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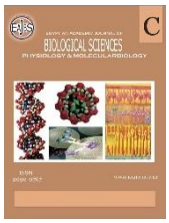

Factors Associated With The Nasal Carriage Rate of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and the Molecular Detection of the mecA Gene Among Athletes

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common cause of infectious diseases among athletes, globally. There is very little data on the prevalence of these strains in Kurdistan region of Iraq, and none on the carriage among athletes. This study aimed to determine the prevalence and associated risk factors with MRSA and molecular detection of *mec*A gene among athletes. This study was conducted in Zakho City, Kurdistan Region, Iraq, nasal swabs were collected from 510 participants among various types of athletes following the completion of a questionnaire. Traditional bacteriological methods were used for the isolation of MRSA *Staphylococcus aureus* and oxacillin susceptibility test was performed as a preliminary step in MRSA identification. Then MRSA isolates were further analysed by PCR in order to detect the *mec*A gene. Out of 510 participating athletes, MRSA nasal carriage rate was 8.04% (41/510). The highest rate of infection was observed among football (10.71%) followed by gym (9.39%), but there was no significant difference between the various types of sports with MRSA (p=0.41). There was a significant relationship between gender and type of athletes (p=0.018). Nasal colonization of MRSA was significantly influenced by body mass index (p=0.006), previous use of antibiotics (p=0.02), previous surgical operation (p=0.002), duration of training/ day (p=0.025) and number of training sessions/week (p=0.047). *mec*A gene was then confirmed in 38/40 (95%) MRSA isolates. The MRSA infection rate in our study was higher compared to other studies conducted elsewhere and was significantly higher among male athletes; this was associated with personal hygiene and inappropriate use of antibiotics. More studies were recommended on molecular analysis of virulent genes associated with MRSA in athletes.

INTRODUCTION

Staphylococcus aureus (S. aureus) is the most infectious *Staphylococcus* species and the most frequent bacterium found in hospital-acquired infections (Kong Eric and Johnson Jennifer, 2016). It is also the second most prevalent pathogen among patients in outpatient clinics. *S. aureus* can cause infections ranging from moderate to severe, including skin and soft tissue infections (SSTIs) and sepsis (Kong Eric and Johnson Jennifer, 2016). Furthermore, it may result in toxin-mediated infections, which have been associated with high mortality.

Although Community-associated Methicillin-resistant *Staphylococcus aureus* infections (CA-MRSA) seem to occur rarely, their prevalence has increased in Europe and ranges from less than 0.5 to 15% (Otter and French, 2010). Molecular identification of Methicillin-resistant *Staphylococcus aureus* (MRSA) is an essential method for epidemiological surveillance and the establishment of infection control measures aimed at preventing the emergence and spread of epidemic clones within hospitals, from community to hospitals, and within the community (Shady *et al.*, 2015, Rasheed and Hussein, 2020a).

S. aureus including MRSA has become increasingly problematic within athletic settings and it has been previously well-documented (Grosset-Janin *et al.*, 2012). The majority of research on *S. aureus* infections in athletes has been undertaken in the United States, United Kingdom, Germany, and Japan (Cohen, 2008, Grosset-Janin *et al.*, 2012). For CA-MRSA outbreaks, skin-to-skin contact and inadequate hygiene are a major risk factor for infection. Inmates, military people, and sports groups are among the categories at risk of acquiring CA-MRSA (Tenover and Goering, 2009). CA-MRSA outbreaks are also linked to sports involving little-to-no physical contact but the sharing of equipment, such as fencing, martial arts, cross-country running, volleyball, basketball, football, baseball, and weightlifting (Cohen, 2008). Additional risk factors for S. aureus infection in athletes include higher body mass, use of equipment that abrades the skin, and poor sanitation (sharing of personal items, inability to cover up skin sores) (Grosset-Janin *et al.*, 2012).

