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Review Article

Mycotic Keratitis in the Middle East: A Systematic Review and Meta-Analysis

Mahmoud Karimizadeh Esfahani
Department of Parasitology and Mycology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Mohsen Najjari
Department of Parasitology and Mycology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Saeed Hosseini Teshnizi
Food Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Somayeh Dolatabadi
Department of Biology, Hakim Sabzevari University, Sabzevar, Iran

Mohammad Javad Najafzadeh
Department of Parasitology and Mycology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding author: Somayeh Dolatabadi

Email: somayeh99@gmail.com

Tel: +985144012457

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ABSTRACT

Background and objectives: Mycotic keratitis is a fungal infection of the cornea that can cause blindness. Its incidence, risk factors, and the etiological agents vary worldwide and nationwide. Therefore, proper documentation of these data is essential for better disease management. In this review, we aimed to make a clear picture of this infection in the Middle East.

Methods: Data on fungal keratitis from 1986 to 2018 in the Middle East were systematically collected from five English databases (PubMed, Scopus, Science Direct, Web of Science, and Google Scholar) and four Persian databases (Magiran, Scientific Information Database, IranMedex, and Irandoc). A total of 35 studies were included in the review.

Result: The pooled prevalence of fungal keratitis in the Middle East was estimated at 26% (95% confidence interval: 19-32%; $I^2 = 98.88\%, p < 0.001$) using random-effect model, with considerable variation among the countries. The prevalence of fungal keratitis was highest in Egypt (36%) and Iran (34%) and lowest in Oman (9%). *Aspergillus* and *Fusarium* spp. were the most common causative agents (28%) among filamentous fungi, and *Candida* (13%) was the predominant yeast species causing fungal keratitis. Based on the data, fungal keratitis was more prevalent in males (39%) than in females (23%).

Conclusion: Our study is the first systematic review on mycotic keratitis among the Middle Eastern countries. These epidemiological estimates can be used by policy makers to improve treatment strategies, especially in this part of the world.

Keywords: Egypt, Iran, Systematic Review.

INTRODUCTION

Mycotic keratitis is a fungal infection of the cornea, which may lead to vision loss (1). Infiltration of fungi to the cornea layers is mostly invasive and may cause irreversible changes in the eye (2). Compared to other ophthalmic infections, it is more difficult to diagnose and treat due to the aggressive course of infection, limitation of treatment options, and fungal resistance to medications; thus, many cases require surgery to maintain corneal integrity (3). *Aspergillus* and *Fusarium* are the most common filamentous fungi causing keratomycosis, and *Candida* spp. are the most common yeast-like fungi that cause mycotic keratitis (4-6).

The microbial causes of keratitis vary considerably both worldwide and nationwide. The incidence of keratitis is higher in tropical, subtropical (2), and developing countries (7-8). Thus, it is essential to determine the etiology of keratitis within a given region when planning for management strategies.

Ocular trauma is the most common predisposing factor for microbial keratitis (9). There have been increased reports of mycotic keratitis (9) in the past few decades, which can be due to increased clinical awareness, improved diagnostic techniques, and widespread use of corticosteroids, antibiotics, immunosuppressive/chemotherapeutic drugs, and ocular prosthetic devices (10). Proper diagnosis can be affected in case of partial or traditional treatments, mixed infections, and antibiotic resistance. The number of antifungal agents available for the treatment of microbial keratitis is limited compared with the number of pathogens capable of infecting the eye. Fungal keratitis is mainly managed by antifungal agents, and keratoplasty or corneal transplant is usually reserved for acute management of corneal perforation and for visual rehabilitation following corneal scarring (10). Reliable and fast diagnostic methods such as polymerase chain reaction (PCR) can help to overcome these uncertainties (11). Early and proper management of this condition and registration of the patient's clinical history, such as the cause of injury, predisposing conditions, the use of antibiotics or steroids, and occupation are essential for saving vision and improving our understanding of this infection.

This study is the first systematic review on fungal keratitis in the Middle East. In this review, we aimed to make a clear picture of this infection in the Middle East, which could be useful for better management of the disease.

