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ORIGINAL RESEARCH

Characteristics of Virulent ST5-SCC*mec* II Methicillin-Resistant *Staphylococcus aureus* Prevalent in a Surgery Ward

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Objective: To investigate the transmission pathway of a MRSA prevalence in a pancreatic surgery ward in a Chinese teaching hospital.

Methods: Molecular epidemiology investigations were carried out combined PFGE, MLST, SCC*mec* typing and whole-genome sequencing for 20 successive MRSA isolates (2 isolates from the ward environment). Resistance and virulence genes were detected using specific PCR. Bacterial identification and AST were performed using the Vitek 2 Compact System. Clinical data of enrolled cases were retrieved from electronic case records.

Results: From January 2020 to May 2020, successive isolated 20 MRSA strains were clarified to 2 PFGE patterns (A = 19, B = 1) in the ward. Both isolates from environment and patients belonged to sequence type ST5-SCC*mec* II-*spa* type t311. MRSA-related resistance genes *mecA, blaZ, ermA, ant(4')-Ia* and *norA* were found in each clone. All 20 isolates carried *tst, hlg, hla, eta, eap, fnbA* and *seo* virulence genes, other virulence genes such as *sea, sec, seb, seg, sei, sem, sen, ebpS* and *fnbB* were also found in partial stains. All patients had fever symptom, 27.8% were accompanied by diarrhea, 88.9% had undergone surgery or invasive procedures within 30 days. Finally, 94.4% of these patients recovered.

Conclusion: This study confirmed a prevalence of ST5-MRSA-II-t311 clone in a surgery ward, indicated MRSA is a risk factor for post-surgery nosocomial infection and hand hygiene and environmental surveillance should not be ignored.

Keywords: methicillin-resistant*Staphylococcus aureus*, ST5, SCC*mec* II, *spa* type t311, diarrhea, virulence genes

Introduction

Staphylococcus aureus (S. aureus) as one of the most common pathogens in hospitals and the community has been implicated in a variety of clinically important infections ranging from skin infections to invasive infections. The pathogenicity of *S. aureus* is related to various virulence factors. Hemolysin, enterotoxin, leukotoxin and toxic-shock syndrome toxin-1 (TSST-1) are common toxins that can induce severe infection symptoms.[1,2] Additionally, enzymes produced by *S. aureus* destroy host cells and tissues, incapacitating host immune defenses, thereby accelerating the growth and spread of bacteria in host cells. Immune evasion cluster (IEC) genes, such as *sak, chp, scn* and *sea*, are important for isolates to escape the immune response of the human host.[2,3]

S. aureus infections are particularly hard to treat for frequently occurring antibiotic resistance in clinical isolates, among which methicillin-resistant *S. aureus* (MRSA) are the most important clinically.[4] Moreover, MRSA has become one of the most popular healthcare associated pathogens in hospitals worldwide.[5] Nosocomial MRSA infections can lead to increased hospitalization costs and prolonged hospital stay.[6] The popular mode of MRSA transmission is through

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direct contact, usually skin-to-skin contact with the hosts or infected persons, although contact with objects and surfaces may also have effects.[7,8] Nosocomial infections and outbreaks of MRSA are also closely related to hospital environmental contamination.[9] An important means to control the prevalence of MRSA is to identify the epidemic link and cut off the transmission route. Therefore, detecting the molecular typing of MRSA in patients and the environment is of great significance for identifying the correlation between strains and controlling their transmission and outbreaks.

Here, we report a MRSA prevalence identified as ST5-MRSA-II-t311 clone within a surgery ward, two homologous MRSA strains from the ward environment were isolated and further infection prevention and control (IPC) measures were carried out. Meanwhile, the characteristics of MRSA resistance, virulence and clinical symptoms of patients were also investigated.

