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Systematic Review

Manifestations of Ocular Surface Diseases in Patients with Laboratory-Confirmed COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Introduction: The epidemiology of ocular manifestations and associated complications in patients with Corona Virus Disease 2019 (COVID-19) have been investigated worldwide. Herein, we aimed to summarize the frequency of ocular symptoms of COVID-19 in the current systematic review and meta-analysis using available literature.

Materials and Methods: A search of PubMed, Scopus, Web of Science, EBSCO, and Embase electronic databases to review the systematic literature until August 2021. The Hoy et al., 2012 tool was used to evaluate the quality of studies. For Data extraction, two reviewers blind and independently extracted data from the abstract and full text of the studies included. 95% confidence interval for effect size with random effect model and restricted maximum likelihood (REML) method were calculated. Meta-analysis was performed using Stata/MP v.16 software (The fastest version of Stata).

Results: Initially, 210 studies were retrieved, of which we reviewed the full text of 24 records, and eight were selected for final meta-analysis. The prevalence of redness in patients with COVID-19 was 12.37% (ES, 95% CI -1.11%, 25.85%), and heterogeneity was found (I2 = 99.37%; p <0.001) (High heterogeneity). The prevalence of Ocular manifestations as the first symptom of COVID-19 in patients was 2.63% (ES, 95% CI 1.23%, 4.03%).

Conclusions: This systematic review and meta-analysis found the prevalence of redness, dryness, ocular pain, foreign body sensation, discharge, itching, follicular conjunctivitis, and watering as 12.37%, 26.70%, 30.64%, 14.47%, 19.93%, 8.77%, 12.77%, and 10.23%, respectively.

Keywords: Eye Diseases, COVID-19, Ocular Surface

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Introduction

Coronavirus disease 2019 was first reported in Wuhan, China, in December 2019 and spread rapidly worldwide,[1,2] and in March 2020, the World Health Organization approved the disease.[3] The causative agent of this potentially deadly disease was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4,5] The first symptoms of this disease are fever, cough, fatigue, sore throat, and headache, and deaths were reported in all age groups, especially the elderly.[6-8] It has been reported that the disease can cause manifestations in ocular tissues, while the main transmission route is through respiratory droplets.[9,10] Studies have shown that during the COVID-19 epidemic, ocular involvement is identified as a feature of the follicular conjunctiva.[9,11-14] A virus in these patients' conjunctival or tears specimens confirms these results.[15-17] However, ocular involvement and its consequences are unclear and need further study. Evaluation of the incidence of ocular manifestations and its nature associated with COVID-19 disease, the percentage of positive cases of reverse transcriptase polymerase chain reaction (RT-PCR) for viral RNA in ocular fluids is of great importance.[18-21] The present study investigated the epidemiology and clinical features of ocular surface manifestations, their complications in patients with COVID-19, and the risk of transmission through this study. Therefore, the current systematic review and meta-analysis study focused on ocular signs and symptoms related to ocular surface manifestations among patients with laboratory-confirmed COVID-19.

Materials and Methods

A search of PubMed, Scopus, Web of Science, EBSCO, and

Embase electronic databases to review the systematic literature from 2021 to 2021/08/30.

Use the MeSH Database to build search syntax in PubMed: (("Eye Infections"[Mesh]) AND ("Eye Diseases"[Mesh]) AND ("COVID-19"[Mesh]) OR ("COVID-19/complications"[Mesh]) AND (2021:2021/08/30[dp])).

Other databases were searched based on the following keywords:

Ocular surface manifestations, Eye Infections, Eye Diseases, ocular symptoms, COVID-19, severe acute respiratory syndrome coronavirus 2. Key considerations PRISMA was the basis of the present study.[22]

Selection Criteria

Inclusion criteria: cross-sectional studies, randomized controlled trials studies, ocular symptoms, and patients with COVID-19 in English. Prospective and Retrospective cohort studies, in vitro studies, case studies, case reports, and reviews; other infections were excluded from the study.

