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Methicillin-Resistant *Staphylococcus aureus* Using Broth Micro Dilution Method in Iran: A Meta-Analysis (2007-2016)

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most signifuicant pathogens in Iran; it is one of the WHO-declared microbial resistance emergencies; and also one of the most important challenges facing the prevalence of resistance. The aim of this study was to detect MRSA using Broth Micro Dilution method and meta-analysis in Iran from 2007 to 2016.

Methods: Persian databases (including Magiran, Irandoc, and SID) and International databases (including pubmed, science direct, and scopus) were searched during this period (2007-2016), such that the high heterogeneity (50% < I2) in this study was analyzed using the DerSimonian Laird method. Data were categorized into subgroups based on year of study and province. Due to the high validity of the diagnosis of organisms and quantitative results, antimicrobial susceptibility test (AST) was used to detect MRSA. Data analysis was performed using statsdirect software.

Results: Based on the available data in medical databases, 678 articles were selected. In total, 29 remaining studies entered the meta-analysis phase. In this study, the overall prevalence of MRSA using MIC is 53% (95% CI: 0.42.31, 63.90); in 2016 it was 77.56% (95% CI: 76.07, 78.99) and in 2007 was 57.49% (95% CI: 53.17, 61.72). The heterogeneity was estimated to be 98.5% (95% CI: 98.4, 98.6).

***Conclusion*:** Based on the results, there is an increasing prevalence of MRSA in Iran. These may be due to the failure or lack of infection control activities and antimicrobial selection pressure.

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Introduction

Today, the resistance of microorganisms to antibiotics is a major global problem and is considered as a disturbing threat by the World Health Organization (WHO). When discussing about the increase in microbial resistance in the world, the WHO has a frequent and consistent recommendation for the control and care of important antibiotics resistant microbes (1-3). One of the most important microbes is *Staphylococcus aureus*, which is a compromised organism and part of the normal flora of the skin and nose (4). Today methicillin-resistant *S. aureus* is one of the most prevalent causes of infections in nosocomial and community is hospital (5, 6).

Staphylococcal resistance to beta-lactam family antibiotics is related to the mec-A gene, which is an indicator of the resistance of MRSA. The risk of *S. aureus* in the intensive care unit (ICU), burn, surgery, and dermatology units is higher. The prevalence of MRSA in different parts ranged between 50 and 73% and multiple drug resistance (MDR) increases by 30 to 80% (5, 7). According to WHO, the burden of microbial disease in hospitals and general population of developing countries is increasing (8). More than 59% of the MRSA cases in Iran have been detected in over 50-years old people (9).

Transmission of S. aureus varies, based on the climatic, cultural, and social conditions of each country (10). According to the resent estimations over 53 million people carry MRSA. The first MRSA resistance was reported in England in 1961 (11). In USA, MRSA caused deaths of between 11,000 and 18,000 people each year (12). The incidence of MRSA in Iran has also been shown to be increasing (13). According to a meta-analysis published in 2012, the average prevalence of MRSA in Iran was 52.7% (14).

In the past two decades, infection with *S. aureus* has increased and the mortality rate had been between 15 and 60% (15, 16). The MIC method was considered in this study because of its ease of usage and quantitative presentation of results.

In recent years, the WHO has warned against determining the microbial resistance of important pathogens, including MRSA (17-20). Considering the concern of the WHO regarding increased microbial resistance and identification of targeted microbes (*Escherichia coli*, *Klebsiella pneumonia*, Methicillin-resistant *S. aureus*, *Streptococcus pneumonia*, Non-typhi *Salmonella*, *Shigella* species, *Neisseria gonorrhoeae*, *Clostridium difficile*, and *Pseudomonas*), this study examined the prevalence of MRSA. So far, no meta-analysis has been conducted on the prevalence of MRSA using the MIC method in Iran.

The purpose of this study was to determine the prevalence of MRSA using the MIC antibiotic method in studies conducted in Iran.