Materials and Methods

Clinical Information and Strains

The pancreatic surgery ward is located in a large medical center with more than 3000 beds in Jiangsu Province, China. It has more than 30 beds, and most of the patients admitted had undergone surgery. Due to the continuous reporting of MRSA infection cases in this surgical ward, 27 MRSA strains were cultured from 18 patients from January 2020 to May 2020. Among which, 19 stains were aggregation isolated in April 2020 and aroused the attention of hospital infection prevention and control (IPC). During the IPC investigation, totally of 41 swabs from the ward environment, the nasal cavities and hands of medical staff were collected. Only 2 MRSA isolates with same resistant phenotype were found from the environment, one from the bed bar and the other from the caller of 2 patients, respectively. Clinical data were collected, including patient gender, age, invasive medical therapies and treatment outcomes.

Antimicrobial Susceptibility Testing

All these MRSA strains were identified with antimicrobial resistance characteristic by the VITEK-2 compact system (bioMérieux, France) with the operating instructions. Fifteen routine antibiotics were tested. According to the results provided by VITEK-2, strains with positive cefoxitin screening test and oxacillin resistance (oxacillin minimum inhibitory concentration ≥4 μg/mL) were identified as MRSA. ATCC 29213 was used as the quality control stain, and the results were interpreted according to the Clinical and Laboratory Standards Institute guidelines (CLSI M100-S30).

PFGE Analysis

The diversity of MRSA strains was analyzed using the PFGE methodology, as previously described[10]. We used *Salmonella enterica* serotype H9812 as the molecular size marker. Following digestion of chromosomal DNA with *SmaI* (TaRaKa, Dalian, China), the isolates were subjected to agarose gel electrophoresis on a Bio-Rad CHEF Mapper Pulsed Field Electrophoresis System at 14°C for 18 h with switch times of 4s and 40s at 6 V/cm. Computer-assisted analysis was performed using BioNumerics software (Applied Maths, Kortrijk, Belgium) and banding patterns were compared by the Unweighted Pair Group Method using the Arithmetic Mean (UPGMA). Clustering was defined as a group of isolates sharing >90% of pattern similarity.

MLST Typing

The MRSA genomic DNA of the strains was extracted by TIANamp Bacteria DNA Kit (Tiangen Biotech, Beijing, China) according to the manufacturer's instructions. Primers for housekeeping genes were designed as described on the *Staphylococcus aureus* multilocus sequence typing website (https://pubmlst.org/organisms/staphylococcus-aureus/primers) and were synthesized by Nanjing Kingsley Company. PCR was carried out with reference to the protocol, and the amplified products were sent to Nanjing Kingsley Company for sequencing. Chromas software was used to read the sequencing results and observe peak values, and the DNA Star software package was used for sequence editing and correction followed by submission to the website (https://pubmlst.org/bigsdb?Db=pubmlst_Saureus_Seqdef&page=sequenceQuery) for comparison. Then, a number was given to each allele. Sequence types (STs) were assigned according to the combination of 7 allele numbers listed in the online database.

SCC*mec* Typing

The SCC*mec* type was determined using multiplex PCR as previously described,[11] which generated specific amplification patterns for each SCC*mec* structure type (see Supplementary Table 1 for primers). The PCR reaction mixtures contained 12.5 μL Premix Taq^{TM} (Ex Taq^{TM} Version 2.0) (TaRaKa, Dalian, China), 5 μL chromosomal DNA, 4.95 μL oligonucleotide primers (10 mM) and 2.55 μL Ranse-free water (TaRaKa, Dalian, China) in a final volume of 25 μL. PCR conditions were as follows: incubation at 94°C for 5 min, followed by 25 cycles of 94°C for 30s, 56°C for 30s and 72°C for 1 min; 25 cycles of 94°C for 30s, 52°C for 30s and 72°C for 1 min and a final extension step at 72°C for 10 min. Then the PCR products were analyzed by gel electrophoresis.

