Genetic diversity of healthcare-associated methicillin-resistant Staphylococcus aureus isolates from Southern Iran

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Received: December 10, 2020 • Accepted: May 6, 2021
Published online: June 2, 2021

ABSTRACT
Staphylococcus aureus is a common pathogen causing hospital infections. The increasing rate of healthcare-associated infections caused by methicillin-resistant Staphylococcus aureus (MRSA) in developing countries has led to many public health problems. This study aimed to investigate the molecular epidemiology as well as the antibiotic resistance pattern of clinical isolates of MRSA from Southern Iran. A total of 135 S. aureus isolates were collected from the patients referred to three hospitals in South Iran. The phenotypic and genotypic diagnosis of MRSA isolates was performed by disk diffusion and PCR methods, respectively. The antibiotic resistance pattern for MRSA isolates was performed using Kirby–Bauer method. The molecular epidemiology of isolates was performed by MLST, Spa typing and SCCmec typing. From 135 S. aureus isolates, 50 (37%) MRSA strains were detected from which two different sequence types including ST239 and ST605 were identified. SCCmec type III was the most common profile (50%) and t030 was the predominant spa type (48%) among the strains. The MRSA isolates had the highest resistance to penicillin (100%), tetracycline (88%), levofloxacin (86%), ciprofloxacin (84%), erythromycin (82%), gentamicin (80%), and clindamycin (78%). The results of this study show that the most common genetic type among the MRSA isolates was ST239-SCCmec III/t030. The rapid and timely detection of MRSA and the administration of appropriate antibiotics according to the published antibiotic resistance patterns are essential. Furthermore, the continuous and nationwide MRSA surveillance studies are necessary to investigate clonal distribution and spreading of MRSA from community to hospitals.

KEYWORDS
MRSA, meca gene, SCCmec typing, Spa typing, MLST

INTRODUCTION
Staphylococcus aureus is a Gram-positive bacterium causing a wide variety of suppurative infections in both humans and animals. In humans, it is one of the most common causes of skin and soft tissue infections as well as bacteremia. S. aureus is an opportunistic pathogen carried by approximately 30–50% of the human population worldwide [1]. The anterior nares are the primary niche for S. aureus, although the throat and perineum are also important reservoirs [2]. Moreover, methicillin-resistant Staphylococcus aureus (MRSA)
has emerged as a major threat to human health. MRSA strains are generally classified into healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) and community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), which differ with respect to several characteristics in addition to the source of infection [3]. The infections are predominantly due to healthcare-associated (HA) strains linked to the advanced age, comorbidities, surgical procedures or indwelling medical devices [4]. MRSA isolates are resistant to the majority of the antibiotics commonly used to treat *S. aureus* infections in humans. It is a significant cause of severe nosocomial infections and a major public health concern globally [5, 6]. One of the interesting conclusions that have emerged from large international surveillance studies using molecular typing techniques is that a relatively few MRSA clones have been responsible for a disproportionately large fraction of all MRSA disease worldwide [7-9]. Modern MRSA has evolved from several successful clonal lineages of methicillin-susceptible *S. aureus* strains via acquisition of a mobile genetic element called staphylococcal cassette chromosome mec (SCCmec). This element contains the mecA gene, which encodes penicillin-binding protein 2 (PBP2) with significantly reduced affinity for β-lactams. Other mec genes such as mecB and mecC can also lead to methicillin resistance in *S. aureus* [10]. Increased emergence of multidrug resistance among MRSA strains has become a major concern in the hospital environment, as it invokes a tremendous financial burden and enhanced morbidity and mortality due to difficulties in treatment of systemic infections [11]. Genotyping data from large international studies have shown that a limited number of major clones of MRSA display an enhanced propensity to spread and cause opportunistic human infections in various parts of the world [7]. There are some studies reporting the prevalence of HA-MRSA in some areas of Iran, including Tehran [12], Isfahan [13], the West [14], and Southwest [15] of the country. However, due to lack of information on the prevalence and molecular epidemiology of MRSA in the South of Iran, the present study was performed. The aim of this study was to investigate the antibiotic resistance pattern and evaluate the molecular epidemiology of clinical isolates of HA-MRSA from three hospitals in the Southern Iran.

