Bacterial Ocular Infections in Iran: A Systematic Review and Meta-Analysis

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Abstract

***Objectives*:** Eye infections can be caused by several microorganisms and the most common causative bacterial agents are staphylococci, streptococci, and *Pseudomonas aeruginosa.* This study aimed to estimate the prevalence of *Staphylococcus aureus, Staphylococcus epidermidis,* viridans group streptococci, and *P. aeruginosa* that caused ocular infections in Iran. ***Methods*:** Systematic search was conducted on the studies published by Iranian authors from January 2000 to December 2020 in Web of Science, PubMed, Scopus and EMBASE. Eligible studies were selected according to the defined inclusion/exclusion criteria. Statistical heterogeneity between and within groups was estimated by the Q statistic and the I^2 index. The funnel plots were also obtained to evaluate the evidence of publication bias, as well as the Duval and Tweedie trim and fill methods. ***Results*:** Twenty-seven studies were included in this review. According to the meta-

analysis results, the prevalence of *S. epidermidis* was 19.1% (95% confidence interval (CI): 12.5%-28.1%). It was estimated 6.9% (95% CI: 4.4%-10.6%), 6.7% (95% CI: 4.6%-9.6%), and 3.3% (95% CI: 1.8%-5.8%) for *P. aeruginosa*, *S. aureus*, and viridans streptococci, respectively. ***Conclusions*:** Our results contribute to the understanding of the prevalent bacterial agents responsible for eye-associated infections in Iran.

Keywords: Eye infection, *S. aureus*, *S. epidermidis*, viridans streptococci, *P. aeruginosa*, Systematic review, Meta-analysis, Iran

Introduction

The eye is a unique anatomical organ, protected by the continuous flow of tear having antimicrobial compounds. However, it is often colonized by a range of microorganisms.[1] Eye infections can be caused by several microorganisms, such as bacteria, viruses, parasites, or fungi, and they are able to develop a spectrum of diseases and symptoms. The symptoms of infections are variable, depending on the type of infection and causative agents.[2] Ocular infections comprise of keratitis, endophthalmitis, conjunctivitis, blepharitis, stye, orbital cellulitis, and dacryocystitis manifestations.[3] Infectious keratitis is an infection of the cornea that might be associated to ocular surgery, trauma, contact lens, suppression of the immune system, such as diabetes, chronic use of topical steroids, or immunomodulatory therapies. Bacterial infection is the most common cause of infectious keratitis.[4] Endophthalmitis is a potentially blinding intraocular infection and inflammation, resulting from the entry of bacteria into the interior part of the eye.[5] Other aforementioned inflammatory diseases of the eye usually occur through bacterial infection.[6-8] The

most common causative bacteria are *Staphylococcus aureus*, coagulase-negative staphylococci, viridans group streptococci, and *Pseudomonas aeruginosa*.[9,10]

Understanding the epidemiology of eye infections in a region is essential to reinforce effective prevention and control strategies. There is no comprehensive data regarding bacterial ocular infections in Iran. Therefore, the aim of the present study was to assess the prevalence of frequent bacteria that cause ocular infections during 21 years in Iran using a systematic review and meta-analysis.

Methods

In the present systematic review and meta-analysis study, all procedures for identification of papers were carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines. This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (Register code: IR.SKUMS.REC.1400.091).

Search strategies

A systematic search was conducted on studies published by Iranian authors from January 2000 to December 2020 in Web of Science, PubMed, Scopus and EMBASE. Records were managed by EndNote X9.0 software to exclude the duplicates. We used eye infection-related key terms (conjunctivitis, Keratitis, Stye, Uveitis, endophthalmitis, eye disorder, ocular infection, and eye infection) and key terms to identify Iran. To identify the missing studies, we also searched bibliographies of retrieved articles for additional references.

Eligibility Criteria and Study Selection

Cross-sectional or cohort studies that reported the prevalence of *S. aureus* or *S. epidermidis* or viridans streptococci or *P. aeruginosa* in eye infections were considered. The titles, abstracts and full texts were screened independently by two reviewers to determine the articles which met the inclusion criteria, and any discrepancies were resolved with a third investigator or by consensus. The articles published in the English or Persian language which were indexed in PubMed or Scopus with the following characteristics and reported the prevalence of *S. aureus* or *S. epidermidis* or viridans streptococci or *P. aeruginosa* in eye infections were included. Additionally, studies conducted by non-Iranian authors on the Iranian population or samples were also assessed. The studies without reports of bacterial prevalence in eye infections were excluded. The studies with insufficient, unclear, or missing information were also excluded from the meta-analysis.