Several studies have been performed in the Kurdistan region study MRSA carriage among hospitals and communities (Hussein *et al.*, 2019), students (Habeeb *et al.*, 2014) and refugees (Rasheed and Hussein, 2020b), and preoperative patients (Abdulkareem W, 2020), while no studies have been conducted among athletes. Therefore, the aims of the study were to determine the prevalence of MRSA in various types of athletes, the association of MRSA carriage with particular risk factors among athletes, and molecular analyses of *mec*A gene.

MATERIALS AND METHODS

Study Design And Periods:

This cross-sectional study was conducted between September 2021 and February 2022. A total of 510 nasal swabs were collected from different athletes in Zakho city, Kurdistan Region, Iraq. The age of participants ranged from 14 to 55 years. Samples were collected from different contact sports including gyms, football, boxing and university student-athletes (Fig. 1).

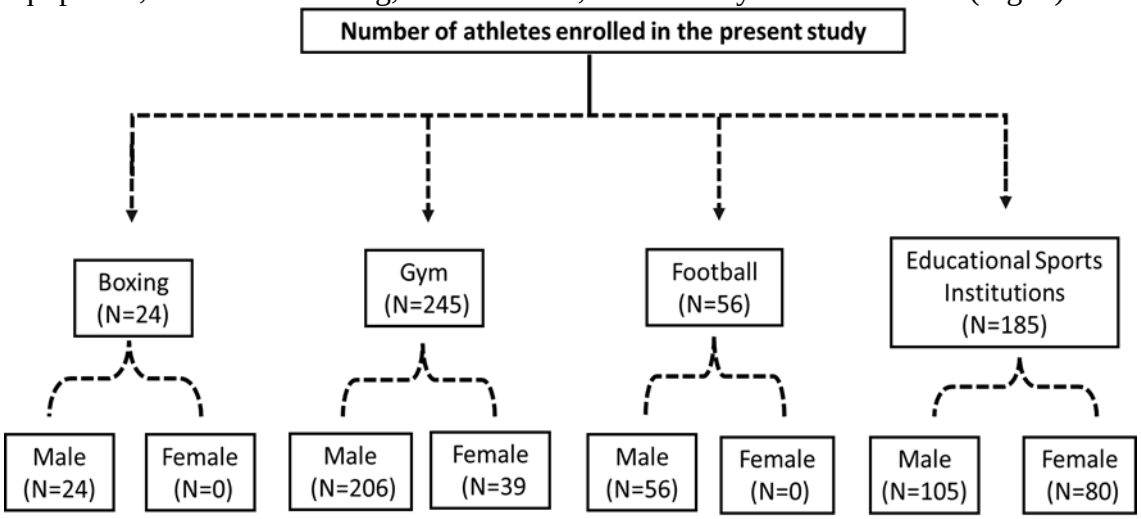

Fig. 1: Flow chart of participants for different types of athletes.

Sample Collection:

An Informed questionnaire was used for collecting demographic characteristics and risk factors associated with MRSA of enrolled athletes. Pure sterile swabs were used to obtain samples from the participants' anterior nares. These were lightly moistened with sterile normal saline to avoid irritation that happened by dry swabs and the swab rolled for 2 to 3 seconds in both nares.

Inclusion and Exclusion Criteria:

The inclusion criteria of the study were subjects involved in the athletes and agreed to participate in our study. However, people who were not involved in the athletes; were administered antibiotics for less than three months, and the patients who did not agree to participate were excluded from our study.

Cultural and Biochemical Identification of MRSA and Antimicrobial Susceptibility Testing:

The swabs were directly streaked on mannitol salt agar after sample collection, and they were then incubated at 35 °C for 48 hours. Based on mannitol salt agar fermentation, Gram stain, morphology, catalase test, and coagulase test results, the strains were identified as *S. aureus*. Using the Kirby-Bauer disk diffusion on Muller-Hinton agar, antimicrobial susceptibility testing for both oxacillin and vancomycin was carried out in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines for the detection of MRSA. Polymerase chain reaction (PCR) assays for the *mec*A gene were conducted as further investigation of MRSA isolates.