Materials and Methods

Search strategy

The present research was conducted based on the available data in the domestic and either international databases. Persian databases including www.magiran.com, www.Irandoc.ac.ir, and www.sid.com were searched. For Persian databases, a search strategy was developed from 2007 to 2016 with a combination of phrases and keywords (including *Staphylococcus aureus*, Golden *Staphylococcus*, Staph, Microbial resistance, Antimicrobial resistance, Antibiotic resistance, and Microbial susceptibility). The English databases including pubmed, sciencedirect, and scopus were searched over the mentioned period and with terms and keywords including ("*Staphylococcus aureus*") and ("antimicrobial") or ("anti-infective agents") and ("resistant") and ("prevalence") or ("epidemiology") and ("Iran").

Inclusion and exclusion criteria

All cross-sectional studies in Persian and English, which confirmed prevalence of MRSA using the MIC method from 2007 to 2016 in Iran were included in the study. Also, studies conducted

on human samples based on the population of the hospital, non-migrant, and community were included.

Articles that did not estimated the prevalence of MRSA and were not related to the topic and title of study were excluded. Non-cross-sectional studies (review, meta-analysis, case-control, and cohort) performed on non-humane samples; studies with duplicate data were also deleted. Also, studies that estimated the incidence of MRSA with a non-MIC method and articles that did not qualify for a qualitative study were also excluded.

Selection of studies

Collected data

Among the selected cross-sectional studies performed on human samples, information about the author's name, date of publication, year, geography, type of study, sample size, gender, mean age, antibiotic resistance, antibiotic groups, and finally antibiogram methods were extracted.

Quality of studies

In this study, Strob's checklist was used to assess probabilistic bias and quality assessment of studies (21). Strob's checklist consists of 22 items categorized into seven.

Items used in the Strobe checklist: The exact reference to the study design, the exact expression of the method of exposure and outcome measurement, the method for calculating the sample size, the flowchart for selecting the subjects, the reference to the time of data collection, and reference to inclusion and exclusion criteria.

After evaluating the aforementioned cases, the studies were divided into three groups: high, moderate, and low bias. Low-bias and high-quality studies are studies that had followed all the seven items listed in Strob's statement. Studies with moderate bias and quality are studies that had followed six of the provisions of Strob's statement. Studies with high bias and low quality were studies that have not followed two or more provisions of the Strob's statement. The criteria used to measure the bias in the researcher's studies include: bias in outcome evaluation, bias in exposure assessment, sample size calculation, information bias, and selection bias. All stages of the quality evaluation of the articles were also conducted independently by two researchers. PRISMA checklist (2009) was used to assess the quality of the reporting of structured browsing studies and meta-analysis (22).

Information analysis

The index studied in this study was the prevalence that was calculated as P(ratio) with a confidence interval (CI) of 95%. To test heterogeneity, Q test was used at an error level of less than 10% and its quantity was satisfied with index I2. I2 is for estimation of variance within the study. T2 method was used to estimate the variance between studies. If I2>50% (p-value<0.1), then the heterogeneity is significant (23). Based on the results of heterogeneity of studies, two statistical models of constant and random effects were used at 95% confidence level for data analysis. Based on the high heterogeneity (50%<I2) in this study, the data was analyzed using the DerSimonian Laird method. Analysis in subgroups was based on the province of residence and year of study. The Begg rank correlation test (24) and Eggers regression test (25) were used to measure the bias rate. If p-value <0.1 indicates a significant bias. In order to evaluate the propagation bias, a funnel plot was used. Also, in bilateral statistical tests, a significant level ($\alpha = 0.05$) was considered (26). After extracting the information from the articles in question using the Statsdirect software, a meta-analysis was performed on the data of the articles.

Results

In this study, 678 articles were found based on the used search strategy. Articles 46 were excluded due to repetition of similar titles. Among the 632

remaining articles, 288 were excluded from the study due to the fact that their titles were not relevant to the study. Then, reviewing the titles and abstracts of articles, 344 articles related to the topic were selected, of which 70 were excluded due to the inaccessibility of the full text and lack of information on the subject. Finally, the full text of 274 articles was reviewed and 182 articles that had not met the criteria were deleted. At the end, the 29 remaining studies entered the meta-analysis phase. All studies were reviewed at each stage of the study (Figure 1).