We also excluded the studies with sample size < 10 isolates, non-human studies, published studies in languages other than English or Persian, review articles, meta-analyses or systematic reviews and congress abstracts.

Data extraction and definitions

Data collection was performed in parallel by two investigators who performed the literature searches. Variables such as first author's name, the time the study was performed, publication date, the study setting, site of infection, sample size (number of bacterial isolates obtained from eye infections), and the prevalence of the mentioned bacteria were extracted.

Statistical analysis

Analysis of data was performed using Comprehensive Meta-Analysis Software Version 2.2 (Bio stat Company). Meta-analysis was performed using random effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Statistical heterogeneity between and within groups was estimated by the Q statistic and the I^2 index. The funnel plots were also carried out to evaluate the evidence of publication bias, as well as the Duval and Tweedie's trim and fill methods.

Results

A total of 345 articles were retrieved using the search strategy; 285 were excluded based on the index and review of the titles and abstracts, leaving 60 articles for full text review. Full-text screening resulted in exclusion of 33 studies, resulting in 27 eligible studies. Figure 1 shows the study selection process and reasons for exclusion. The main characteristics of the included studies and the prevalence of *S. aureus*, *S. epidermidis*, viridans streptococci, and *P. aeruginosa* in eye infections are shown in Table 1.

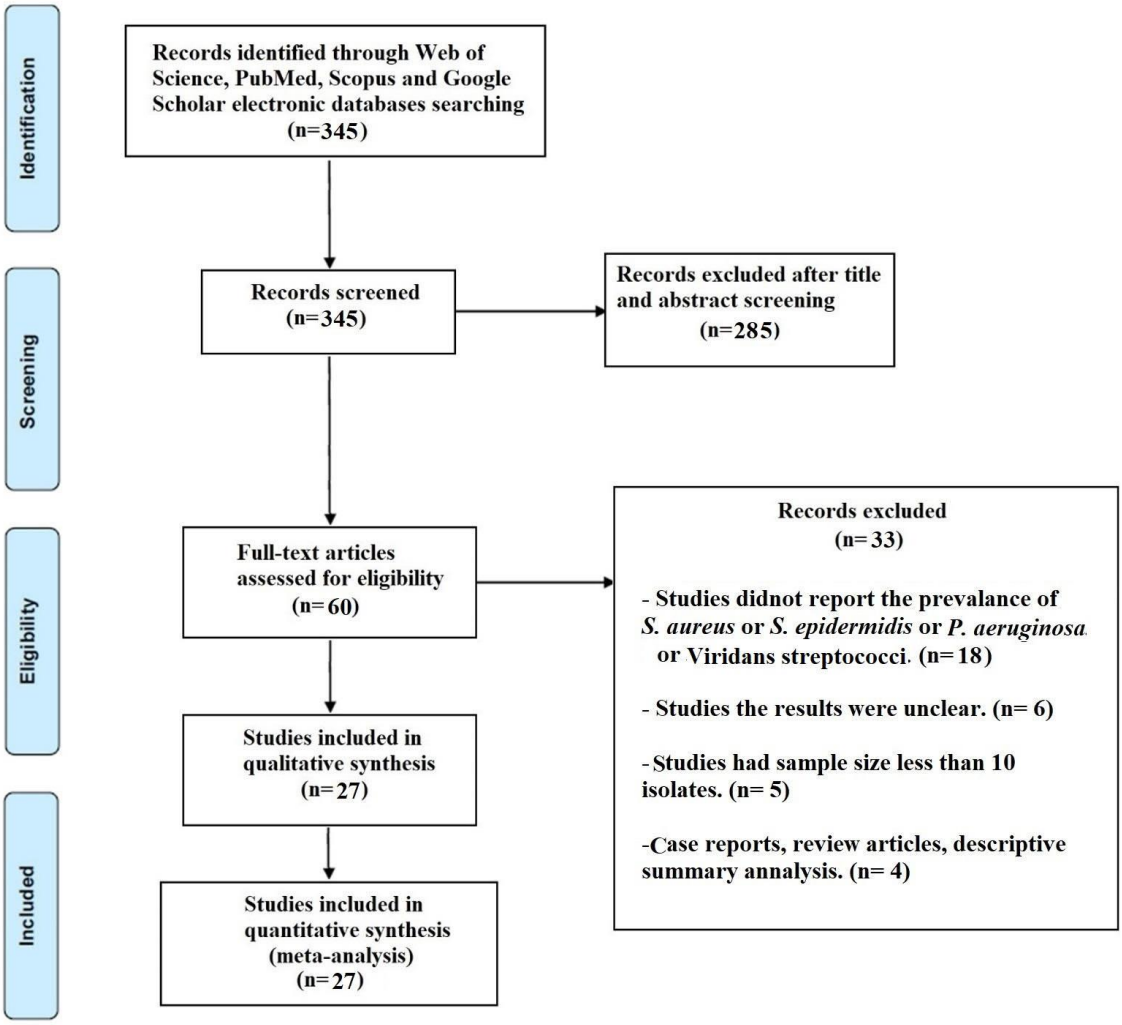

Figure 1: Summary of the literature search and study selection.

Table 1: Characteristics of studies included in the meta-analysis.

Study details					Infectious agents				
Author	**Publication year**	**Years of study**	**City or Region**	**Site of infection**	***S. aureus* (%)**	***S. epidermidis* (%)**	**Viridans streptococci (%)**	***P. aeruginosa* (%)**	**Reference**