MATERIALS AND METHODS

Five major English databases (PubMed, Scopus, Science Direct, Web of Science, and Google Scholar) and four Persian databases (Magiran, Scientific Information Database, IranMedex, and Irandoc) were searched for articles about fungal keratitis in the Middle East that have been published from 1986 to 2018. The search terms used alone or combined both in Persian and in English languages were: keratitis, fungal keratitis, mycotic keratitis, keratomycosis, and each of the Middle East countries (i.e. Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, the United Arab Emirates, and Yemen). To avoid missing any papers, references of each paper were checked with accuracy.

Full text of the articles in both English and Persian with available data on epidemiological parameters, laboratory findings, identification methods, and causative fungal species were retrieved. Case reports, case series, duplicates, and studies on non-fungal keratitis were excluded.

Eligibility of the articles was evaluated by two independent experts (KM and NM) based on inclusion criteria. Study variables included the first author, study period, year of publication, country, sample size, number of male and female participants, number of positive cases, sex, age distribution, diagnostic methods, and causative fungal species. Duplicated records, studies with insufficient data, and unrelated articles were excluded after the initial screening. Citations to these articles were searched for additional relevant articles published in peer-reviewed journals not retrieved by the initial search.

After extracting the sample size (n), the number of positive cases, and prevalence of fungal keratitis (P), standard error ($SE=\sqrt{\frac{P(1-P)}{n}}$) for each study was calculated.

Heterogeneity among primary studies was assessed by the I^2 statistics (25%: low; 50%: medium, 75%: high) and the Cochrane's Q test (with a significance level of $p<0.1$). Wherever the Cochrane's Q test and I^2 confirmed the

study heterogeneity, random effect meta-analysis based on the DerSimonian and Laird method (12) was used to combine the outcomes; otherwise a fixed-effect meta-analysis was used.
The results for each study and pooled estimates were presented in a forest plot, in which, standard error (SE) with 95% confidence intervals (CI) was considered. A forest plot was used to visualize the prevalence of different diagnostic methods. Subgroup analysis and meta-regression were used to compare prevalence of different variables such as age, sex, sample size, and publication year.
Potential publication bias was assessed by Egger's test (quantitative method) and funnel plot (which plots the prevalence of each study against its standard error). All analyses were performed using the STATA statistical software package (version 14, StataCorp LP, College Station, Texas, USA).

RESULTS

A total of 573 studies were retrieved from the databases and other resources. After excluding 188 duplicates, 385 papers were checked for the inclusion criteria, and finally, 35 eligible studies from six countries (Egypt, Iran, Turkey, Iraq, Saudi Arabia, and Oman) were included. To estimate the pooled prevalence of keratitis, results of the studies were combined. Based on the random-effects meta-analysis ($I^2 = 98.88\%$, $P < 0.001$), the pooled prevalence of fungal keratitis in the Middle East was 26% (95% CI: 19-32%; $I^{\wedge 2}$=98.88%, p<0.001) (Figure 1).