Resistance and Virulence Genes Assays

PCR was used to detect resistance genes, including: *blaZ, mecA, ermA, ermB, ermC, ermT, msrA, tetK, tetM, tetL, tetO, aac(6')/aph(2''), ant(4')-Ia, aph(3')-III* and *norA*. Virulence genes as follows: cytolysins (*hla, hlg, pvl*), SAgs *(sea, seb, sec, sed, see, seg, seh, sei, sem, sen, seo, tst*), exfoliative toxins (*eta, etb*), adhesins (*bbp, cna, ebpS, fnbA, fnbB, eap*) and genes related to biofilm production (*icaA* and *sasG*) were also detected. Reaction mixtures contained 12.5 μL Premix Taq^{TM} (Ex Taq^{TM} Version 2.0) (TaRaKa, Dalian, China), 2 μL chromosomal DNA, oligonucleotide primers (10 mM) and 8.5 μL Ranse-free water (TaRaKa, Dalian, China) in a final volume of 25 μL. The PCR primers, reaction conditions and references are shown in Supplementary Table 2 [12–14] and Supplementary Table 3.[15] PCR products were analyzed by agarose gel electrophoresis.

Whole Genome Sequencing

Three strains (two strains were isolated from patients, one strain was isolated from ward environment) among the MRSA clusters were selected for further analysis through whole genome sequencing (WGS). The cluster generation and sequencing were performed on Novaseq 6000 S4 platform, using NovaSeq 6000 S4 Reagent kit V1.5. The sequencing data was preliminarily assembled using software Newbler (version 2.8), and the assembled data was corrected by blasR comparison of single molecule sequencing data. The assembled sequence is used for molecular typing such as *spa*, MLST, SCC*mec* typing and analysis of resistance and virulence genes according to the methods previously reported.[16]

Results

Clinical Characteristics

A total of 27 MRSA strains from 18 patients were isolated in the general surgery ward from January 2020 to May 2020, and 1 to 3 samples were obtained from each patient. Different strains from the same patient showed identical resistance phenotypes and belonged to the same PFGE type. Finally, 18 nonrepetitive MRSA isolates recovered from 18 patients along with 2 environmental MRSA strains were selected for further molecular typing, resistance genes analysis and virulence genes detection. The specimens of selected 18 strains included ascites (11/18, 61%), pus (4/18, 22.2%), blood (1/18, 5.6%), sputum (1/18, 5.6%), and feces (1/18, 5.6%). Among the 18 patients, 22.2% (4/18) were female, 77.8% (14/18) were male, and 66.7% (12/18) were ≥60 years old; All patients had fever symptom, 27.8% (5/18) were accompanied with diarrhea, 88.9% (16/18) had undergone surgery or invasive procedures within 30 days. Finally, 94.4% (17/18) of these hospitalized patients finally recovered, and only 1 died (Table 1).

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility tests were performed on all MRSA strains, and their susceptibility profiles are listed in Table 2. All MRSA strains exhibited 100% resistance to cefoxitin, penicillin, oxacillin, ciprofloxacin, levofloxacin, moxifloxacin, erythromycin and clindamycin. In addition, the resistance rate of tetracycline was 95%, and only 1 of these 20 MRSA strains was sensitive to tetracycline. Furthermore, these 20 isolates were 100% sensitive to gentamicin, quinupristin/dafopristin, linezolid, vancomycin, tigecycline, rifampicin and trimethoprim-sulfamethoxazole.

Table 1 Characteristics of the 18 MRSA Isolates from Hospitalized Patients

Item	Group	Number	Ratio
Specimen Origin	Ascites	11	61.0%
	Pus	4	22.2%
	Blood	1	5.6%
	Sputum	1	5.6%
	Faeces	1	5.6%
Gender	Female	4	22.2%
	Male	14	77.8%
Age	≤60 years old	6	33.3%
	>60 years old	12	66.7%
Symptoms	Fever	18	100%
	Diarrhea	5	27.8%
Risk factor	Surgical/invasive procedures	16	88.9%
Outcomes	Recovered	17	94.4%
	Death	1	5.6%
No. of total	Total	18	

Table 2 Antimicrobial Susceptibilities Among the 20 MRSA Isolates

Antibiotics	R	S	MIC Range (μg/mL)	Resistance Rate (%)
Penicillin	20	0	≥0.5	100
Oxacillin	20	0	≥4	100
Gentamicin	0	20	≤4	0
Ciprofloxacin	20	0	≥8	100
Levofloxacin	20	0	≥8	100
Moxifloxacin	20	0	≥4	100
Erythromycin	20	0	≥8	100
Clindamycin	20	0	≥8	100
Quinupristine/dafopristine	0	20	≤0.5	0
Linezolid	0	20	1–4	0
Vancomycin	0	20	≤2	0
Tetracycline	19	1	≥8 (R),≤1 (S)	95
Tigecycline	0	20	≤0.25	0
Rifampicin	0	20	≤0.5	0
Trimethoprim-sulfamethoxazole	0	20	≤0.5	0