Study features

Twenty-nine studies entered the meta-analysis phase. All these studies were conducted in Iran and the prevalence of MRSA in the provinces of Ardebil, Kerman, Isfahan, Tehran, Khuzestan, Bandar Abbas, Chaharmahal and Bakhtiari, Khorasan, Fars, Qom, Kermanshah, Golestan, Mazandaran, Central and Hamedan. The Antibiogram method was used for the MIC and the sample size varied from 20 to 927 (Table 1).

MRSA prevalence using MIC

29 studies reported the prevalence of methicillin resistance using MIC in Iran from 2007 to 2016. The prevalence of MRSA was calculated using MIC antibiogram. The results of the analysis of these studies showed that the prevalence of MRSA using the MIC method is 53% (95% CI: 42.31, 63.90). The level of heterogeneity in the prevalence rates is 98.5%, which is according to the Cochrane division in 2008; this amount is normally classified as heterogeneous (27). For subsequent studies, the random effects model was used. Based on this model, it was assumed that the observed difference resulting from the different samplings and the differences in the measured parameters of the MRSA prevalence were studied in different studies.

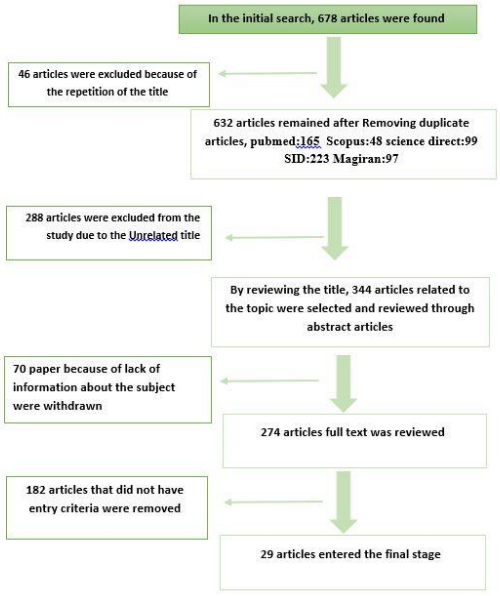

Figure 1. Flow of data through the different phases of the systematic review.

Table 1. Characteristics of studies on the prevalence of MRSA MIC.

First Author	Publication year	Province	Survey year	Design	Sample(N)	Resistant methicillin (n)	Prevalence
Rahimi	2015	Tehran	2011-2012	cross-sectional	575	127	**0.22**
Godarzi	2013	Markazi	2011-2012	cross-sectional	98	53	**0.54**
Mohajeri	2011	Kermanshah	2009	cross-sectional	45	13	**0.28**
Hassanzade	2013	Tehran	2012-2013	cross-sectional	120	60	**0.5**
Rahimi Alang	2010	Golestan	2009	cross-sectional	333	10	**0.03**
Saffari	2012	Esfahan	2011	cross-sectional	150	93	**0.62**
Ahmadi	2013	Kermanshah	1392	cross-sectional	100	36	**0.36**
Mosavian	2014	Khouzestan		cross-sectional	124	60	**0.48**
Mazlomi	2016	Tehran	2011-2012	cross-sectional	172	40	**0.23**
Mazlomi	2016	Tehran	2011-2012	cross-sectional	93	40	**0.43**
Mahmoodzade	2016	Tehran	2011-2014	cross-sectional	188	188	**1**
Davoudi	2016	Mazandaran	2012-2014	cross-sectional	33	18	**0.54**
Imani	2015		2009-2012	cross-sectional	192	104	**0.54**
Mohammadi	2014		2010-2011	cross-sectional	100	100	**1**
Farahani	2013	Kermanshah		cross-sectional	186	91	**0.48**
Shahsavan	2011	Ilam	2009	cross-sectional	239	140	**0.58**
Hatefi	2016	Tehran	2014-2015	cross-sectional	100	50	**0.5**
Mohajeri	2014	Kermanshah	2013	cross-sectional	85	85	**1**
Zamani	2007	Hamedan	2005-2006	cross-sectional	70	35	**0.5**
Fatholazadeh	2008	Tehran	2004-2005	cross-sectional	277	99	**0.35**
Aligholi	2008	Tehran	2005	cross-sectional	356	149	**0.41**
Azimian	2012	Tehran	2011	cross-sectional	235	108	**0.45**
Aligholi	2008	Tehran	2001-2005	cross-sectional	927	306	**0.33**
Najjar Pyrayeh	2009	Tehran		cross-sectional	174	84	**0.48**
Armin	2013	Tehran	2011	cross-sectional	20	7	**0.35**
Havaei	2012	Esfahan-Mashhad-Tehran	2011	cross-sectional	171	115	**0.67**
Hasibi	2016	Tehran	2003-2005	cross-sectional	41	41	**1**
Rahimi	2015	Tehran	2013-2014	cross-sectional	79	12	**0.15**
Rahimi	2009	Tehran	2005-2006	cross-sectional	321	202	**0.62**
Total					5604	2466	**0.53**

