Iranian Journal of Microbiology
Volume 15 Number 1 (February 2023) 10-18

REVIEW ARTICLE

A five-year systematic review and meta-analysis study on methicillin resistant *Staphylococcus epidermidis* strains in Iran

Setareh Soroush[1], Faranak Rezaei[1], Fatemeh Ghanbari[2], Shahnaz Halimi[3], Morovat Taherikalani[1*]

[1]Department of Microbiology, School of Medicine, Razi Herbal Medicine Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[2]Department of Microbiology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received: October 2022**, Accepted:** December 2022

ABSTRACT

Background and Objectives: One of the most prevalent drug-resistant bacteria is methicillin-resistant *Staphylococcus epidermidis* (MRSE) causing healthcare infections. Previously, a meta-analysis study on the frequency of MRSE was conducted from Mar 2006 to Jan 2016 in Iran. The present study aimed to evaluate the changes in this prevalence in the last 5 years in different cities in Iran.

Materials and Methods: Published articles on the frequency of MRSE were collected from the Web of Science, PubMed, Scopus, Google Scholar, Cochrane Library, and Iranian databases from the beginning of 2016 to the end of 2020. Of the 503 records identified, 17 studies met the inclusion criteria, and their extracted data were analyzed using comprehensive meta-analysis version 2.0 (Biostat).

Results: The analysis showed that the frequency of MRSE has decreased significantly in the last five years and reached 60.8 [95% confidence interval (95% CI) 54.2-66.9] among culture-positive cases of *S. epidermidis* in Iran.

Conclusion: The noticeable reduction in the prevalence of MRSE in Iran could be due to the improvement of infection control programs and interruption of the pathogen transmission cycle. Another influential reason is the significant reduction in methicillin prescriptions by physicians for infections caused by staphylococci.

Keywords: Iran; Meta-analysis; Methicillin resistant; *Staphylococcus epidermidis*; Systematic review

INTRODUCTION

Recently, the role of coagulase-negative staphylococci; CoNS, as opportunist microbial flora, has become much more prominent in nosocomial infections. Given the increasing use of indwelling or implanted foreign bodies in modern medicine, the impact of CoNS infections on human life and health has increased dramatically (1). The most important and abundant problematic species in this group is *Staphylococcus epidermidis.* Although the main source of infection is endogenous, but medical and nursing interventions are a very main role in transmission (2).

Formerly, the identification of *S. epidermidis* in clinical samples was confusing and mostly reported as accidental contamination (3). Identifying the pathogenic factors and determining their effect on its pathogenicity helped researchers to understand its

*Corresponding author: Morovat Taherikalani, Ph.D, Department of Microbiology, School of Medicine, Razi Herbal Medicine Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran. Tel: +98-6633413083 Fax: +98-6633413083 Email: taherikalani@gmail.com

relationship to infections (4).

In recent years, extensive studies have emphasized the role of *S. epidermidis* in infections caused by the use of catheters and devices placed in the body. Due to pathogenic factors affecting colonization and biofilm production, these infections are difficult to eradicate from the patient's body (5).

When antibiotic resistance spread among these strains, *S. epidermidis* became a significant problem worldwide. The widespread prevalence of antibiotic resistance has also been another reason for the reduction in the success of effective treatment of patients so that a high percentage of these infections be reported by methicillin-resistant *S. epidermidis*; MRSE strains (6). MRSE also is known as one of the main elements of infection after various surgeries (7).

Given the importance of MRSE in causing hospital-acquired infections, increasing length of stay and hospitalization costs, and even increasing patient mortality, careful evaluation of the increased number of isolated MRSEs affects effective control and treatment (8). Razavi et al. conducted a systematic review and meta-analysis between 2006 and June 2016 in Iran, which reported a prevalence of MRSE of 73.9% [95% confidence interval (95% CI) 61.4-83.4] (9). Due to this issue's importance, the present study's purpose was to investigate the frequency of MRSE in Iran in the last five years (2016-2020).

MATERIALS AND METHODS

Search strategies. All original research articles about the prevalence of MRSE infections in Iran which were published in Persian or English in the last five years (January 2016 to December 2020) were collected from the following databases: Web of Science, Scopus, PubMed, Google Scholar, Cochrane Library, and Iranian databases includes; Iranian National Library (NLAI), Scientific Information Database (SID), Iranmedex, Irandoc, and Magiran.