Tabatabaei et al.	2020	2008-2018	Tehran	Iritis and/or vitritis	27.1	-	2.8	4.9	11
Soleimani et al.	2020	2008-2017	Tehran	Keratitis	4.3	10.8	1.1	10.8	12
Abtahi et al.	2020	2016-2019	Shiraz	Orbital cellulitis	2	2	-	-	13
Feizi et al.	2019	2017	Tehran	Persistent corneal epithelial defects	2	17.5	2	-	14
Zare et al.	2019	2017-2018	Tehran	Corneal ulcers	6	-	1	3	15
Nemati et al.	2018	2014-2015	Guilan	Nasolacrimal duct obstruction	4.1	16.6	-	11.1	16
Owji et al.	2018	UN	Shiraz	Nasolacrimal duct obstruction	18	62.6	6	-	17
Eghtedari et al.	2018	UN	Shiraz	Corneal ulcer	7.9	6.3	-	9.5	18
Heidari et al.	2018	2016-2017	Shiraz	Corneal infection	7.1	-	-	12.5	19
Faridi et al.	2018	2016	Tehran	External ocular infection	9.8	-	-	-	20
Eshraghi et al	2016	UN	Tehran	Unilateral nasolacrimal duct obstruction	7	40.8	11.2	-	21
Faghri et al.	2016	2013	Isfahan	Severe pain and corneal ulcers	2.5	49.3	-	6.4	22
Rahimi et al.	2015	2008-2012	Tehran	Bacterial keratitis	3.8	6.1	6.6	24.7	23
Abrishami et al.	2015	UN	Mashhad	Post-operative endophthalmitis	9.3	9.3	-	6.2	24
Oryan et al.	2014	2012-2013	Isfahan	Keratitis Infections	2.6	49.3	-	6.5	25
Sharifi et al.	2013	2007-2010	Yasuj	Ocular Trauma	2.8	3.8	1	1	26
Eshraghi etl al.	2013	2007-2010	Tehran	Acute dacryocystitis, lacrimal sac empyema underwent incision and drainage	25	-	12.5	-	27
Ghasemi et al.	2013	UN	Tehran	Serious sulfur mustard induced ocular injuries	3.5	7	0.7	-	28
Ghasemi Falavarjani et al	2012	2006-2011	Tehran	Endophthalmitis	15.3	24.6	1.5	23	29
Rahimi et al.	2012	2005-2009	Shiraz	Acute Endophthalmitis	17.1	5.7	-	5.7	30
Bagheri et al.	2012	1997-2007	Tehran	Orbital and preseptal cellulitis	7.5	-	-	-	31
Hosseini et al.	2011	2008	Shiraz	Endophthalmitis	11.3	31.8	18.1	2.2	32
Karimian et al.	2011	UN	Tehran	Chronic Blepharitis	3	57	-	-	33
Sedghipour et al.	2011	2000-2003	Tabriz	Corneal ulcer	-	23.2	-	-	34
Etezad Razavi et al.	2010	2007-2008	Mashhad	Acute and chronic dacryocystitis	13.1	47.5	1.6	3.2	35
Khosravi et al.	2007	2005-2006	Ahwaz	Ocular infection	2.8	7.2	1.5	5.3	36
Feizi et al.	2007	UN	Tehran	Ocular infection	21.5	0.5	1	0.5	37