Based on the analysis subgroup of population and the year of publication of the articles showed that the overall prevalence was calculated as 40% (95% CI: 30.37, 51.18). The highest incidence rate is 77.5% (95% CI: 76.07, 78.99) in 2016 and the lowest incidence rate is 22.2% (95% CI: 21.29, 23.14) in 2013 and the heterogeneity among studies (p<0.001, I2 = 99.8%) in the quantitative evaluation of Begg test (z = 0.4, p- value = 0.07) and Egger test (z = 36.4, p-value = 0.1) was calculated. Based on provincial analysis, the overall prevalence was calculated as 39% (95% CI: 31.94, 46.40). The highest prevalence was found in Qom province as 78.2% (95% CI: 71.74, 83.84) and the least prevalence was found in Kermanshah province as 13.4% (95% CI: 12.50, 14.44) and the heterogeneity between studies was reported (p < 0.001, I2 = 99.4%). In the quantitative evaluation, the distribution bias of Begg test (z = -0.08, p-value = 0.6) and Egger test (z = 5.04, p-value = 0.4) was calculated (Table 2).

Subgroups analysis

Based on the year of publication, the incidence of MRSA in 2016 was 77.56% (95% CI: 76.07, 78.99) and in 2007, it is 57.49% (95% CI: 53.17, 61.72). From the province of study, the prevalence of MRSA in Qom was estimated about 78.23% (95% CI: 71.74, 83.84) and in Kermanshah it was estimated around 13.23% (95% CI: 12.50, 14.40).

Bias distribution

In studies of the prevalence of MRSA, the bias distribution was shown by a funnel graph (Figure 3). The Egger and Begg tests (Manzumdar) were used for the quantitative evaluation of the propagation bias. Egger's regression model considers the effect of size ratio on the standard error (Z-score) as an associated variable and predicts its value using the reverse of the standard error. The Begg method was used to calculate the Kendal tau nonparametric correlation coefficient between the standard index and the relevant criterion error in this study. Based on the results obtained in this study, Begg test (z = 10.83, p-value = 0.4) and Egger test (z = -13.22, p = 0.01) were calculated showing the bias propagation.

Discussion

When considering the importance of disease and high prevalence of methicillin resistance, one of the most important concerns of the health system in each country is coping with resistance to microbial agents in the community (28). This study was conducted to determine the prevalence of MRSA in Iran.The prevalence of MRSA in Iran varied from 3 to 100% (29-32). In a meta-analysis study conducted in 2012, the prevalence of mecA-MRSA in Iran was 52.7%, which was consistent with the results of our study (14). The incidence of MRSA varies across regions. In comparison, MRSA rate in Italy was 43