Extraction of Chromosomal DNA and Polymerase Chain Reaction (PCR):

Addprep Bacterial Genomic DNA Extraction Kit (add bio, Korea) to extract DNA from *S. aureus* isolates was used according to the kit manufacturing procedure, the purification was carried out utilizing lysosomes and proteinase K.

Two previously designed primers mecA1'GTAGAAATGACTGAACGTCCG ATAA-3' and mecA2 5'-CCAATTCCAC ATTGTTTCGGTCTAA-3' were used to amplify *mecA* gene (Rasheed and Hussein, 2020b). PCR was carried out in a total volume of 20 ul: 2 ul of genomic DNA, 10 µl of hot start master mix (Dongsheg Biotech, China), that consists of Hot Start Prime Taq DNA polymerase (1 unit/10ul), 2x reaction buffer, Mgcl2 (4Mm), enzyme stabilizer, loading dye, PH 9.0, and 0.5 mM of each dATP, dCTP, dGTP, and dTTP, and 2 µl of primer (10 pmol/ul) in a final concentration, 1 µl for each forward and reverse, and 6 µl of distilled water.

A thermal cycler was used to carry out the amplification in accordance with the recommended thermal cycle conditions of each primer. The amplification conditions for *mec*A gene were: Initial heat denaturation at 94°C for 5 minutes, followed by 30 cycles of denaturation at 94°C for 45 seconds, annealing at 60°C for 45 seconds, extension at 72°C for 90 seconds, and final extension at 72°C for 6 minutes. ATTC 43300 was used as a positive control for the *mec*A gene. Agarose gel (2%) containing Safe Dye with green fluorescence (GeNet Bio, Korea) was used to electrophorese the PCR products, DNA ladder 100bp (GDSBio, China) was run alongside the samples to enable analysis of DNA fragment size in the samples and the gels were visualized under UV light to detect the expected band sizes.

RESULTS

Characteristics of Athletes:

In total, 510 athletes, comprising 390 (76.5%) men and 120 (23.5%) females were recruited for the current study. The average body mass index was 23.8 (±4.2 SD) and the mean age of the participants was 22.4 years (±6.1 SD). Other characteristics of participants are listed in Table 1.

The number of athletes who participated in the present study was previously described (2022). The frequency of athletes who performed boxing was 24 (4.7%), gym 245 (48.1%), football 56 (10.9%), and students at educational sports institutions 185 (36.3%), among other sports (Table 2).

Table 1: Characteristics of athletes used in this study.

Variable	Frequency	Percentage
Age (Mean ± SD)	22.4 ±6.1	
Body Mass Index (Mean ± SD)	23.8±4.2	
Gender		
Male	390	76.5
Female	120	23.5
Duration of training /Day		
1 hr	188	36.9
2 hr	176	34.5
3 hr	146	28.6
No. of training sessions/ Week		
1 Session	14	2.8
2 Session	36	7.1
3 Session	460	90.2
Use of antibiotics		
Yes	178	34.9
No	332	332
Previous Hospitalisation		
Yes	93	18.2
No	417	81.8
Previous Surgical Operation		
Yes	55	10.8
No	455	89.2

Distribution of MRSA Nasal Colonization Among Various Types of Athletes:

Out of 510 subjects, 41 (8.04%) were identified as MRSA. The frequency rate ranged from 5.41% for students at the Educational Sports Institutions to 10.71% for football players. The highest rate was observed among football players (10.71%), followed by gym (9.39%) (Table 2). There was no statistically significant difference between the various types of sports with MRSA (p=0.41) (Table 2).