Based on search strategy in each database, the following keywords with/without Medical Subject Headings (Mesh) in titles or abstracts were searched in English or Persian; "coagulase-negative *Staphylococcus*", "CoNS", "*Staphylococcus epidermidis*", "*S. epidermidis*", "methicillin-resistant *Staphylococcus epidermidis*", "MRSE", and "Iran". Also, bibliographies of retrieved papers were revised for any additional studies (10, 11).

Inclusion and exclusion criteria. The following criteria were considered for the inclusion of original articles in this study: (i) Studies to have checked the frequency, prevalence, or proportion of MRSE at health centers in Iran; (ii) Studies were included if they were conducted in the general population; (iii) Studies published between 2016 and 2020; (iv) The language of publication was English or Persian; and (v) Identification of MRSE (disk diffusion for cefoxitin, broth microdilution, E-Test, and PCR) was made according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

Each of the following reasons excluded studies from the analysis: irrelevancy of the title, review articles (narrative, systematic reviews, or meta-analyses), case reports, non-human samples, specific subpopulation, not reporting *S. epidermidis* numbers, duplicate data, nonstandard methods for detection of MRSE, and articles only abstracts were available.

Data extraction and definitions. Data extracted from the studies were: author name; period of study; year of publication; study setting; method of studies; source of isolates; the number of investigated cases; frequency of *S. epidermidis*, frequency of MRSE, and diagnostic methods. Two investigators independently extracted all data from included studies, and a third investigator reviewed the results. Finally, to achieve consensus, inconsistencies were discussed. In the present study, PRISMA guidelines were used (12).

Quality assessment. The quality of eligible studies was checked using The Joanna Briggs Institute checklist (12). Methodological features, which were evaluated by ten items, included: representativeness of the study population, sample size, study setting, and statistical analysis. After giving a score for each item in a study (0 or 1), if the total score were >7, it was considered low risk of bias. Two reviewers carried out every stage of critical appraisal independently, and a third reviewer solved discrepancies to reach a consensus.

Meta-analysis. Comprehensive meta-Analysis (CMA) software v.2.0 (Biostat Inc., Englewood, NJ) was used for data analysis. Random-effects models were used to combine the studies. The possibility of heterogeneity between studies was calculated using the Cochrane Q test and I2 test. Possible publication bias was also assessed using Egger's weighted regres-

sion methods. A P-value of <0.05 was considered indicative of statistically significant publication bias.

RESULTS

Characteristics of included studies. From 503 articles selected in the first stage, 479 articles were excluded in the secondary screening based on title and abstract evaluation (Fig. 1). In the third stage, out of the remaining 24 studies, seven articles were excluded upon a full-text search. Finally, 17 studies remained eligible for meta-analysis. (13-22, 23-28). Fig. 1 details the reasons for study exclusion. As well, Table 1 presents the characteristics of the included studies. All positive samples were collected inside hospital settings; most likely, they are hospital-acquired. The geographic location of the studies mostly covered the north, center, and west of Iran. MRSE is isolated from various clinical samples including blood, wound, catheter tips, etc. In all studies, standard methods were used in diagnosing MRSE.

The frequency of MRSE infections. The results of the meta-analysis showed that the prevalence of MRSE infection among culture-positive *S. epidermidis* was 60.8% (95% CI: 54.2-66.9) (Table 2), and there was heterogeneity among the articles (I2 = 84.289, P < 0.001). Table 2 and Fig. 2 present the Forest plot of meta-analysis on the rate of MRSE infections. As well, the results presented in Table 2 and Fig. 3 showed that there was no publication bias in the current study (P > 0.05 for Egger weighted regression analysis). Stratified analyses based on the geographi-