## MATERIALS AND METHODS

### Sample collection and bacterial isolates

During six months (from December 2018 to May 2019), a total of 135 *S. aureus* isolates, were collected from different clinical samples of patients referred to three hospitals in the South of Iran, one of which located in Bushehr city (Shohadaye Khajie Fars hospital), and two others in Bandar Abbas city (Khalije Fars and Shahid Mohammadi hospital). The majority of the isolates was recovered from blood and wound samples (Table 1). In order to identification, the isolates were cultured on Blood Agar (Merck, Germany) medium, and then single colony was inoculated on Mannitol Salt Agar (Merck, Germany) at 37 °C for 24 h. The suspicious colonies were subjected to biochemical tests including catalase, coagulase, clumping factor, DNase, thermo-stable nuclease, as well as Gram staining. Then, all isolates were also evaluated for the presence of the *sa442* gene by polymerase chain reaction (PCR) using the forward: 5’-AACTTTGTCGTTACACGATATTCTTCACG-3’ and reverse: 5’-CGTATGAGATTTCAGTAGATAATACAAC-3’ primers [16]. The *S. aureus* ATCC 29213 strain was used as the reference strain [17]. Finally, the colonies, after approval, were stored in Luria Bertani Broth (LB) supplemented with 20% Glycerol (Merck, Germany) and kept at −80 °C until use.

# MRSA detection

Methicillin resistance was detected by disk diffusion testing with an oxacillin 10 μg disk (Mast, UK) and a cefoxitin 30-μg disk (Mast, UK), in accordance with the guidelines issued by the Clinical and Laboratory Standards Institute (CLSI). The minimum inhibitory concentrations (MICs) of the isolates were also determined for oxacillin using the E-test system (bioMérieux, Marcy l’Etoile, France). *S. aureus* ATCC 29213 strain was used as a positive control and distilled water as a negative control [18]. The DNA of strains was extracted using an extraction kit prepared by Biofluxbior (South Korea), according to the manufacturer’s instructions. The presence of the *meca* gene was evaluated using the PCR amplification. *meca* gene was amplified by two specific primers: *meca* F (5’-TCCAGATTACAACCTGACCAGG-3’) and *meca* R (5’-CCACTTCATATCGGAGAGGAG-3’).

<table>
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<tr>
<th>Department</th>
<th>Clinical sample isolate no. (%)</th>
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<tr>
<td>Blood</td>
<td>Urine</td>
<td>Absseses</td>
</tr>
<tr>
<td>Surgery</td>
<td>5 (10%)</td>
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<td>0 (0%)</td>
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<td>Neurology</td>
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<td>2 (4%)</td>
</tr>
<tr>
<td>ICU</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (36%)</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of MRSA strains isolated from patients.
TTGTAACG -3') as previously described, and S. aureus ATCC 25923 strain was used as a positive control [16].

The MRSA infection, labeled as HA-MRSA if patients were hospitalized >48 h prior to the current infection (i.e., patient was not infected with MRSA at the time of hospitalization but culture and infection were identified >48 h after admission) [19].

**Antimicrobial susceptibility testing**

Antimicrobial resistance patterns were determined for all isolates using a panel of 14 antibiotic disks (Table 2) with Kirby–Bauer method, according to the CLSI instruction. The MIC to vancomycin was determined by E-test (bioMérieux). S. aureus ATCC 25923 was used as a control strain in the antibacterial susceptibility testing. Intermediate sensitivity was scored as resistance. Enterococcus faecalis ATCC 29212 and Enterococcus faecium BM4147 were used as controls for vancomycin susceptibility and vancomycin resistance, respectively [18].

**Conventional Spa typing**

Spa typing of strains was performed by amplification of variable short sequence repeat (SSR) X region of the spa gene using the primers forward: 5'-AGACGATCCTTGCAGTGGAC-3', and reverse: 5'-GCTTTGCAATGTCATTATCGT-3', as described previously by Shopsin et al. [20]. A ready-to-use PCR master mixture (SinaClone, Tehran, Iran) was used in a final volume of 50 µL, consisting of 10 µL of master mix, 0.5 µL of forward primer and 0.5 µL of reverse primer, 38 µL of distilled water, and 1 µL of DNA template in a 0.5-µL microcentrifuge tube. PCR program was carried out as described by Japoni-Nejad et al. [21]. The sequences obtained were subjected to spa repeat analysis and spa typing using the SpaServer (http://www.spaserver.ridom.de).