Table 2: Frequency distribution of Methicillin Resistant *Staph aureus* (MRSA) nasal colonization among athletes from Zakho, Kurdistan Region, Iraq**.**

Athletes	Total, n (%)	Nasal Carriage Rate of MRSA No. (%)		*P value
		Positive	Negative	
Boxing	24 (4.71)	2 (8.33)	22 (91.67)	
Gym	245 (48.04)	23 (9.39)	222 (90.61)	0.41
Football	56 (10.98)	6 (10.71)	50 (89.29)	
Educational Sports Institutions	185 (36.27)	10 (5.41)	175 (94.59)	
Total	510 (100)	41 (8.04)	469 (91.96)	

*p value is determined using Chi-square test

Association Between Gender and Type of Athletes with MRSA Nasal Colonization:

There was a significant relationship between gender and type of athletes (p = 0.018) (Table 3). Male athletes had a carriage rate of MRSA of 31 (75.61%), which was significantly higher than female athletes' carriage rate of 10 (24.39%) (Table 3).

Table 3: Association between gender and type of athletes with MRSA colonization (n=41)**.**

Type of Athletes	Total MRSA positive	Gender (no. %)		P value
	No.%	Male	Female	
Boxing	2 (4.87)	2 (6.45)	0 (0)	
Gym	23 (56.09)	19 (61.29)	4 (40)	0.018
Football	6 (14.63)	6 (19.35)	0 (0)	
Educational Sports Institutions	10 (24.39)	4 (40)	6 (60)	
Total	41 (100)	31 (75.61)	10 (24.39)	

Risk Factors Associated with MRSA Among Athletes:

The potential risk factors associated with the prevalence of MRSA nasal colonisation in athletes in the present study were the high body mass index (p=0.006), previous use of antibiotics (p=0.02), surgical operation (p=0.002), duration of training/ day (p=0.025) and the number of training session/week (p=0.047) (Table 4).

Table 4: Risk factor associated with MRSA nasal colonization among athletes.

Variables	*Staph. aureus* nasal carrier (no.%)		p-Value
	MRSA	Non-MRSA	
Age, avrg ±STD	22.61 ± 5.97	22.27 ± 6.14	0.73
BMI, avrg ±STD	24.8 ± 4.64	23.1 ± 3.86	0.006
Gender			
Male	31 (7.93)	360 (92.07)	0.84
Female	10 (8.4)	109 (91.6)	
Use of antibiotics			
Yes	13 (5.09)	242 (94.9)	0.02
No	28 (27.45)	227 (72.55)	
Hospitalisation			
Yes	1 (0.54)	184 (99.46)	0.23
No	40 (12.31)	285(87.69)	
Surgical operation			
Yes	5 (38.46)	8 (61.54)	0.002
No	36 (7.24)	461 (92.76)	
Duration of training/day			
1hr	21 (11.73)	158 (88.27)	0.025
2hr	12 (8.69)	126 (91.31)	
3hr	8 (4.15)	185 (95.85)	
No. of training session/ Week			
1 session	1 (7.14)	13 (92.86)	0.047
2 sessions	5 (21.74)	18 (78.26)	
3 sessions	35 (7.4)	438 (92.6)	

P value is determined by the unpaired student t-test; Fisher exact test; and Chi-square test.

STD: Standard deviation, Avrg: Average, BMI: Body mass index.

Molecular Detection of the *mec*A Gene:

The results showed that 38/41 (92.7%) MRSA isolates were positive for *mecA* gene among various types of athletes and 3/41 (7.3%) were undetectable. The detected specific bands of *mecA* gene were 310 bps as shown in Figure 2.

The DNA samples were run on 2% agarose gel. Lanes (1- 5): positive samples for *mec*A gene with 310bp; lane (6); negative sample, Lane 7: PCR negative control (no template DNA); lane (8), ATCC43300 strain used as a positive control; M: DNA marker (100bp to 1500 bp).