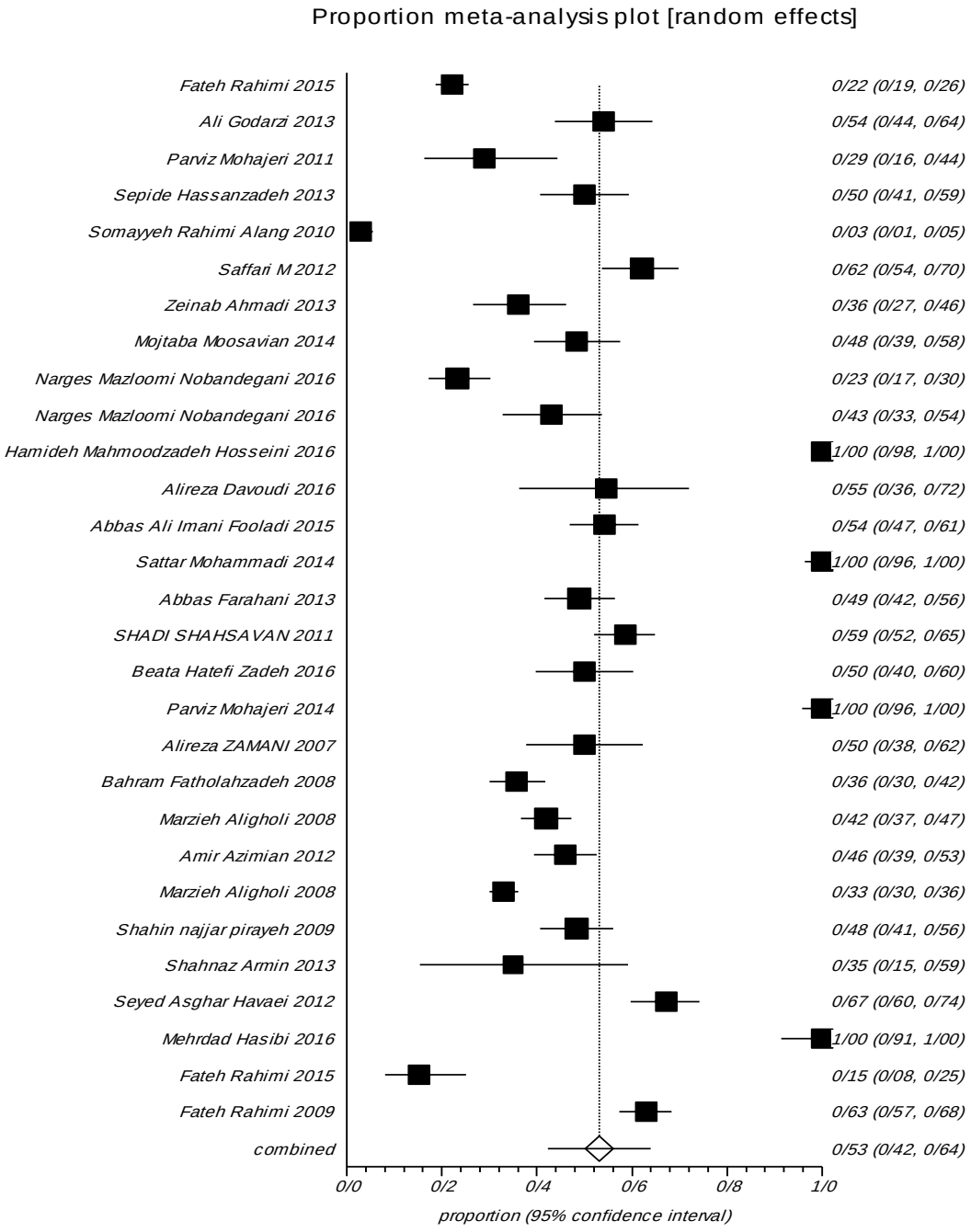

Figure 2. Forest plot of prevalence from MRSA of using MIC studies in Iran from 2007-2016.

Table 2. Prevalence MRSA of MIC by subgroups.