**Conventional Multi-locus sequence typing (MLST)**

The sequence type (ST) for each MRSA isolate was characterized by MLST as described by Enright et al. [22]. The test was carried out by sequencing an internal fragment of seven unlinked housekeeping genes to identify the following allelic profiles: phosphate acetyltransferase (pta), carbamate kinase (arcC), triosephosphate isomerase (tpi), shikimate dehydrogenase (aroE), guanylate kinase (gmk), acetyl-coenzyme A acetyltransferase (ptaL), and glycerol kinase (glp). The entire PCR products were purified and then sequenced (Bioneer Co., Korea). Finally, STs were obtained using the S. aureus MLST database (http://www.mlst.net).

**Screening for of SCCmec elements**

The presence of SCCmec genes in S. aureus isolates was determined by the method developed previously by Ghaznavi-Rad et al. [16].

**RESULTS**

A total of 50 strains (37%) of MRSA were detected over a six-month period all of which had the mecA and sa442 genes and were resistant to cefoxitin. The antibiotic resistance pattern of these strains is shown in Table 2.

Out of the 50 MRSA isolates, 47 belonged to ST239 and 3 isolates to ST605, identified by MLST. Also nine different spa types were identified including t030 (n = 24, 48%), t037 (n = 13, 26%), t7685 (n = 2, 4%), t459 (n = 4, 8%), t275 (n = 3, 6%), t790 (n = 1, 2%), t701 (n = 1, 2%), t325 (n = 1, 2%), and t122 (n = 1, 2%). Moreover, four different types of SCCmec were identified, including type I (n = 5, 10%), type II (n = 18, 36%), type III (n = 25, 50%), and type IV (n = 2, 4%). SCCmec type III was the most common profile (50%) and t030 was the predominant spa type (48%) among the strains. The detailed results are shown in Table 3 and the association among SCCmec types, spa types, and sequence types is shown in Table 4.

**DISCUSSION**

In our study, the mecA gene was found in 50 isolates (37%). The prevalence of this gene has been reported in other regions of Iran among HA-MRSA with different frequencies [13, 15, 23]. For example, in the Southwest, it has been reported to be 34% and 32% by Mousavian et al. [24] and Tajik et al. [12], respectively. This rate in the West [14] and central [21] Iran was reported to be 39% and 32%, respectively. These results indicate an almost similar prevalence of MRSA in the South to West of Iran, as well as the predominance of similar molecular types in these regions.

There is a continuous increase in the global prevalence of MRSA in European countries. In Belgium and Spain, 19% and 29% of the S. aureus strains were methicillin-resistant, respectively [5, 9]. However, the prevalence of the mecA gene in our study was comparable to previously studies reported from other countries including 36.6% in Greece, 46% in Israel, 38.3% in Italy, and 45.76% in the Philippines [25]. The differences in the distribution of the mecA gene can be...
explained by the various studied populations or by the
different types of the clinical specimens.

Our study showed that the prevalence of MRSA and
resistance to antibiotics used in this study was higher in the
infectious disease (32%), surgical (30%), and neurological
(20%) sections rather than other wards. In the study con-
ducted by Khosravi et al. in Alhz, most MRSA isolates were
detected from hospitalized patients in intensive infectious
disease, intensive care unit (ICU), and outpatient (OP) de-
partments [23]. The potential risk of MRSA in the intensive

<table>
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<th>SpaType</th>
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<td>Surgery</td>
</tr>
</tbody>
</table>

infectious disease and surgical units has been considered continuously due to the greater problems of patients and the present study has reported an abundance of these strains in this section. Furthermore, intensive infectious disease departments are considered to be high risk areas for spreading of MRSA infections.

The present study found that the resistance of *S. aureus* to cefoxitin in the South of Iran was very high, and all MRSA isolates were recognized as multidrug resistant. Resistance to, erythromycin, clindamycin, tetracycline, gentamicin, levofloxacin, and ciprofloxacin was observed in more than 70% of MRSA isolates. Furthermore, all MRSA isolates were sensitive to vancomycin and quinupristin/dalfopristin. In the study of Mousavian et al., the highest sensitivity of MRSA was to vancomycin and linezolid and the lowest one was to clindamycin [24]. In 2010, Javan et al. isolated a total of 150 samples of *S. aureus* from hospitalized patients in Tehran hospitals, of which 68 strains (45%) were MRSA strains all of which were resistant to penicillin, amikacin, kanamycin, ciprofloxacin, erythromycin, gentamicin, tetracycline, and clindamycin [26].