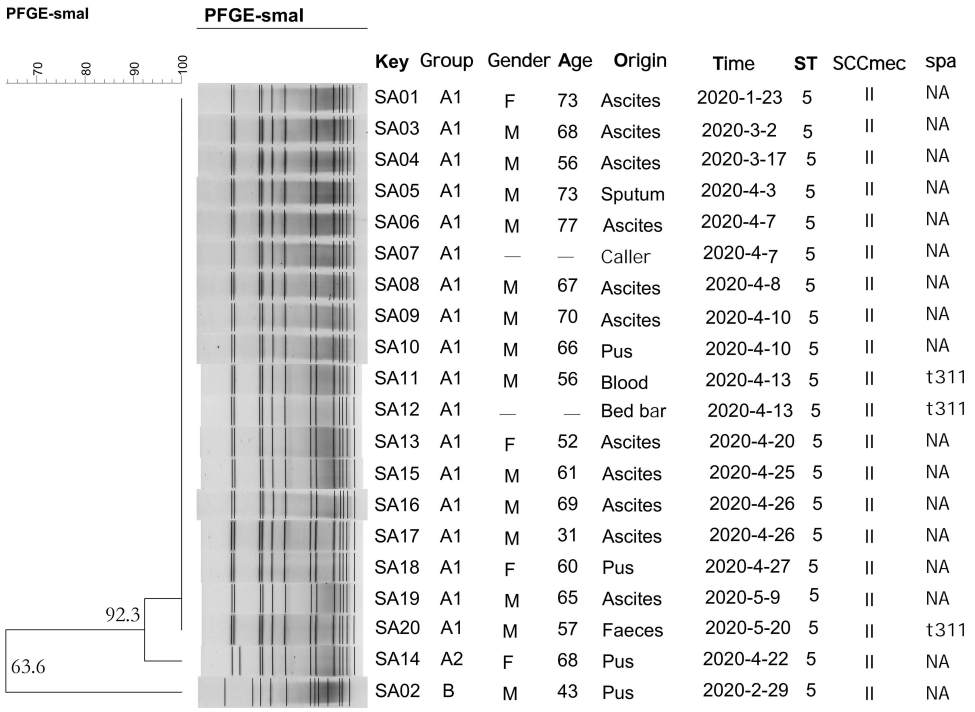
Abbreviations: R, resistant; S, susceptible; MIC, minimal inhibitory concentration.

Molecular Genotyping

Dendrogram of PFGE patterns and molecular genotyping results of each strain were summarized and shown in Figure 1. PFGE results showed that 18 clinical strains and 2 environmental strains were divided into 2 types, 19 strains belong to type A (18 strains of type A1, including 2 environmental strains, and 1 strain of type A2), and 1 strain belong to type B. All of these MRSA strains were identified as ST5 (1,4,1,4,12,1,10), CC5, SCC*mec* II. Results of selected 3 strains (PFGE type A1) WGS analysis belong to ST5-MRSA-II-t311 (*spa* type repeats succession: 26–23-17-34-20-17-12-17-16).

Resistance Genes Detection

Most resistance genes of each MRSA isolates were detected. Among which, 100% isolates contain *blaZ, mecA, ermA, ant(4')-Ia* and *norA* genes, positive rate of *tetK* and *aac(6')/aph(2")* was 95%, *aph(3')-III, msrA* and *tetL* was 5%. Representative PCR results are shown in Figure 2A. These 20 strains showed 4 different resistance gene