In 26 studies, the prevalence of *S. aureus* in eye infections was investigated. The pooled prevalence for *S. aureus* isolates was 6.7% (95% CI: 4.6%-9.6%), ranging from 0.5% to 27.1% (Figure 2). There was a significant heterogeneity among the 26 studies ($\chi 2 = 136.101$; $P < 0.001$; $I^2 = 81.6\%$). The symmetric funnel plot showed no evidence of publication bias (Supplement 1A). Furthermore, using the Duval and Tweedie's Trim and Fill procedures, no evidence of publication bias was found for any of the measures.

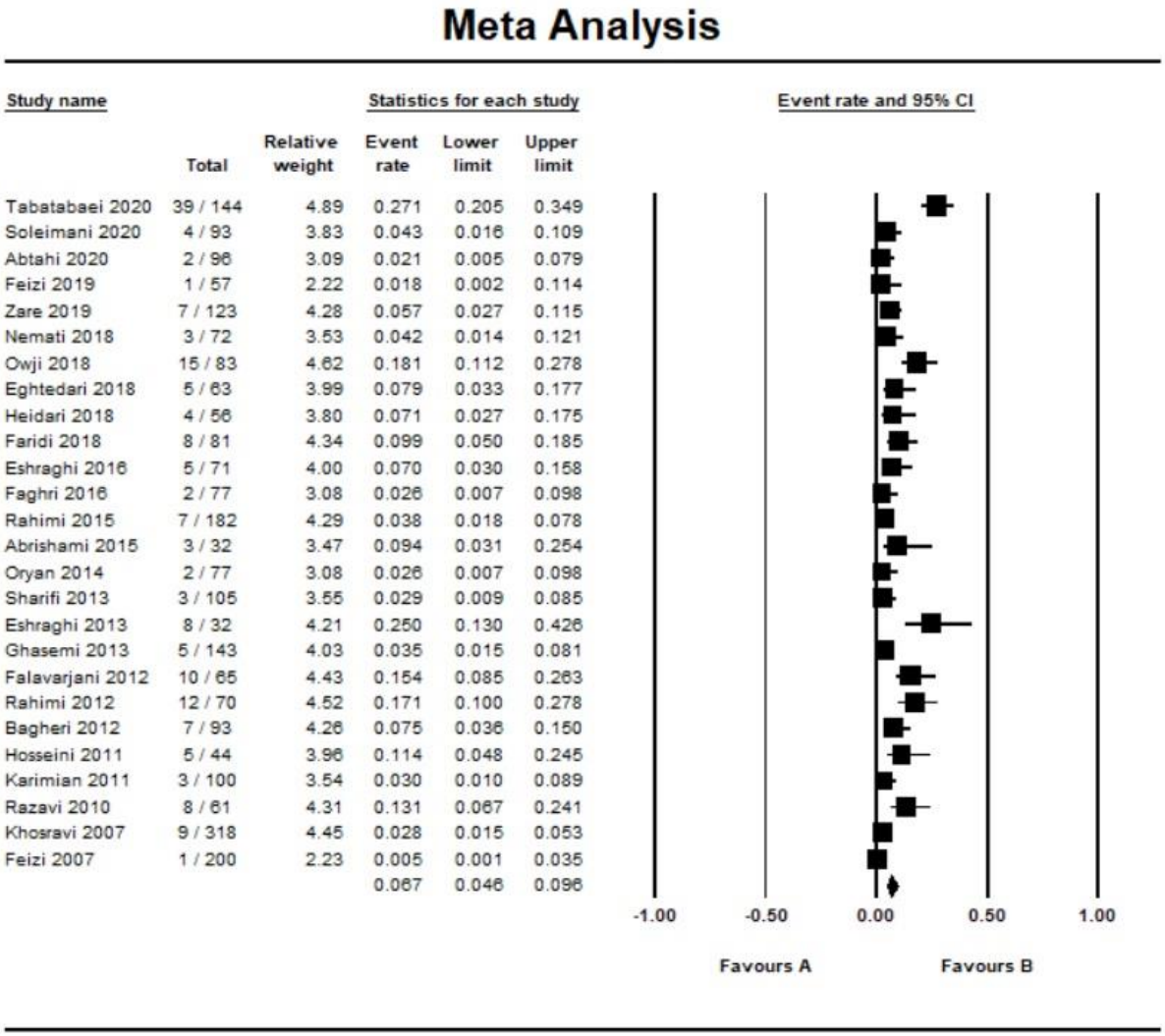

Figure 2: Forest plot of prevalence of ocular infections causative *S. aureus* isolates in Iran.