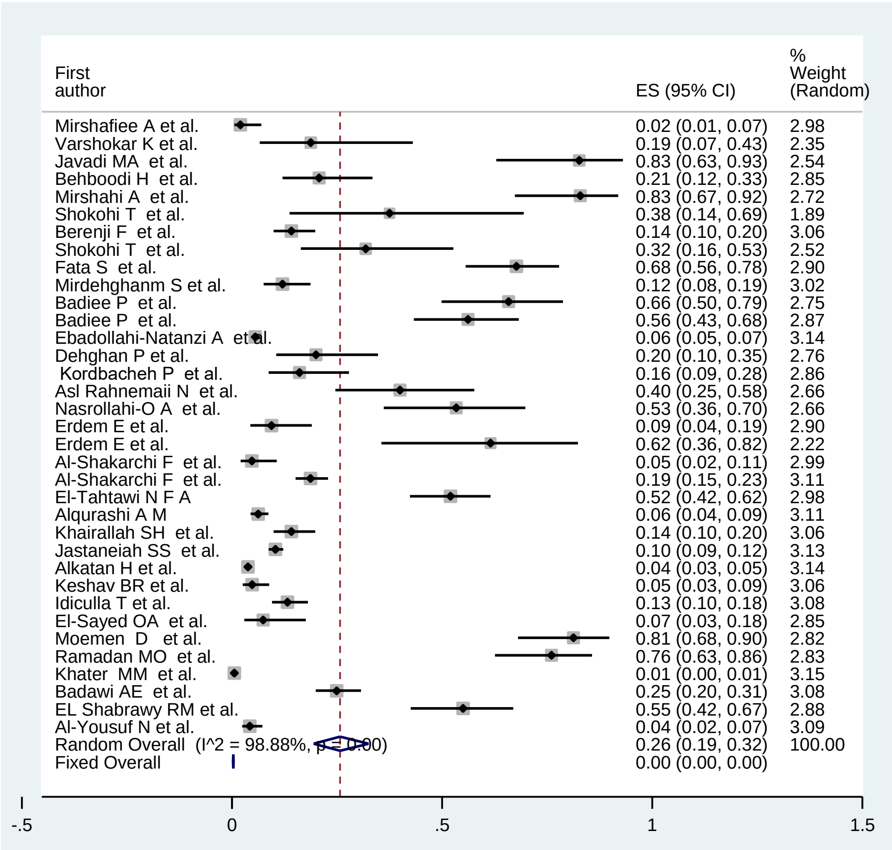

Figure 1-Forest plot diagram of the included studies (n=35). Effect size (ES) in each line indicates the prevalence of fungal keratitis, and the length of each line indicates 95% confidence interval (CI) of each study. Diamonds indicate the 95% CI for all studies. The vertical dash line represents overall estimate.

According to the fixed and random effect models, *Fusarium* (28%) and *Aspergillus* (28%) had the highest prevalence, while *Alternaria* (4%) and *Acremonium* (2%) had the lowest prevalence. Among the yeasts, *Candida* was seen in 13% of cases (Table 1). The prevalence of fungal keratitis was highest in Egypt (36%) and Iran (34%) and lowest in Oman (9%) (p<0.001). The potassium hydroxide-calcofluor white stain (KOH-CFW) (65%) and PCR (53%) were the most commonly used detection methods (p<0.001).

Fungal keratitis was significantly more prevalent in males (39%) than in females (23%) (p=0.041) (Table 1, Figure 2).
To explore the source of heterogeneity, meta-regression analysis was performed. The heterogeneity was related to variables such as age, sex, and sample size (p<0.05). The meta-regression analysis also showed a significant increasing trend for fungal keratitis (p=0.493) (Figure 3). Based on the results of the Egger's test, there was a significant publication bias (t=3.30, p=0.003).

Table1- Comparison of the prevalence of fungal keratitis based on fungi, countries, diagnostic methods, and gender

Characteristics	Fungal spp.	Method	N	Prevalence (95% CI)	I^2 (%)	*p*-v
	***Aspergillus* spp. ssspp.spp.**	Random	45	28.0 (21.0 , 35.0)	91.77	<.0
Fungi	***Fusarium* spp.**	Random	25	28.0 (21.0 , 37.0)	80.78	<.0
	***Candida* spp.**	Random	17	13.0 (8.0 , 19.0)	83.08	<.0
	***Alternaria* spp.**	Random	11	4.0 (1.0 , 7.0)	55.71	.01
	***Penicillium* spp.**	Fixed	10	6.0 (5.0 , 8.0)	48.85	.12
	***Acremonium* spp.**	Fixed	6	2.0 (0.0 , 4.0)	23.94 4	.55
	***Mucor* spp.**	Random	5	9.0 (1.0 , 22.0)	92.08	<.0
	***Cladosporium* spp.**	Fixed	5	9.0 (6.0 , 12.0)	36.91	.31
	***Trichophyton* spp.**	Random	2	20.0 (14.0 , 27.0)	-	-
	Other	Random	17	14.0 (8.0 , 21.0)	70.91	<.0
Country	Iran	Random	17	34.0 (21.0, 49.0)	96.98	<.0
	Egypt	Random	6	36.0 (7.0, 72.0)	99.93	
	Saudi Arabia	Random	5	14.0 (7.0, 23.0)	97.91	
	Turkey	Random	2	15.0 (8.0, 25.0)	98.73	
	Iraq	Random	2	15.0 (12.0, 18.0)	97.92	
	Oman	Random	2	9.0 (7.0, 12.0)	99.61	
	Culture	Random	17	28.0 (14.0, 45.0)	98.6	
Diagnostic methods	KOH	Random	8	22.0 (11.0, 36.0)	93.7	<.0
	PCR	Random	3	58.0 (43.0, 72.0)	98.7	
	KOH-CFW	Random	2	65.0 (54.0, 76.0)	97.1	
Gender	Male	Random	27	39.0 (27.0, 51.0)	99.4	.04
	Female	Random	27	23.0 (15.0, 33.0)	99.1	