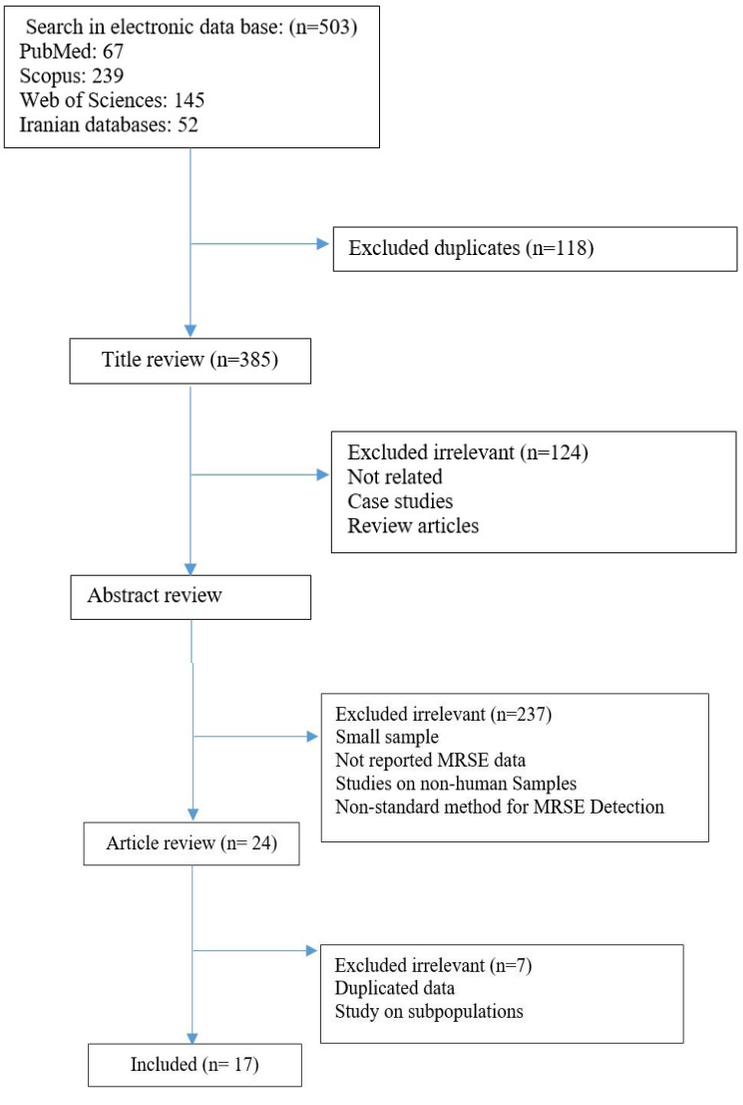

Fig. 1. Flow chart of study selection for inclusion in the systematic review

Table 1. Characteristics of studies included in Meta-analysis

Study	Publication year	Study period	Province	No. of cases	No. of *S. epidermidis*	No. of MRSE	Diagnostic Methods(s)	Source of Sample
Nasaj (14)	2020	2017-2018	Hamedan	91	49	26	DD, PCR	Blood, Urine, etc
Behshood (13)	2020	2019	Isfahan	120	100	60	DD	Urine, Blood, etc
Montazeri (12)	2020	2018	Ahvaz	90	44	20	DD, PCR	Urine, Wound, etc
Borooni (16)	2019	2016-2017	Isfahan	90	90	45	DD	Urine
Mamishi (15)	2019	2017-2018	Tehran	138	76	68	DD	Blood, CSF, etc
Chabi (17)	2019	2017	Ahvaz	100	46	21	PCR	Blood, Urine, etc
Ghaznavi (18)	2018	2013-2014	Arak	102	47	31	PCR	Blood, Wound, etc
Behrooz (19)	2018	2017-2018	Tehran	107	107	65	DD	Blood, Wound, etc
Tahmasebi (20)	2018	2016-2017	Hamedan	100	55	25	PCR, Etest	Blood, Urine, etc
Ebrahimzadeh (23)	2017	2016	Isfahan	183	183	137	DD	Blood, Wound, etc
Halaji (22)	2017	2014-2015	Isfahan	130	130	70	DD, PCR	Wound, Blood, etc
Sharifinejad (21)	2017	2015	Tehran	50	50	23	PCR	Ocular Samples
Tahmasebi (16)	2016	2014-2015	Zahedan	710	198	97	DD, PCR	Urine
Saffari (27)	2016	2012-2013	Tabriz, Tehran	177	82	61	DD, PCR	blood, Catheter, etc
Mirzaei (26)	2016	2014-2015	Tehran	123	63	47	DD, PCR	Blood, Wound, etc
Soroush (25)	2016	2012-2013	Tehran	256	151	80		

MRSE, Methicillin-resistant *Staphylococcus epidermidis*; BMD, broth microdilution; DD, disk diffusion.