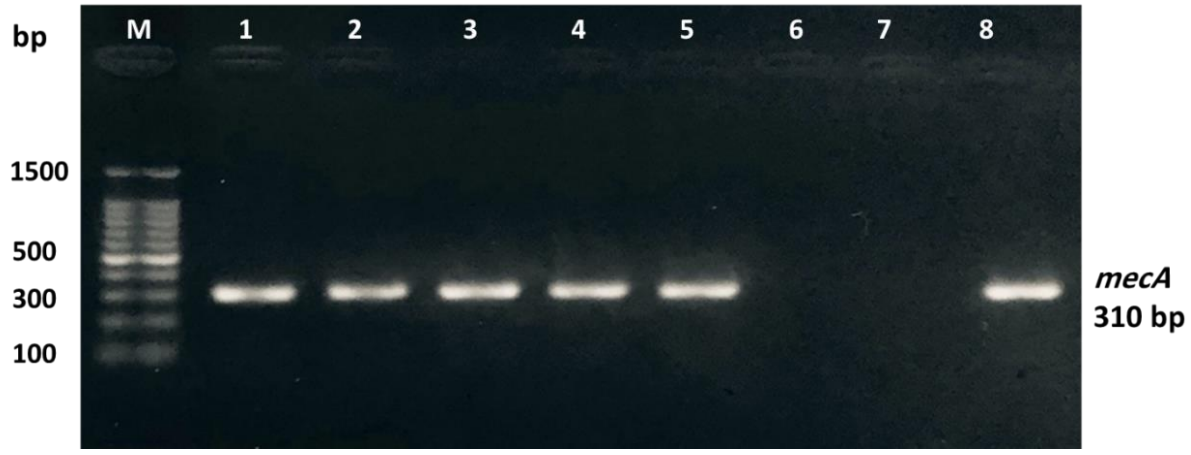

Fig. 2: Molecular detection of the methicillin resistance (*mecA*) gene on gel electrophoresis.

DISCUSSION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a strain of *S. aureus* that is characterized by its resistance to antibiotics such as penicillins and cephems, including penicillin, oxacillin, and other limited spectrum β-lactamase-resistant penicillin antibiotics (Redziniak *et al.,* 2009). MRSA is a fast-emerging and serious infection in the community. Community-acquired MRSA (CA-MRSA) is becoming more common in the athletic population. The Centers for Disease Control and Prevention (CDC) in 2005 has identified athletes as one of the groups most at risk of developing community-associated MRSA (Many, 2008). The burden of MRSA colonization is alarming because MRSA is a leading cause of skin and soft tissue infections (SSTIs) and invasive infections. MRSA infections always result in more severe outcomes compared to MSSA infections (Cosgrove e*t al.,* 2003, Ellis *et al.,* 2004, Lodise Jr *et al.,* 2007). MRSA infections are associated with longer hospital stays and higher hospitalization costs compared to MSSA infections (Cosgrove *et al.,* 2005). In the current study, we evaluated the prevalence rate of MRSA and identified the associated risk factors among athletes in Zakho City, Iraq. This study is the first to report the frequency of MRSA and its correlated risk factors among athletes in our region.

We documented a total MRSA prevalence of 8.04% in our athletic community. This figure is notably higher than that reported among sport groups in other countries, including Italy (1.3%) (Mascaro *et al.,* 2019), Taiwan (1.54%) (Wang *et al.,* 2017), Ohio (5.3%) (Lear et al., 2011). On the other hand, the prevalence of MRSA in our region was lower than that found in Duhok City, Iraq (50.4%) (Hussein *et al.,* 2019) and the USA (35%) (Champion *et al.,* 2014). This discrepancy in prevalence between different study areas may be attributable to the differences in the rate of patient admission, number of samples, culture, and the study timeframe (Gebreyesus *et al.,* 2013). Microbiological procedures antimicrobial

strategy, as well as a variety of levels of commitment to infection prevention measure among hospitals, as well as awareness of MRSA among health care staff regarding MRSA may also participate to the difference.