N: number of study; KOH-CFW: potassium hydroxide-calcofluor white stain; PCR: polymerase chain reaction

DISCUSSION

Microbial keratitis is a potentially blinding condition that must be treated promptly to preserve vision. Although the disease has been long recognized as a significant cause of corneal blindness, our understanding of its true global scale, the associated burden of disease, and etiological patterns is limited. This condition might be epidemic to some parts of the world. Mycotic keratitis is generally more common in tropical and subtropical regions, such as Egypt (14), other Middle Eastern countries (15-16), and India (17). This meta-analysis showed a pooled prevalence of 26% for fungal keratitis with a wide variation between countries. The highest pooled prevalence of fungal keratitis was observed in Egypt (36%) and Iran (34%), while the lowest pooled prevalence was observed in Oman (9%). Based on the analysis, the rate of mycotic keratitis was increasing over these years (Figure 3), which has been also reported by other studies (18-19).

The incidence of mycotic keratitis was significantly higher in developing countries. The incidence rate of mycotic keratitis in the USA increased from 2.5 per 100,000 persons in the 1950s to 11.0 per 100,000 in the 1980s, which could be related to the increased use of contact lenses (20), while in developing countries, an incidence rate as high as 799 per 100,000 in Nepal was reported, which could be related to the predominant professions such as farming (21). With pooled prevalence rate of 28%, *Aspergillus* and *Fusarium* were the most common causative agents of filamentous mycotic keratitis worldwide (15, 22), which is in agreement with other studies (23-24). *Aspergillus* and *Fusarium* species have been isolated from soft contact lenses (25-26). As non-filamentous fungi, *Candida* spp. isolates have been found in temperate climate (27).

Figure 2-Forest plot for diagnostics methods.

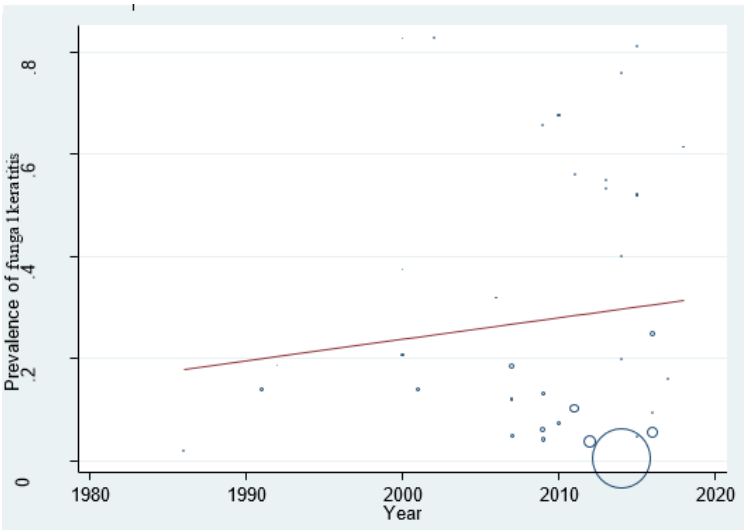

Figure 3- Meta-regression plot of rate of fungal keratitis according to year of publication. The circles represent studies' sample size

Curvularia and other phaeohyphomycetes, *Scedosporium apiospermum*, and *Paecilomyces* are among other common causes of filamentous fungal keratitis (28). In filamentous fungal keratitis, fungi are the sole exposing factor, while keratitis due to yeasts usually occurs in patients with pre-existing ocular conditions, chronic systemic diseases superimposed on viral ocular infections, contact lenses (29-30), and history of ocular surgery, ocular surface disease, or corticosteroids therapy (31-32).