Stratified factors	Prevalence	Lower limit	Upper limit	Model
provinc				
Ardabil	34.39	28.86	40.26	**Random**
Kerman	26.61	24.53	28.77	**Random**
Esfahan	37.35	35.56	39.15	**Random**
Tehran	42.17	41.45	42.90	**Random**
Khozestan	59.88	57.09	62.63	**Random**
Bandarabbas	42.48	38.89	46.11	**Random**
Charmahalo bakhtyary	39.73	35.52	44.05	**Random**
Khorasan	47.21	45.26	49.17	**Random**
Fars	40.89	39.14	42.66	**Random**
QUM	78.23	71.74	83.84	**Random**
Kermanshah	13.43	12.50	14.40	**Random**
Golestan	28.16	24.71	31.83	**Random**
Mazandaran	35.20	31.93	38.59	**Random**
Markazi	41.15	36.95	45.44	**Random**
Hamedan	25.43	21.51	29.67	**Random**
year				
2016	77.56	76.07	78.99	**Random**
2015	51.44	49.88	52.99	**Random**
2014	33.30	32.17	34.45	**Random**
2013	22.20	21.29	23.14	**Random**
2012	29.64	28.03	31.29	**Random**
2011	22.85	21.74	23.99	**Random**
2010	38.28	36.29	40.30	**Random**
2009	29.74	28.61	30.89	**Random**
2008	46.05	44.29	47.82	**Random**
2007	57.49	53.17	61.72	**Random**

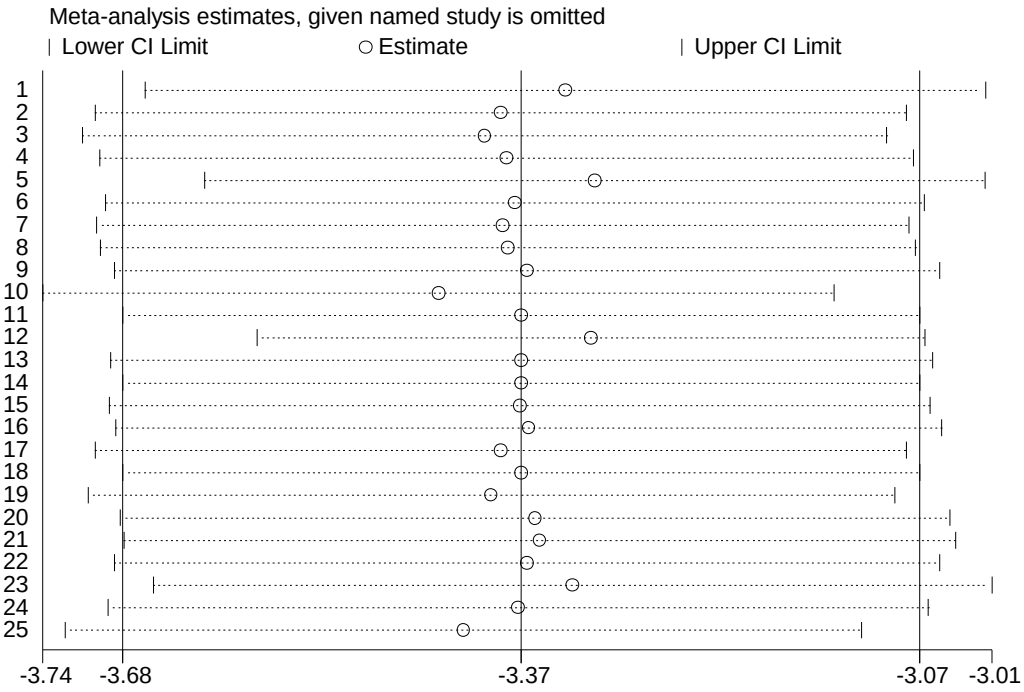

Figure 3. Sensitivity analysis of MRSA prevalence. (A) Results were computed by omitting each study in turn. (B) The two ends of the dotted lines represent the 95% CI.

to 58%, India was 40%, United States was 25 to 50%, and Portugal is 54% (33, 34). The prevalence rates in hospitals in the USA and Europe were between 29 and 35%. In countries in Southeast Asia, the prevalence of MRSA was high (Sri Lanka 86.5%, South Korea 77.6%, Vietnam 74%, Taiwan 65%, Thailand 57%, Hong Kong 56%, India 22.6%, and Philippine 38.1% (35). Iran has a higher prevalence of MRSA than neighboring countries in the Eastern Mediterranean region (except Iraq) (36). This difference in the prevalence of MRSA can be due to a high prevalence as a result of the differences in economic, social, antibiotic consumption, lack of a reviewing system, lack of national program to deal with microbial resistance, and lack of appropriate control measures.

