72 MRSA infec-

**Table 1.** Clinical characteristics of nosocomial MRSA infections caused by hospital- and community-genotype strains

Clinical characteristics	Community-ST72 (n = 40)	Hospital-ST5/ST239 (n = 106)	<i>P</i> -value
Age, mean $\pm$ SD	51 $\pm$ 20	58 $\pm$ 19	0.039
Sex, female	26 (65.0)	21 (19.8)	<0.001
Adult	38 (95.0)	98 (92.5)	0.728
Surgical department	30 (75.0)	56 (52.8)	0.015
Hospital stay before the onset of infection	17 $\pm$ 17	20 $\pm$ 19	0.437
Underlying disease			
Diabetes mellitus	6 (15.0)	11 (10.4)	
IHD or HF	1 (2.5)	20 (19.0)	0.011
Hypertension	5 (12.5)	18 (17.0)	0.507
Hepatobiliary tract disease	11 (27.5)	19 (17.9)	0.202
Liver cirrhosis	7 (17.5)	8 (7.5)	0.122
Renal disease	4 (10.0)	31 (29.2)	0.015
Lung disease	3 (7.5)	29 (27.4)	0.010
Solid tumor	23 (57.5)	40 (37.7)	0.032
Hematologic malignancy	5 (12.5)	6 (5.7)	0.290
Neurologic disease	3 (7.5)	34 (32.1)	0.002
Severity of illness			
Charlson's WIC, mean $\pm$ SD	3.35 $\pm$ 2.35	3.42 $\pm$ 2.27	
Severe sepsis or septic shock	7 (17.5)	26 (24.5)	0.365
Care in the intensive care unit	8 (20.0)	50 (47.2)	0.003
Immunodeficiency			
Solid organ transplantation	3 (7.5)	6 (5.7)	0.706
Receipt of chemotherapy or radiotherapy	7 (17.5)	11 (10.4)	0.265
Use of corticosteroids	8 (20.0)	21 (19.8)	0.980
Neutropenia	3 (7.5)	3 (2.8)	0.346
Conditions prone to MRSA acquisition			
Prior operation within one month	25 (62.5)	61 (57.5)	0.587
Prior antibiotics within one month	33 (82.5)	101 (95.3)	0.019
Colonization of MRSA	9 (22.5)	33 (31.1)	0.304
Ventilator care	8 (20.0)	38 (35.8)	0.066
Catheterization	22 (55.0)	69 (65.1)	0.262
Dialysis	4 (10.0)	9 (8.5)	0.752

MRSA, methicillin-resistant *Staphylococcus aureus*; ST, sequence type; SD, standard deviation; IHD, ischemic heart disease; HF, heart failure; WIC, weighted index of co-morbidity.

tions predominated in females, compared to ST5 and ST239 (65.0% vs. 19.8%;  $P < 0.001$ ). Solid tumors were more commonly found in patients with ST72 MRSA infections, whereas underlying renal, lung, and neurologic diseases were more significantly common in ST5/ST239 MRSA infections. The most common type of infection was pneumonia in both ST72 and ST5/ST239 groups, which accounted for 45.0% and 51.9%, respectively (Ta-

**Table 2.** Type of infection and outcome of patients with nosocomial MRSA infections

Clinical characteristics	Community-ST72 (n = 40)	Hospital-ST5/ST239 (n = 106)	P-value
Type of infection			
Pneumonia	18 (45.0)	55 (51.9)	0.458
Skin and soft tissue infection	16 (40.0)	26 (24.5)	0.100
Cellulitis, simple abscess	1 (2.5)	1 (0.9)	1.000
Surgical site infection	13 (32.5)	24 (22.6)	0.286
Pyomyositis or necrotizing fasciitis	2 (5.0)	1 (0.9)	0.182
Catheter-related infection	2 (5.0)	4 (3.8)	0.666
Intra-abdominal infection	4 (10.0)	12 (11.3)	1.000
Primary bacteremia	0 (0)	1 (0.9)	
Brain abscess	0 (0)	2 (1.9)	
Infective endocarditis	0 (0)	1 (0.9)	
Meningitis	0 (0)	2 (1.9)	
Urinary tract infection	0 (0)	3 (2.8)	
Appropriateness of initial empiric therapy	17 (42.5)	75 (51.4)	0.188
Clinical outcomes			
All-cause mortality	8 (20.0)	32 (30.2)	0.218
Attributable mortality due to MRSA infections	5 (12.5)	23 (21.7)	0.208
Cases with follow-up for over one year	27	56	
Recurrence of infection within a year	3 (11.1)	5 (8.9)	0.684
Interval to recurrence of infections, mean $\pm$ SD	157 $\pm$ 123	116 $\pm$ 53	0.626
Hospital stay, median days (range)	32 $\pm$ 42	52 $\pm$ 97	0.215