Table 2. Meta-analysis of the prevalence of MRSE infections in Iran

Subgroup	No. of Study	Prevalence of MRSE (95%CI)[a]	n/N[b]	Heterogeneity Test		Egger Test	
				I^2 (%)	P Value	t	P Value
Overall effect	17	60.8 (54.2-66.9)	990/1621	84.289	1<0.001	0.676	0.508
2016-2027	8	63 (53.7-72.1)	629/1007	88.651	1<0.001	0.946	0.380
2018-2020	9	58 (49-66.7)	361/614	78.362	1<0.001	0.797	0.451

CI, confidence interval.

[a] Weighted mean of prevalence.

[b] n, number of events (MRSA isolates); N, total number of *S. aureus*

cal locations in reviewed articles are visible in Table 3 which showed that the prevalence of MRSE infection among culture-positive *S. epidermidis* in Tehran was much higher than other locations. Moreover, even the overall result of this article is 68.3% (95% CI: 54.8-77.9) (I2 = 86.724, P < 0.001) (Table 3). Fig. 4 presents the distribution of MRSE infections in different parts of Iran.

DISCUSSION

Since 1961, when the first strain of methicillin-resistant *Staphylococcus* was reported, many articles have been published worldwide on the increasing prevalence of methicillin-resistant *Staphylococcus* species. But in recent years, articles have been published about the reduction of methicillin-resistant *Staphylococcus aureus* (29-33).

Currently, the prevalence of *S. epidermidis* in Iran is reported to be about 27.8%-58.8% according to the sample type, sampling methods, diagnosis methods, and study objectives (12, 14, 21), and until recent years, various studies have reported an increase in resistance to methicillin in this species. The current systematic review and meta-analysis also reports the decline of MRSE infection frequency in Iran. The frequency of MRSE infection in culture-positive samples of *S. epidermidis* (2016-2020) was 60.8% (95% CI: 54.2-66.9) in different parts of Iran (Table

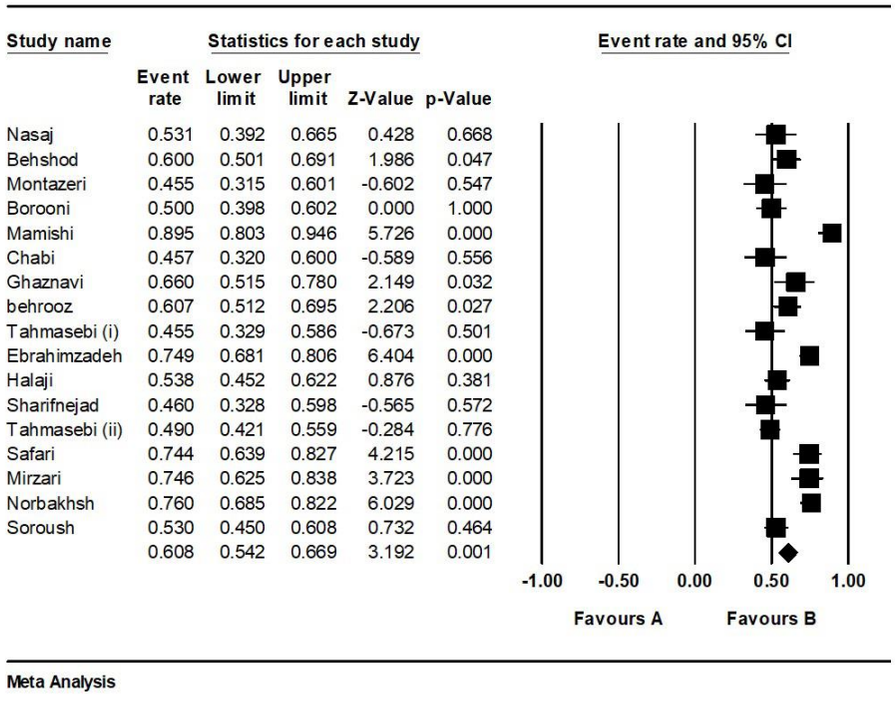

Fig. 2. Forest plot of the meta-analysis on the prevalence of methicillin-resistant *Staphylococcus epidermidis* (MRSE) infections. CI, confidence interval. Tahmasebi (i), published in 2018; Tahmasebi (ii), published in 2016.