In this study, *SCCmec* typing recognized 50% of MRSA isolates as type III. *SCCmec* typing was performed in other regions of Iran, and in all of these published studies, the most frequent *SCCmec* type among nosocomial MRSA strains was type III [27–31]. The frequency of *SCCmec* type III was reported as 74.3% in Shiraz [29], 98% in Tehran [28, 32], 69.8% in Tabriz [27], 91% in Isfahan [31], and 45% in the West provinces of Iran [30]. One of the benefits of *SCCmec* typing of MRSA isolates is differentiation of antibiotic susceptibility patterns. Therefore, we investigated the association between *SCCmec* types and antibiotic resistance patterns. According to our results, most MRSA isolates with type III *SCCmec* were resistant to gentamicin, clindamycin, and ciprofloxacin, while all isolates were resistant to penicillin. These findings are similar to those of Japoni et al. [29] in Shiraz, although they found higher rates of tetracycline resistance than we did.

According to the data, MRSA isolates in the hospital (HA-MRSA) could be CA-MRSA isolates. In the present study, two isolates from the neurology department were *SCCmec* type IV with similar genetics which indicates the dissemination of CA-MRSA in this department. Some researchers have reported an increase in the prevalence of MRSA strains with *SCCmec* type IV occurring in hospital settings [33, 34]. Valsesia et al. reported *SCCmec* type IV as the most frequent type (76.6%) among HA-MRSA strains in Switzerland. Some evidences indicate that the replication of MRSA strains with *SCCmec* type IV is more rapid than the strains with *SCCmec* type II/III, perhaps due to their enhanced fitness compared to *SCCmec* type II/III strains [35]. Our results are similar to those of the previous studies conducted in Iran and other parts of the world [10, 25].

According to our results from *spa* typing, t030 (48%), and t037 (26%), were recognized as the most common *spa* types. Moreover, this study showed that the *SCCmec*III-t030 and *SCCmec*II-t037 are spread in the South Iran. These *spa* types were previously reported from Saudi Arabia, China, Iran, as well as among HA-MRSA isolates found in Europe, America, and other regions of Asia [36–39]. Similar to our results, *SCCmec* type III was the most common type (91.4%) and t030 was the most common *spa* type (85.1%) among MRSA strains isolated from Turkish hospitals [24, 40].

In our study, 94% of MRSA isolates were ST-239. The review of the literature reveals that the multi-resistant ST239 clone is an important HA-MRSA clone in Europe, United States, and some Asian countries including Kuwait and Malaysia [38]. Therefore, the presence of ST239-*SCCmec* III/037 in our healthcare settings might be attributed to neighboring regions. In our study, ST239-*SCCmec* III/030 and ST239-*SCCmec* II/037, had the highest prevalence in the surgical and infectious diseases departments. Furthermore, t275, unlike other types, was reported with ST605 in the infectious diseases and surgical departments.

### Table 4. Comparison among different types of MRSA isolates

<table>
<thead>
<tr>
<th><em>spa</em> types</th>
<th><em>SCCmec</em> I</th>
<th><em>SCCmec</em> II</th>
<th><em>SCCmec</em> III</th>
<th><em>SCCmec</em> IV</th>
<th>Total</th>
<th>ST 239</th>
<th>ST 605</th>
</tr>
</thead>
<tbody>
<tr>
<td>t030</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>18 (36%)</td>
<td>0 (0%)</td>
<td>24 (48%)</td>
<td>24 (48%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t037</td>
<td>2 (4%)</td>
<td>6 (12%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>13 (26%)</td>
<td>13 (26%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t7685</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t459</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t725</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>t790</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t701</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t325</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>t122</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (10%)</td>
<td>18 (36%)</td>
<td>25 (50%)</td>
<td>2 (4%)</td>
<td>50 (100%)</td>
<td>47 (94%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

### CONCLUSION

In conclusion, the results of the present study indicate that the most common genetic type among MRSA isolates was ST239-*SCCmec* III/030. It is recommended to use quinupristin/dalfopristin, teicoplanin, netilmicin, or vancomycin, or a combination of these antibiotics in treatment of the diseases caused by MRSA according to the treatment protocols. The rapid and timely detection of MRSA, as well as the administration of appropriate antibiotics according to the published antibiotic resistance pattern of *S. aureus*, is essential. Continuous and nationwide MRSA surveillance...
studies are necessary to investigate clonal distribution and spreading of MRSA strains from community to hospitals.

Conflict of interest: None.

Funding: None.

REFERENCES