Key	Group	Gender	Age	Origin	Time	ST	SCCmec	spa
SA01	A1	F	73	Ascites	2020-1-23	5	II	NA
SA03	A1	M	68	Ascites	2020-3-2	5	II	NA
SA04	A1	M	56	Ascites	2020-3-17	5	II	NA
SA05	A1	M	73	Sputum	2020-4-3	5	II	NA
SA06	A1	M	77	Ascites	2020-4-7	5	II	NA
SA07	A1	—	—	Caller	2020-4-7	5	II	NA
SA08	A1	M	67	Ascites	2020-4-8	5	II	NA
SA09	A1	M	70	Ascites	2020-4-10	5	II	NA
SA10	A1	M	66	Pus	2020-4-10	5	II	NA
SA11	A1	M	56	Blood	2020-4-13	5	II	t311
SA12	A1	—	—	Bed bar	2020-4-13	5	II	t311
SA13	A1	F	52	Ascites	2020-4-20	5	II	NA
SA15	A1	M	61	Ascites	2020-4-25	5	II	NA
SA16	A1	M	69	Ascites	2020-4-26	5	II	NA
SA17	A1	M	31	Ascites	2020-4-26	5	II	NA
SA18	A1	F	60	Pus	2020-4-27	5	II	NA
SA19	A1	M	65	Ascites	2020-5-9	5	II	NA
SA20	A1	M	57	Faeces	2020-5-20	5	II	t311
SA14	A2	F	68	Pus	2020-4-22	5	II	NA
SA02	B	M	43	Pus	2020-2-29	5	II	NA

Figure 1 Dendrogram of PFGE patterns from 20 MRSA strains.

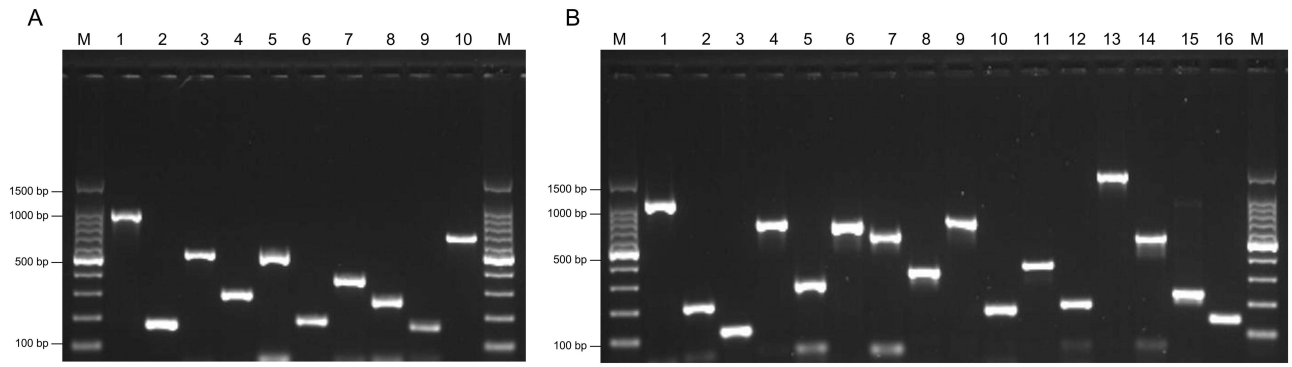


Figure 2 Representative PCR results for resistance genes and virulence genes of MRSA isolates. (**A**). M, marker, lane 1 to lane 10 represent the PCR positive results of resistance genes *mecA, blaZ, aph(3')-III, ant(4')-Ia, aac(6')/aph(2"), ermA, tetK, tetL, msrA* and *norA* respectively; (**B**). M, marker, lane1 to lane16 represent the PCR positive results of virulence genes *hlg, hla, sea, seb, sec, seg, sei, sem, sen, seo, tst, ebpS, fnbA, fnbB, eap* and *eta* respectively.

profiles, and the dominant resistance gene profile (17/20, 85%) contained 7 resistance genes, including *mecA, blaZ, aac(6')-aph(2"), ant(4')-Ia, erm(A), tet(K), norA*. Among these strains, the largest number of resistance genes was 9 (Table 3). More resistance genes were found in 3 selected stains after WGS analysis, such as *aadD* and *ant(9)-Ia*.