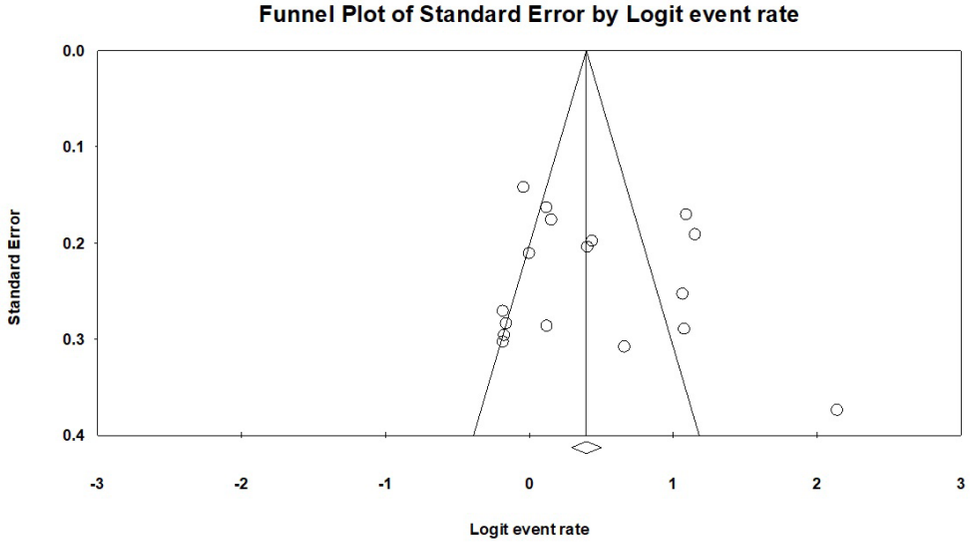

Fig. 3. Funnel plot of the meta-analysis on the prevalence of methicillin-resistant *Staphylococcus epidermidis* (MRSE) infections.

2). While in the previous study (Mar 2006 to Jan 2016), 73.9% (95% CI: 61.4 - 83.4) was reported (9). According to the current study results, the MRSE had a higher incidence rate in Tehran and Isfahan than in Ahvaz, Hamedan, Arak, and Zahedan (Table 3). Although Tehran and Isfahan are both densely populated cities in the central regions of Iran, in a previous study, the prevalence of MRSA was reported to be lower in Tehran than in Isfahan (9). Population density is an essential factor in the development and spread of antibiotic resistance and needs special attention in the epidemiology of resistance (34).