According to the systematic review of Olga, the incidence rate of MRSA in the South African region was on average 46%. In this region, the prevalence of MRSA in Tanzania had risen from 12 to 82% in Egypt (36). It has been shown that the prevalence in Iran was higher as compared to the European and American countries, but was lower than in African and Southeast Asian countries. This difference showed increased microbial resistance. The differences of the prevalence rate among countries can be due to a difference in the geographical situation. In Europe, due to the north-south geographic gradient, the prevalence of MRSA in Scandinavia was lower, but higher in Southern Europe (33). In the study of Lin (24), which was performed as a meta-analysis in Taiwan, the incidence of MRSA was estimated to be about 4.4%. Comparing the results of the present study with other studies suggests a high prevalence of MRSA in Iran. This difference and increase in different regions of Iran could be due to

differences in the provision of health services, increasing the arbitrary use of antibiotics, type of patients, and access to accurate and standard laboratory methods. It was necessary to prevent the phenomenon of increased resistance, and consequently, increased mortality and morbidity through extensive and accurate planning, such as training on the correct use of antibiotics, the implementation of periodic care every 3 or 4 years, and the need to submit and accurately record antibiotic use statistics in the country.

WHO has recently focused on the microbial resistance and antibiotic usage in recent years, and had identified it as a major public health concern. This study, like all other studies had some limitations. Among the limitations of this research, two points were worth mentioning. In all provinces of the country, no study had been performed on the prevalence of MRSA using the MIC antibiogram method, but an overall estimation in the country can be obtained from the prevalence in the fifteen provinces studied. In meta-analysis studies, there is always the possibility of losing some articles and it should be predicted. In this study, the highest prevalence was related to four studies, with an incidence of MRSA of 100%. In a study by Mahmoudzadeh et al. (2016) performed in Tehran with a sample size of 188 patients, the prevalence of 100% (95% CI: 98.05, 100) was estimated (30). In the study by Mohammadi et al. (2014) with a sample size of 100, the prevalence of 100% (95% CI: 96.37, 100) was estimated (31). In the study of Mohajeri et al. (2014) with a sample size of 85 in Kermanshah, the prevalence of this study was 100% (95% CI: 95.75, 100) (32). In a study by Hasibi et al. (2016) with a sample size of 41 in Tehran, the prevalence of this study was 100% (95% CI: 91.39, 100) (37). The lowest prevalence was related to the study of Rahimi et al. (2010) performed in Golestan in 2010 with a sample size of 333 and the prevalence of MRSA was 3% (95% CI: 1.44, 5.45) (29). The overall prevalence rate in Iran was 53.18% (95% CI: 42.31, 63.90). The results of these studies showed that 29 studies were conducted over the period of 2007 to 2016 in the provinces of the country to determine the incidence of MRSA using the MIC method. The sample size varied from 20 to 927. The lowest sample size was in the province of Qom and the highest in Tehran province. The prevalence rate in 2016 was the highest for these 10 years, showing an increase in resistance to antibiotics in recent decades. The highest prevalence in 2016 was 77.56% (95% CI: 76.07, 78.99) and the lowest incidence rate was 22.2% in 2013 (95% CI: 21.29, 23.14).

Conclusion

The results of this study showed that the prevalence of MRSA in Iran has a rising trend, which is a significant warning of public health problem. Considering that the resistance process in microorganisms is faster than the discovery of new and effective antibiotics, planning for the design of a national program to deal with microbial resistance, training and implementation of control measures for all parts of the society should be considered as an integral part of the healthcare system programs of the country.

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Conflict of interest

There is no conflict between the authors.

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