MRSA, methicillin-resistant *Staphylococcus aureus*; ST, sequence type; SD, standard deviation.

ble 2). SSTI was more common in the ST72 group compared to the group of ST5/ST239 (40.0% vs. 24.5%;  $P = 0.100$ ). Twenty-eight patients died due to MRSA infections in the hospital (19.2%), and mortality rates were not significantly different between the two groups with community- and hospital-strains.

## 2. Predictor of infection by community-genotype MRSA

Further analysis was performed to identify independent predictors of ST72 MRSA infections among nosocomial MRSA infections; the results are shown in Table 3. Female gender and underlying solid tumors were identified to be independent predictors for ST72 MRSA infections on multivariate analyses. Old age, underlying neurologic disease, and care in the intensive care unit (ICU) were negatively associated with ST72 MRSA infections, shown to be independent factors for ST5/ST239.

## 3. Antibiotic resistance in MRSA isolates by community- and hospital-genotypes

Antimicrobial activities were tested against 144 MRSA samples acquired from hospitalized patients (Fig. 1). In this study, ST72 MRSA isolates were selected based on susceptibility patterns to RIF, TMP/SMX, ciprofloxacin (CIP), and GEN [10]. Thus, it is inevitable that ST72 MRSA was susceptible to all antibiotics tested. For CLI and ERY, resistance rates in ST72 isolates were 20% and 42.5%, respectively. High antimicrobial resistance rates for CIP, CLI, ERY, and GEN were demonstrated in both ST5 and ST239 isolates. ST5 MRSA was associated with a relatively low rate of resistance to RIF and TMP/SMX (6.4% and 0%), whereas ST239 had a low rate of resistance to fusidic acid (FUS) (25%).

## Discussion

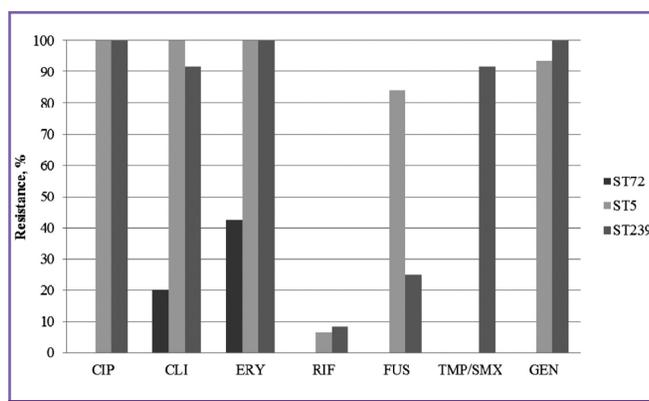
In this study, we identified clinical characteristics of nosocomial MRSA infections by community-genotype, ST72, and hospital-genotypes, ST5/ST239. Compared to infections caused by ST5/ST239 isolates, ST72 MRSA infections predominated in younger patients and females. The most common type of infection was pneumonia in both ST72 and ST5/ST239 groups. Female gender and underlying solid tumors were identified to be independent predictors for ST72 MRSA infections. Twenty-eight patients died due to MRSA infections in the hospital (19.2%), and mortality rates were not statistically different between the two groups, community- and hospital-strains (12.5% vs. 21.9%, respectively). This suggests that