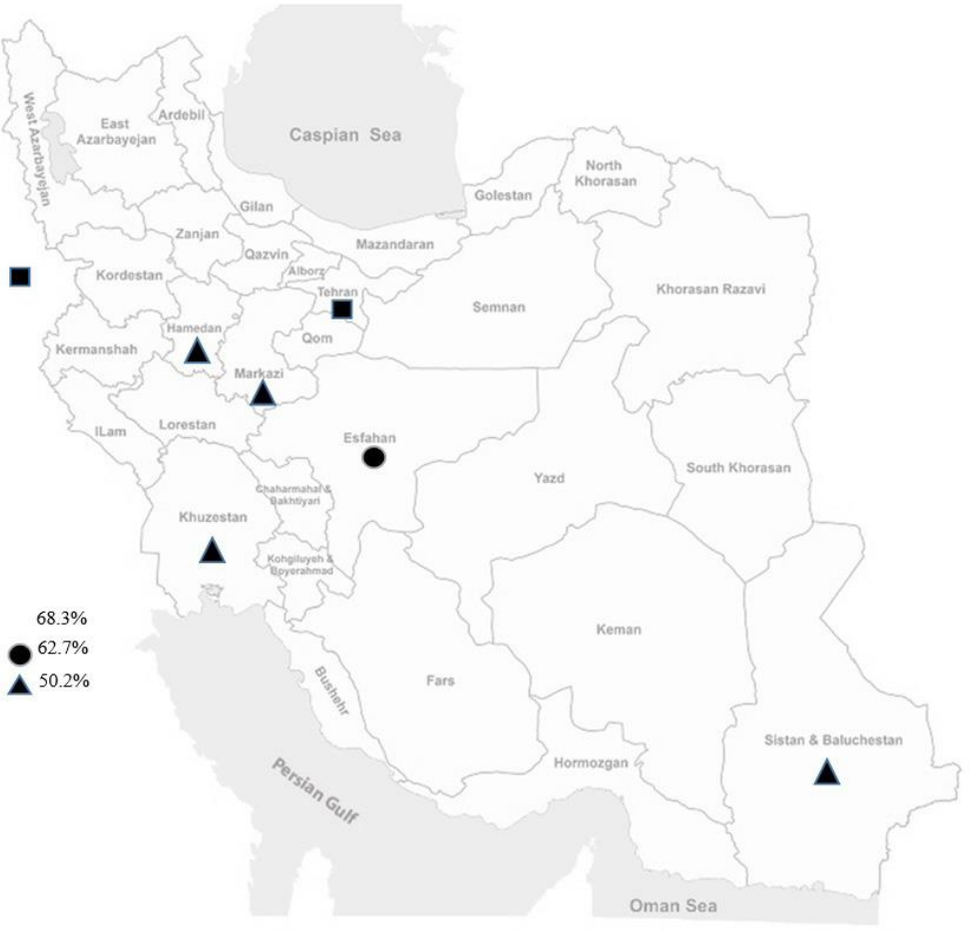

Fig. 4. Distribution of methicillin-resistant *Staphylococcus epidermidis* (MRSE) infections in different parts of Iran.

Table 3. Meta-analysis of the prevalence of MRSE infections in different parts of Iran

Subgroup	No. of Study	Prevalence of MRSE (95%CI)[a]	n/N[b]	Heterogeneity Test		Egger Test	
				I^2 (%)	P Value	t	P Value
Overall effect	17	60.8 (54.2-66.9)	990/1621	84.289	1<0.001	0.676	0.508
Tehran	6	68.3 (56.8-77.9)	391/609	86.724	1<0.001	12.593	0.000
Isfahan	5	62.7 (50-73.8)	397/573	87.766	1<0.001	2.289	0.106
Ahvaz, Hamedan Zahedan, Arak	6	50.2 (44.8-55.6)	220/339	17.267	1<0.001	0454	0672

CI, confidence interval.

[a] Weighted mean of prevalence.

[b] n, number of events (MRSA isolates); N, total number of *S. aureus*

Methicillin resistance in *Staphylococcus epidermidis* has gradually declined over the past 5 years. One of the most important reasons for reducing the prevalence of MRSE in Iran is the development of infection control efforts such as device- and procedure-associated infections (35-37), as well as attempts to break the MRSE transmission cycle in the hospital setting (38, 39). Other reasons include reduced prescription of methicillin by physicians for infections caused by staphylococci. Because methicillin is no longer commercially available due to side effects such as interstitial nephritis and kidney failure, it is less commonly used for treatment today. One of the other reasons that have caused the in-

crease in the reports about the decrease in methicillin resistance among *Staphylococcus aureus* strains in Iran is that some physicians prescribe other drugs for the patient with the mental assumption regardless of the results of antibiotic resistance tests (29, 40-44).

Due to the small number of studies, there is little information about SCC*mec* types in MRSE in Iran. Overall, studies show the most common SCC*mec* types in MRSE are SCC*mec* type IV, V, and III, respectively, but SCCmec types I and II are rarely found (45-49). Due to the widespread resistance of MRSE infections to beta-lactams, aminoglycosides, and glycopeptides, treatment options include a few limited antibiotics such as ciprofloxacin, and gentamicin (50, 51). Dalfopristin, quinupristin, and linezolid as lately offered or empirical drugs may be beneficial (52, 53).

There were some limitations to this study, which included: a) given that meta-analysis was performed only on published studies, the existence of biases between publications and regular reviews is inevitable, b) due to the lack of information presented in the articles and uncertainty of source of strains (nosocomial or community-acquired), only studies were selected that their MRSE strains were extracted from the patient samples, c) heterogeneity was observed among the studies, d) considering that the number of studies on the prevalence of MRSE in different parts of Iran is limited, so the results of this study cannot accurately show the frequency, e) given that the purpose of present study was determination of frequency, we could not provide information on the risk factors for colonization or MRSE infection.

CONCLUSION

This is the first meta-analysis report on the reduced prevalence of MRSE in Iran during 2016-2020. Although a slight decrease in prevalence in Iran is promising, it should be noted that it can rise again if methicillin administration is increased or infection control protocols in hospitals are ignored. Formulation of a definite antibiotic policy and regular surveillance of antimicrobial susceptibility may continue in reducing the frequency of MRSE in Iran. Moreover, rapid and reliable diagnosis of MRSE isolates, physicians' trust in laboratory results, and regular screening of hospital surfaces and personnel are essential.

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