Results from different studies on MRSA carriage among athletes from different countries show substantial differences in the prevalence rate of MRSA, and it is difficult to compare results from different authors because of the differences in sampling populations and sports, swab collection sites, and spreading of MRSA in the community (Mascaro et al., 2019). Several studies were conducted about MRSA colonization in competitive sport participants, for example (Lear *et al.,* 2011, Creech *et al.,* 2010, Rackham *et al.,* 2010, Garza *et al.,* 2009, Champion *et al.,* 2014). They observed that the carriage rate ranged from 0% to 37%. Surprisingly, none of the enrolled competitive athletes tested positive for MRSA in the study conducted in the USA report (Garza *et al.,* 2009). Another study conducted in the state of Tennessee in the USA (Creech et al., 2010) found that the rate of MRSA carriage considerably varied throughout the course of the athletic season, ranging from 4% to 23 %, with a peak occurring at the time of maximum athletic activity. Moreover, in meta-analysis, conducted in Europe reported a 6% prevalence of MRSA colonization in water sports athletes in Russia (Zaborova *et al.,* 2011), whereas no MRSA colonization was revealed in soccer players in the Netherlands (Huijsdens *et al.,* 2006).

This study documented that the highest rate of MRSA carriage was 10.71% among football players, followed by gym sport at 9.39%, but statistically, no significant differences were observed (p=0.41). The high prevalence of MRSA among football players and gym sports in this study may be due to the close contact between team members. This explanation can be supported by previous studies on athletes in contact sports who have higher carriage rates of MRSA (Cohen, 2008, Kazakova *et al.,* 2005). We observed a discrepancy between the results of our present study and those of a study conducted in the USA among healthy university student-athletes (Champion *et al.,* 2014). The highest MRSA carriage rates were found among men's wrestling (76%) and women's tennis (57.1%) (Champion *et al.,* 2014). In the same study, the results showed that there was a significant correlation between MRSA carriage and participation in wrestling (p=<0.0001) and baseball (p=0.036). In another community-based study conducted in a College Student Athlete Population, only five positive CA-MRSA nasal carriers (4 were males, and 1 was female) were identified equalling a prevalence of 1.8% in this population (Rackham *et al.,* 2010).

To effectively control and prevent infections, it is essential to analyse the risk factors associated with MRSA carriage. In the context of this survey, we examined various risk factors associated with MRSA colonization among athletes in our community. Based on the findings, demographic characteristics such as age, gender, and residency did not play a significant role in determining MRSA carrier status. There is an agreement with studies carried out in USA (Archibald *et al.,* 2008, Champion *et al.,* 2014) and Iran (Askarian *et al.,* 2009). Meanwhile, this result showed inconsistency with another study performed among the general population in central Iran (Ahmadi *et al.,* 2019). They found a significant association between MRSA frequency with age and gender. In this study, we demonstrated that the major risk factors for MRSA were high body mass index (BMI) (p=0.006), previous use of antibiotics (p=0.02), surgical operations (p=0.002), duration of training per day (p=0.025), and number of training sessions per week (p=0.047). In contrast to the findings of the study conducted among professional football players, they found that previous surgical operation was not a significant risk factor for MRSA colonization (Kazakova *et al.,* 2005) and college student-athlete population (Rackham *et al.,* 2010). Furthermore, our results were analogous to the findings of a study conducted among professional football players, which found that higher BMI was a

significant risk factor for MRSA infection (p= 0.03) (Kazakova *et al.,* 2005). Moreover, the results of this study were not in line with findings found in studies conducted in America (Creech *et al.,* 2010), Ethiopia (Legese *et al.,* 2018), and Italy (Mascaro *et al.,* 2019). They reported that the previous use of antibiotics and MRSA were not significantly associated with MRSA infection. In addition, the results of the current study were contradictory to the findings of a study conducted among a college football team, which showed that prior surgical operation was not associated with MRSA colonization. (Begier *et al.,* 2004). Our findings showed that there was no statistically significant association with a previous history of hospitalization and carrier status of MRSA (p= 0.23). Similar to studies that were carried out among professional football players, university athletes, and sports athletes in USA and Italy. They found no correlation between prior hospitalization and MRSA nasal carriage (Mascaro *et al.,* 2019, Kazakova *et al.,* 2005, Creech *et al.,* 2010). Another study among college football players in California found no relation between MRSA colonization and previous hospitalization (Begier *et al.,* 2004). Analogously, studies conducted among healthcare workers in Iran (Askarian *et al.,* 2009), Ethiopia (Legese *et al.,* 2018), showed that the previous hospitalization had no influence on MRSA nasal carriage.