**Table 3.** Predictors of community-genotype MRSA in nosocomial MRSA infections

Clinical characteristics	Unadjusted		Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, mean ± SD	0.98 (0.96-1.00)	0.039	0.96 (0.94-0.99)	0.005
Sex, female	7.52 (3.36-16.84)	<0.001	10.69 (4.02-28.41)	<0.001
Underlying disease				
IHD or HF	0.11 (0.01-0.84)	0.011		
Renal disease	0.27 (0.09-0.82)	0.015		
Lung disease	0.22 (0.06-0.75)	0.010		
Solid tumor	2.23 (1.07-4.68)	0.032	2.85 (1.06-7.70)	0.039
Neurologic disease	0.17 (0.05-0.60)	0.002	0.18 (0.05-0.75)	0.019
Severity of illness				
Care in the ICU	0.28 (0.12-0.66)	0.003	0.35 (0.13-0.99)	0.049
Conditions prone to MRSA acquisition				
Prior antibiotics within one month	0.23 (0.07-0.79)	0.019		

Age, female sex, IHD or HF, renal disease, lung disease, solid tumor, neurologic disease, care in the ICU, and receipt of prior antibiotics (all  $P \leq 0.05$ ) were included for multivariate analysis.

MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit; IHD, ischemic heart disease; HF, heart failure.

**Figure 1.** Antibiotic resistance in MRSA isolates by ST72 and ST5/ST239.

MRSA, methicillin-resistant *Staphylococcus aureus*; ST, sequence type; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; RIF, rifampicin; FUS, fusidic acid; TMP/SMX, trimethoprim/sulfamethoxazole; GEN, gentamicin.

the introduction of ST72 MRSA strain into the healthcare setting has fewer adverse effects with regard to disease distribution and all-cause mortality in patients with nosocomial MRSA infections. This is the first clinical study to compare nosocomial MRSA infection outcomes between ST72 and ST5/ST239 isolates in the era of introduction of community genotype strain in the hospital.

In particular, pneumonia was found to be the most frequent infection in nosocomial settings caused by ST72 and ST5/ST239 MRSA strains, and pneumonia significantly increased the odds of mortality compared to other types of infection.

Similar to results from a previous study [10], the mortality rate of patients with nosocomial pneumonia in the current study was 31.5% (23/73), and nosocomial pneumonia also increased the risk of deaths significantly in this study (OR: 4.48, 95% CI: 1.53-13.10,  $P = 0.006$ ). Interestingly, in a subgroup analysis with patients with nosocomial pneumonia, the mortality rates between both groups of ST72 and ST5/ST239 were not different (38.9% vs. 43.6%); this suggests the specific clone does not affect the outcomes in nosocomial MRSA pneumonia. Despite many conflicting results regarding the role of Panton-Valentine leukocidin (PVL) in CA-MRSA infection, high mortality rates of pneumonia by CA-MRSA as a result of necrotizing infections were reported [18, 19]. In our study, the mortality rate in nosocomial pneumonia by PVL-negative ST72 MRSA was similar to that of the ST5/ST239 MRSA. Apart from the virulence of CA-MRSA, this might be explained by inappropriate empiric therapy in the ST72 MRSA group, as the same agents were used in the ST5/ST239 MRSA group (38.9% and 41.8%, respectively), which is known to be major risk for mortality. In a prior study with nosocomial *S. aureus* bacteremia, delayed treatment was found to be an independent predictor of infection-related mortality [20, 21], and a meta-analysis of MRSA bacteremia showed that appropriate empirical antibiotic treatment had a significant survival benefit [21]. Thus, the appropriateness of empiric therapy and underlying severity of illness may be significant factors for mortality in nosocomial pneumonia caused by MRSA, rather than the spe-

cific sequence types.