Virulence Genes Detection

The frequencies of virulence genes were *hlg, hla, tst, seo, eta, eap* and *fnbA* (100%), *sea* (95%), *ebpS* (90%), *sec* (85%), *seb* and *seg* (75%), *sei* (45%), *sem* (35%), *sen* (25%) and *fnbB* (5%), respectively, none of which contained *sed, see, seh, pvl, etb, bbp, cna, icaA* and *sasG* genes. Representative PCR results are shown in Figure 2B. The 20 strains exhibited 11 different virulence gene profiles, and 85% of the 20 strains had more than 10 virulence genes (Table 4).

Table 3 Resistance Gene Profiles Among 20 MRSA Isolates

Resistance Genes	Resistance Gene Profiles	Patients	Ratio
5	*mecA, blaZ, ant(4')-Ia, erm(A), norA*	1	0.05
7	*mecA, blaZ, aac(6')-aph(2''), ant(4')-Ia, erm(A), tet(K), norA*	17	0.85
8	*mecA, blaZ, aac(6')-aph(2''), ant(4')-Ia, erm(A), msr(A), tet(K), norA*	1	0.05
9	*mecA, blaZ, aac(6')-aph(2''), aph(3')- III, ant(4')-Ia, erm(A), tet(K), tet(L), norA*	1	0.05

Table 4 Virulence Gene Profiles Among 20 MRSA Isolates

Virulence Genes	Virulence Gene Profiles	Patients	Ratio
9	*hlg, hla, tst, eta, sea, seo, eap, ebpS, fnbA*	3	0.15
10	*hlg, hla, tst, eta, sea, sec, seg, seo, eap, fnbA*	1	0.05
10	*hlg, hla, tst, eta, sea, sec, seo, eap, ebpS, fnbA*	1	0.05
11	*hlg, hla, tst, eta, sea, seb, sec, seo, eap, ebpS, fnbA*	2	0.10
11	*hlg, hla, tst, eta, sea, seb, sec, seg, seo, eap, fnbA*	1	0.05
11	*hlg, hla, tst, eta, sea, seb, seg, seo, eap, ebpS, fnbA*	1	0.05
12	*hlg, hla, tst, eta, sea, seb, sec, seg, seo, eap, ebpS, fnbA*	3	0.15
13	*hlg, hla, tst, eta, sea, seb, sec, seg, sei, seo, eap, ebpS, fnbA*	2	0.10
14	*hlg, hla, tst, eta, sea, seb, sec, seg, sei, sem, seo, eap, ebpS, fnbA*	*2*	*0.10*
15	*hlg, hla, tst, eta, sea, seb, sec, seg, sei, sem, sen, seo, eap, ebpS, fnbA*	*3*	*0.15*
15	*hlg, hla, tst, eta, seb, sec, seg, sei, sem, sen, seo, eap, ebpS, fnbA, fnbB*	*1*	*0.05*

Discussion

S. aureus is a key pathogen of nosocomial infection, especially MRSA, which poses a great challenge to health due to its multidrug resistance, prevalence and refractoriness.[17–23] *Staphylococcus aureus* is the most common pathogen causing surgical site infections (SSIs).[24] MRSA can survive for a long time in nature, increasing the risk of nosocomial infection of patients undergoing complex surgical procedures.[25–27] Previous reports unfold that methicillin-resistant *S. aureus* (MRSA) accounts for a high proportion of isolates in SSIs,[24,28–30] the possible cause is related to MRSA colonization.[31–35] Furthermore, advanced age and invasive operations have been confirmed as important risk factors for MRSA colonization.[36–41] From our investigation, 66.7% (12/18) of patients were ≥60 years old and 88.9% (16/18) had undergone surgery or invasive procedures within 30 days, all these may increase the risk of MRSA colonization and subsequent infection. As a pancreatic surgery ward, most patients underwent abdominal surgery or invasive operation. Of the 18 patients, most infections were surgical-site-related infections, in which, 11 infection samples were ascites and 4 were pus. Otherwise, health-care staff hand hygiene and ward environmental maintenance are important for infection control. In this study, two homologous MRSA strains from the ward environment were isolated, the transmission routes of MRSA in relation to environment should not be ignored. Indeed, the MRSA prevalence was successfully controlled after comprehensive infection control measures were applied in the ward.