According to the included studies, the frequency of *S. epidermidis* isolates was investigated in 21 studies. The pooled prevalence of *S. epidermidis* isolates was estimated 19.1% (95% CI: 12.5%-28.1%), ranging from 2.1% to 62.7% (Figure 3). There was a significant heterogeneity among the 21 studies ($\chi 2$ = 328.470; P <0.001; I^2 = 93.9%). There was no evidence of publication bias (Supplement 1B).

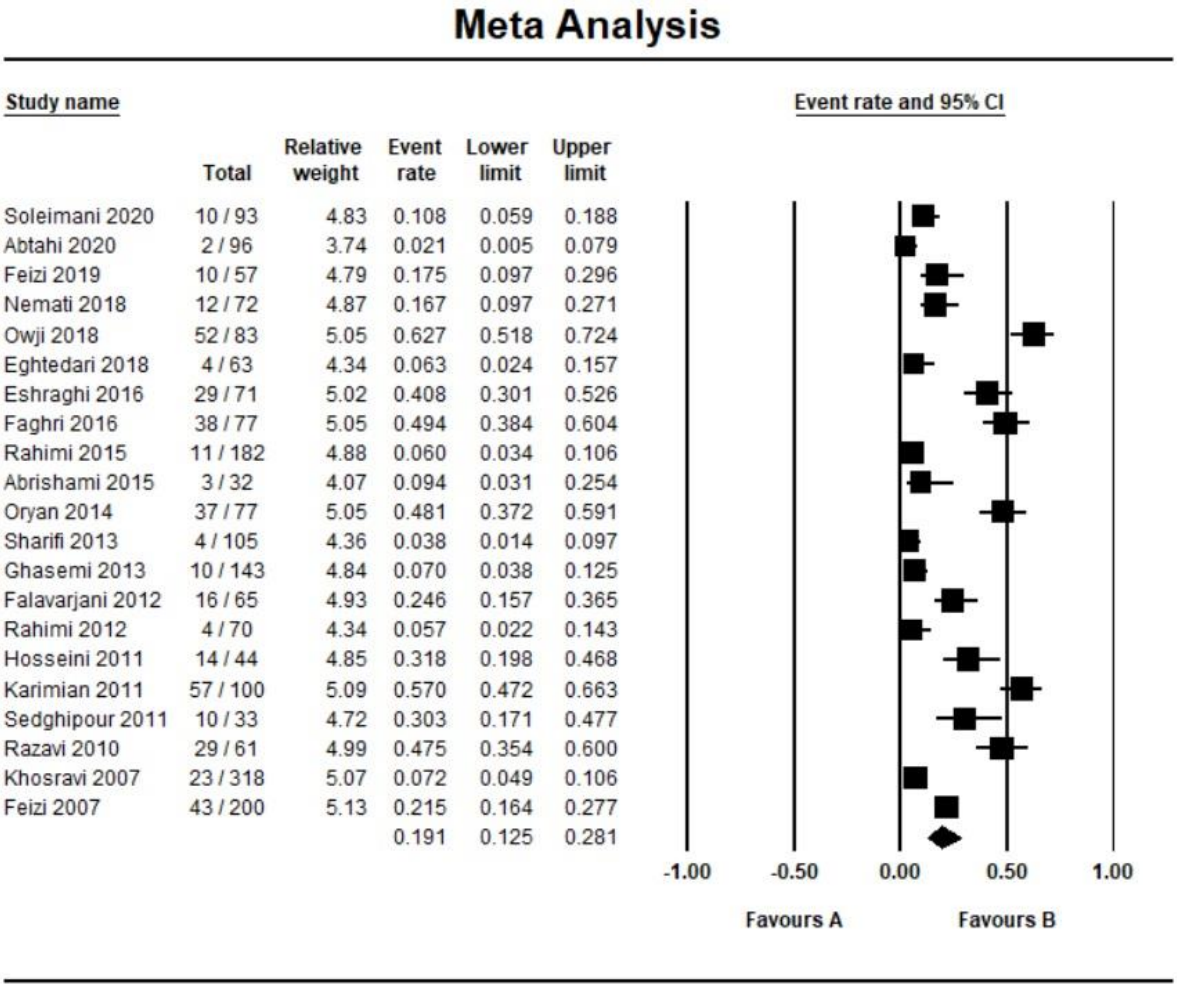

Figure 3: Forest plot of prevalence of ocular infections causative *S. epidermidis* isolates in Iran.