The highest rate of MRSA infection was reported among males (75.6%) more than females (24.4%). The results showed that there was a significant correlation between gender and types of sport for MRSA colonization (p=0.018). The differences in infection rates between males and females could be attributed to physiological and anatomical variations in their cutaneous environments, such as sweat production, hormone levels, and potentially the smaller sample size among females (Giacomoni *et al.,* 2009). Remarkably, this was in agreement with the results observed in a study performed among university student-athletes in USA (Champion *et al.,* 2014), which found that there was a significant association between MRSA colonization among different types of sports and gender (p=0.0004) (Champion *et al.,* 2014). In contrast, the results were discrepant with a study in USA among college student-athletes (Rackham *et al.,* 2010), the study confirmed that there was no significant association between sex and different types of sport for MRSA carriage rate.

Recognition of the *mec*A gene is regarded as the gold standard for the diagnosis of MRSA isolates in the present study. However, studies showed varied rates of the *mec*A gene existing among MRSA isolates among healthy individuals (i.e. CA-MRSA) (Kwoji *et al.,* 2019). The MRSA isolates (41 positives using oxacillin susceptibility test) in the present study were confirmed and amplified molecularly by PCR using *mec*A gene and showed specific DNA bands at 310 bp. The results showed that *mec*A gene was 92.7% positive and 7.3% were undetectable. Comparing our findings to that of a study among student-athletes in northern Taiwan (Wang *et al.,* 2017), MRSA carriage rate was 1.54% of 259 students. Only four students carried MRSA and all four isolates carried SCC*mec* IV or VT (100%). Furthermore, molecular results of a study among healthy university student-athletes in USA showed that MRSA carriage was 34.9%, and over 32 MRSA isolates, 26 could be typed (81.2%), and all of these carried the SCC*mec* type IV cassette (Champion *et al.,* 2014). Additionally, results of a study among players on a college football team in Los Angeles, California showed MRSA carriage rate of 10% and all MRSA isolates carried *mec*A and SCC*mec* gene (100%) (Begier *et al.,* 2004). In this study, the undetectable strains could be due to the presence of other pathways for antibiotic resistance, such as an additional homologue of the *mec*A gene known as *mec*C. It is possible that this factor contributes to the development of resistance to MRSA (Kim *et al.,* 2012, Lakhundi and Zhang, 2018). For undetectable bacteria, another perspective was conducted a traditional antibiotic sensitivity test in

addition to molecular confirmation (Elhassan *et al.*, 2015, Lakhundi and Zhang, 2018). The absence of the *mec*A gene within resistant MRSA isolates could be due to the hyper-production of β-lactamase by the *S. aureus* (Lee, 2006) or due to particular changes in different amino acids presenting in penicillin-binding proteins cascade, which may be the origin of resistance. These support the idea that there are specific mechanisms or alternative genes rather than the existence of the *mec*A gene which contributes to beta-lactam resistance of MRSA.

In conclusion**,** the MRSA infection rate in the present study was relatively higher compared to other studies conducted elsewhere. The infection rate was significantly higher among male athletes; these were associated with personal hygiene and inappropriate use of antibiotics. We also demonstrated that the major risk factors for MRSA were a high body mass index, previous use of antibiotics, surgical operations, duration of training per day and the number of training sessions per week. The *mecA* gene is a powerful way to detect MRSA. More studies were recommended on molecular analysis of virulent genes associated with MRSA in athletes.

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