The predominant sequence type of MRSA in this study is ST5-II-t311, which belongs to clonal complex 5 (CC5). ST5-MRSA-II are also known as New York/Japan clone, UKEMRSA-3, USA100, Rhine-Hesse Epidemic Strain, Irish AR7.3, AR7.4, AR7.11 and Canadian MRSA-2 clone.[42] Previous reports point out that ST5-SCC*mec* II is one of the most common types of hospital-associated MRSA isolate, widely prevalent in Asia, Europe, Africa, North and South America.[43–45] Furthermore, ST5-SCC*mec* II-t311 has also been reported as the predominant clone and spread between different hospitals in some areas of China,[46,47] to our knowledge, here is the first report of ST5-SCC*mec* II-t311 prevalence in Jiangsu Province.

A multicentre longitudinal study in China reported that CC5 harbored more adhesion-associated genes (*fnbA* and *sdr*) and superantigenic toxin gene *tst*, while ST5 often had *sec-sell*, exfoliative toxin encoding genes *eta/etb* were extremely rare and only detected in CC121.[48] ST5-MRSA-II-t311 strain reported by Wu et al contained *tst* and many enterotoxin genes including *sec, seg, sei, sel, sem, sen, seo* and *seu*. From our results, 20 MRSA strains in our investigation also

found virulence genes *tst, sec, seg, sei, seo* in different frequencies, but the *sel and seu genes* were not detected. While exfoliative toxin A gene (*eta*) was contained in each strain never reported in ST5-MRSA-II-t311 previously. In addition, this cluster of ST5-MRSA-II-t311 strains had high rate of *sea* gene (95%), which is more common in ST239; and high rate of *seb* gene (75%), which is more common in CC59.[48]

MRSA isolates were characterized by multiple drug resistance; there are slight differences in the resistance characteristics of MRSA ST5 isolates among different regions in China. MRSA ST5 isolates in Wuhan showed high resistance rate to erythromycin, clindamycin, ciprofloxacin, levofloxacin, moxifloxacin, tetracycline and gentamicin.[49] In shanghai, MRSA ST5 strains show high rate of resistance to penicillin, cefazolin, cefoxitin, erythromycin, fosfomycin, gentamicin, levofloxacin.[50] In Zhejiang, MRSA ST5 strains show high rate of resistance to erythromycin, clindamycin, ciprofloxacin, levofloxacin, tetracycline, and but exhibit low rate of resistance to linezolid, vancomycin, trimethoprim-sulfamethoxazole, rifampicin, tigecycline and gentamicin.[51] Similar to MRSA ST5 isolates in Zhejiang, all MRSA isolates in this study exhibited extremely high resistance rate of cefoxitin, penicillin, oxacillin, erythromycin, clindamycin, ciprofloxacin, levofloxacin, moxifloxacin and tetracycline, but all showed sensitivity to gentamicin, quinupristin/dafopristin, linezolid, vancomycin, tigecycline, rifampicin and trimethoprim-sulfamethoxazole, which suggested their potential use for fighting infections with MRSA strains. In this study, most prevalent ST5-MRSA-II-t311 stains contained *blaZ, mecA, ermA ant(4')-Ia, norA, tetK* and *aac(6')/aph(2')*, little difference to previously reported ST5-MRSA-II-t311 in resistance genotype.[47]

Conclusion

There is a prevalence of ST5- MRSA-II-t311 in a pancreatic surgery ward, and environmental pollution is an important transmission factor. Patients post abdominal surgery or invasive operation should enhance MRSA infection prevention and control, especially for elder patients.

Data Sharing Statement

The clean data of whole-genome sequence of 3 selected MRSA strains can be obtained from the corresponding author.

Institutional Review Board Statement

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) (Approval number.2022-SR-286).

Informed Consent Statement

The study received hospital IRB approval (Approval number.2022-SR-286), and the requirement for written informed consent was waived because of the retrospective study design and the patients' original identification was anonymized.

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Disclosure

All authors report no conflicts of interest relevant to this article.

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