In 15 studies on viridans group streptococci, the pooled prevalence was 3.3% (95% CI: 1.8%-5.8%), ranging from 0.7% to 18.2% (Figure 4). There was a significant heterogeneity among the 15 studies ($\chi 2 = 54.2$; $P < 0.001$; $I^2 = 74.2\%$). Publication bias was assessed by a funnel plot for the standard error by logit event, with no evidence of bias (Supplement 1C). Additionally, Duval and Tweedie's Trim and Fill tests suggested that there was no notable evidence of publication bias.

We found 17 articles which investigated the prevalence of *P. aeruginosa* in bacterial eye infections. The pooled prevalence of *P. aeruginosa* isolates was estimated 6.9% (95% CI: 4.4%-10.6%), ranging from 0.5% to 24.7% (Figure 5). Based on Q statistic and the I^2 index, heterogeneity was significant ($\chi 2 = 91.699$; $P < 0.001$; $I^2 = 82.6\%$). Also, there was no evidence of publication bias (Supplement 1D).

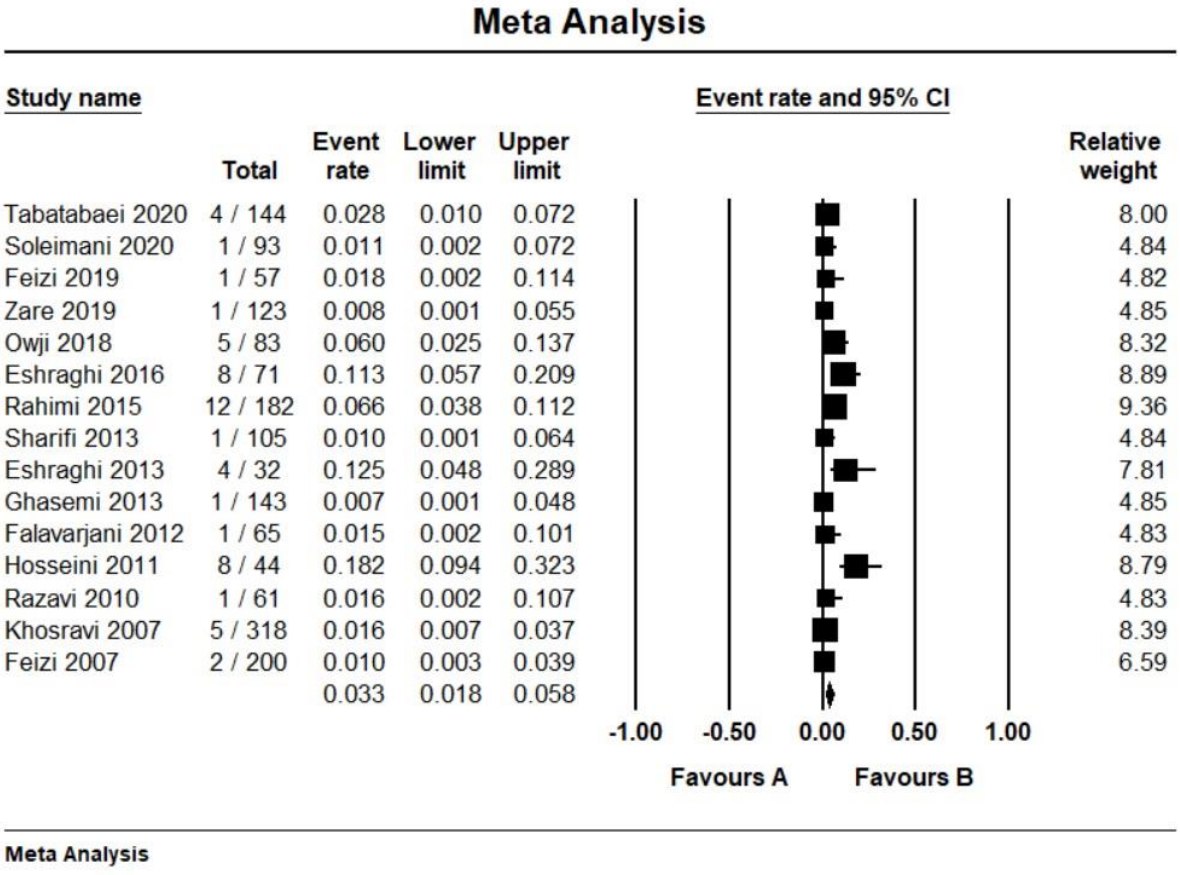

Figure 4: Forest plot of prevalence of ocular infections causative viridans streptococci in Iran.

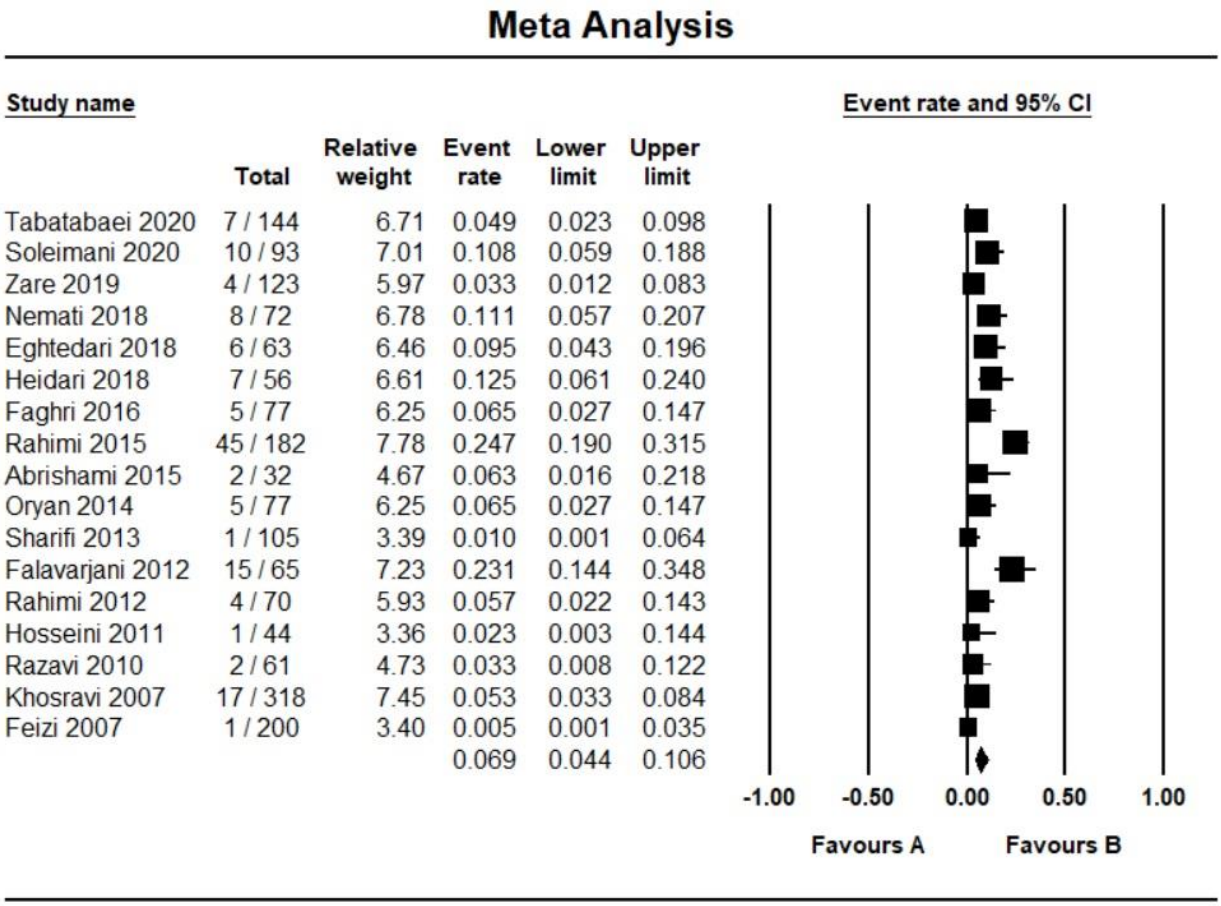

Figure 5: Forest plot of prevalence of ocular infections causative *P. aeruginosa* isolates in Iran.