Female sex predominated in the ST72 MRSA infection (65%). The biased sex discrepancy was more distinct in the ST5/ST239 group (female sex, 19.8%). Underlying neurologic disease and care in ICU predominated in the male gender (25/34, 73.5% and 41/50, 82%), which were identified as independent predictors for ST5/ST239 MRSA infections. This may result in the male predominance in ST5/ST239 MRSA infection, inversely affecting the female predominance in ST72 MRSA. Underlying solid tumors were found to be an independent risk factor for ST72 MRSA infections. In our study, twenty-three patients had underlying solid tumors among those with ST72 MRSA (23/40, 57.5%); of these, 18 patients underwent cancer surgery within a month of infection onset. It is possible that infection by ST72 MRSA occurs as a result of MRSA acquisition after a recent cancer surgery. In surveillance data for SSI from a single center in USA, USA300 genotype, which belongs to CA-MRSA strain, accounted for 57% of MRSA strains [22]. A prospective study in Colombia showed the CA-MRSA presented as primary bacteremia and SSI as result of nosocomial infection [23]. While the pathogenicity has not been fully elucidated, considering that the most superficial incisional SSI develops due to contamination of the surgical site by endogenous flora of the patient [24], and there is an increasing prevalence of colonization and infection by community-genotype MRSA strains in healthcare settings [10, 25], operations for solid tumors may contribute to colonization of community-genotype MRSA and the subsequent development of infections. On the other hand, underlying neurologic disease and care in the ICU were found to be associated with MRSA infections by hospital-genotype strains. These states facilitate HA-MRSA colonization on patients' skin and respiratory system. Once acquired, MRSA colonization can be last months or years, especially during care in the ICU. As a result, it is an inevitable consequence that these patients at risk of MRSA colonization have an increased risk for hospital-genotype associated MRSA infections.

The present study demonstrated that the community-genotype MRSA strain, ST72 that appears to be localized in Korea, has emerged in hospital settings similar to hospital-genotype strains, ST5 and ST239. With an increase in the annual incidence of infections by ST72 MRSA [10], nosocomial infections accounted for 32% of infection cases by ST72-MRSA, and among them, nosocomial pneumonia was the most frequent type of infection. This phenomenon reflects that ST72 MRSA has emerged as a nosocomial pathogen in Korean hospitals,

similar to ST5/ST239 MRSA. The survival of ST72 MRSA in healthcare-settings is multi-factorial, dependent on a series of adhesions, toxins, immune evasion, and other determinants contributing to survival in various conditions [26]. It has been reported that ST72 MRSA showed a relatively lower virulence [9], because it generally does not produce PVL. Complete genome analysis showed that other toxins may not substitute for the lack of PVL in ST72 [27]. Thus, it is supposed that virulence may not contribute to the emergence and increase of ST72 MRSA as a nosocomial pathogen. In addition to virulence, a crucial factor that allows the spread of ST72 MRSA in hospitals may be a tolerance to stressful environments such as hypotonic water or desiccation [28]. Although further study should be performed, such phenotypic resistance to environment stress would contribute the ability to survive and spread in hospital settings.

We note that our study had several other limitations. First, clinical data were collected retrospectively, so some data may be incorrect or missing. Secondly, this study was performed in PVL-negative community-genotype MRSA strains. Although the role of PVL has not been clearly shown in the pathogenesis of the disease, it is presumed that clinical outcomes between PVL-positive and negative genotype strains may be quite different, yet our clinical data were generalized to outcomes caused by infection with PVL-positive CA-MRSA strains. Third, antibiotic susceptibility patterns to non-beta-lactam antimicrobial agents were used to select MRSA candidates of ST72 and ST5/ST239 in previous [10] and current studies. Although multidrug resistance to non-beta-lactam agents is the specific characteristics of ST5 and ST239 MRSA isolates in Korea [29], this approach based on antimicrobial susceptibility results may underestimate a substantial proportion of ST5/ST239 MRSA. Furthermore, such algorithm may affect the results of antimicrobial resistance to non-beta-lactam agents in this study. Despite these limitations, this study is significant in that it is the first study to evaluate the clinical impact of introduction of community-genotype ST72 MRSA into hospitals on outcomes in nosocomial MRSA infections.

In conclusion, pneumonia was the most common type of nosocomial MRSA infection caused by ST72 and ST5/ST239 isolates. Female gender and solid tumors were associated with infections caused by ST72 MRSA. Despite the emergence of a community-genotype strain, ST72 MRSA into hospital settings, ST72 MRSA infections were not associated with adverse outcomes in HA-MRSA infections compared to ST5/ST239.

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## Conflicts of Interest

No conflicts of interest.

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