Ocular trauma is the major risk factor for fungal keratitis (33-35). The ooccurrence of fungal keratitis was higher in men (39%) than in women (23%) (16-17, 36-37). This could be partly related to the occupation of men (i.e. farmers or construction workers) (38). In studies from Saudi Arabia and Egypt, trauma was reported as the predominant risk factor (39-40). The prevalence of trauma was highest in Egypt (51%) and lowest in Iran (0.3%). Systemic diseases such as diabetes mellitus and rheumatoid arthritis were observed in 16.6% of cases from Egypt 0.1% of cases from Saudi Arabia.

Improper use of contact lens (50% in Turkey), history of eye surgery (30% in Turkey), use of topical steroids (22.7% in Egypt), and diabetes (18% in Egypt) were other predisposing factors. Steroid therapy was seen in 10 cases from Oman.

Common clinical signs were pain (82%), foreign body sensation (80%), photophobic (77%), reduced vision (52%), excessive tearing (39%), and redness (39%).

Environmental factors and climate (17), the extent of urbanization, and differences in socio-economic groups might affect the incidence of mycotic keratitis (41). An increase in the incidence of microbial keratitis was observed during the hot and humid months in Turkey (42). Increase in the relative frequency of keratomycosis during 1997–2007 was correlated with rises in temperatures in Cairo due to the climate changes (43).

Diagnosis could be confirmed by culture, direct microscopy, and confocal microscopy (44-45). In recent years, PCR has been proven to be a reliable diagnostic method in terms of specificity and sensitivity compare with other conventional methods (46-48). In our review, KOH-CFW (65%) and PCR (53%) were the most commonly used diagnostic methods. In fact, PCR is an effective, rapid, and accurate method that needs small quantity of sample (corneal scrape or corneal biopsy material), which can reduce the need of culturing. However, PCR cannot be relied upon to monitor response of keratitis to treatment, to differentiate active from latent infection, and to distinguish viable from nonviable microorganisms (49).

Using conventional methods, causative agents have not been identified at species level in most of the included studies, indicating a need for applying molecular methods more commonly.

Management of mycotic keratitis is still challenging due to poor corneal penetration of medications and the limited efficacy of the available drugs. Topical natamycin (5%) and amphotericin B drops (0.1–1%) were the most frequently used antifungal agents. Natamycin and intrastromal voriconazole are key therapeutic agents for treatment of fungal keratitis. In developing countries, where the incidence of fungal keratitis is higher, the costs and availability of these polyene drops may be an issue (50). Therapeutic surgery, such as therapeutic penetrating keratoplasty is needed when medical therapy fails (51).

Our work suffers from the absence of synchronized data in some of the included papers such as age, occupation, predisposing factors, etc. Many related published manuscripts were excluded due to these insufficiencies, leaving us with only 35 included studies at the end. Most of the studies were only from six countries. No study from Bahrain, Cyprus, Israel, Jordan, Kuwait, Lebanon, Palestinian, Qatar, Syria, the United Arab Emirates, and Yemen were included in the review. Moreover, the predisposing factors, treatment strategies, and the outcome had not been investigated in some studies.

CONCLUSION

Early and proper management of fungal keratitis is crucial.

Epidemiological estimates will be useful for policy makers to improve treatment strategies, especially in the Middle East.

Early and proper management of this condition and registration of the patient's clinical history, such as the cause of injury, predisposing conditions, the use of antibiotics or steroids, and occupation are is essential for saving eye vision and improving our understanding of this infection.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest regarding publication of this article.

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