Discussion

Bacteria are the major contributors of ophthalmic diseases worldwide. The dominant causative bacterial agents of ocular infections are staphylococci, streptococci, and *P. aeruginosa*.[9.10.38] To the best of our knowledge, this study is the first systematic review regarding the prevalence of *S. aureus, S. epidermidis, P. aeruginosa,* and viridans group streptococci isolates that caused eye infections in Iran. According to the meta-analysis results, the pooled prevalence of *S. aureus* isolates that caused these infections was 6.7%. In a previous systematic review conducted on bacterial profile of ocular infections in several developed and developing countries (such as, Nigeria, India, Ethiopia, Japan, USA, Malaysia), the average prevalence of *S. aureus* was more

than 20%.[38] Furthermore, our analysis indicated that the pooled prevalence of *S. epidermidis* isolates was 19.1%, and it was the most common agent responsible for eye infections. Various prevalence rates of *S. epidermidis* or coagulase negative staphylococci were reported in previous studies.[38-46] These discrepancies may be related to the type of eye-associated infections. Besides, a variety of factors, such as contact lens wearing, immune system status, anatomical disruption, and traumatic inoculation of the organisms by foreign bodies, could determine the prevalence and distribution of the type of bacterial agents associated with ocular infections. These factors may lead to infection development by normal flora such as members of the staphylococci.[38] *S. epidermidis* is the most commonly found bacteria, colonizing the mucosa and lid margins. Also, underlying diseases (such as, diabetes) may affect the *S. aureus* colonization in eyes and its subsequent prevalence in such infections. Geographical climate (heat and humidity) has been reported as another factor that affects the composition of ocular surface flora.[47]

Our analysis indicated that the pooled prevalence of viridans streptococci isolates was 3.3%. In a retrospective study in the US, the viridans streptococci were responsible for the majority of endophthalmitis caused by *Streptococcus* species (71%).[48] Another retrospective researches in USA indicated that 11% of ocular infections and 12.1% of endophthalmitis cases were related to viridans group streptococci.[46,49] The prevalence of these bacteria was 2.8% in community-acquired bacterial ocular infections in India.[40] Various rates of viridans group streptococci associated with ocular infections were reported from several regions, such as Spain (5%)[50], Mexico (14.3%)[51], Nigeria (1.5%)[38], and UK (0.4%).[52] This diversity may be related to different types of ocular infections.

The pooled prevalence of *P. aeruginosa* isolates was estimated 6.9%. More rates were reported from Taiwan (35.2%)[43], Ethiopia (11.7%)[44], India (10.7%)[53], 21%[38] and 44%[54], Nigeria (10.1%),

Japan (9.7%), Malaysia (16%)[38] and USA (8-16%)[38,46]. An analysis in UK showed that the prevalence of *P. aeruginosa* was 7.2%.[45] However, lower frequencies were reported from India (3%) and Ethiopia (4.9%), previously.[38] *P. aeruginosa* utilizes various virulence factors and mechanisms, such as exotoxins, proteases, elastases, and biofilm formation to develop infection in the eye tissues. It is a common causative agent in cases of ocular infections, especially corneal ulcer infection and keratitis associated with contact-lens. Moreover, the current evidence suggests that the majority of such infections are related to *P. aeruginosa* genotypes which encode the exotoxin U. Constant exposure to sub-inhibitory concentration of lens cleaning solutions and biocides can contribute to resistance to disinfectants. Prevalence of infection caused by *P. aeruginosa* also depends on other predisposing factors, such as ocular surgery, immunodeficiency, diabetic mellitus, and rheumatoid arthritis. These situations may lead to severe infections such as endophthalmitis.[38, 55-58]

Conclusions

The present systematic review indicated that *S. epidermidis* was the most common bacterial agent responsible for ocular infections in Iran (19.1%). The prevalence of *P. aeruginosa* isolates was 6.9%, and *S. aureus* and viridans group streptococci accounted for 6.7% and 3.3% of eye-associated infections. Our results will contribute to understanding bacterial agent contributions in ocular infections in Iran.

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Conflict of interest

All authors declare that they have no competing interests.

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