Study Selection, Data Extraction, and Method of Analysis

Studies data were reported by the study, years, study design, age, population, data collection, and ocular fluid analysis. The Hoy et al., 2012 tool was used to evaluate the quality of studies.[23] The scale scores for High and unclear risk were one, and low risk was 0. The risk of bias assessment is indicated by the following: score 0-3 is low risk, 4-6 is moderate risk, and 7-9 is high risk. For Data extraction, two reviewers blind and independently extracted data from the abstract and full text of the included studies. Before the screening, kappa statistics were carried out to verify the agreement level between the reviewers. Disagreements between reviewers are either resolved by consensus or by the decision of a third independent reviewer. The kappa values were higher than 0.80. A 95% confidence interval for effect size with the random effect model and REML method were calculated. Random effects were used to deal with potential heterogeneity, and I^2 showed heterogeneity. I^2 values less than 50% indicate low heterogeneity, and above 50% indicate moderate to high heterogeneity. Meta-analysis was performed using Stata/MP v.16 software (The fastest version of Stata).

Results

In the review of the existing literature using the studied keywords, 210 studies were found. In the initial review, duplicate studies were eliminated, and abstracts of 108 studies were reviewed. At this stage, 84 studies did not meet the inclusion criteria, so they were excluded, and in the second stage, the full text of 24 studies was reviewed by two authors. At this stage, 16 studies were excluded from the study due to incomplete data, inconsistency of results in a study, poor studies, lack of access to full text, and inconsistent data with the purpose of the study. Finally, eight studies were selected (Figure 1).

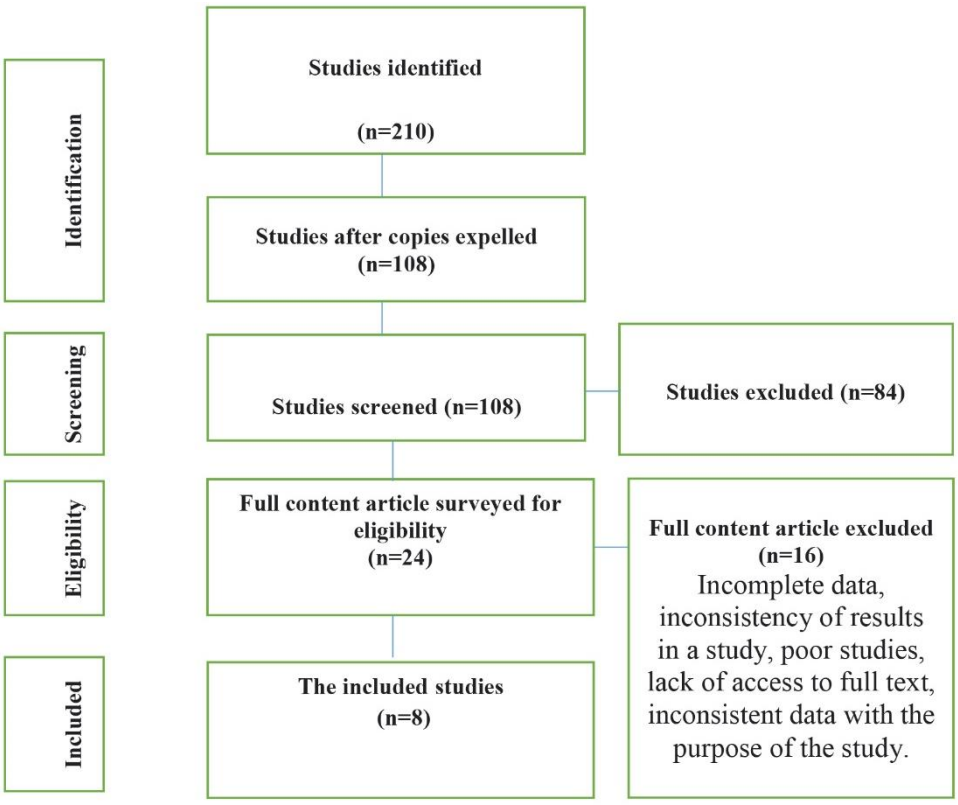

Figure 1. Study Attrition

Table 1. Studies Selected for Systematic Review and Meta-Analysis

Study. Years	Study Design	Number of patients (%)		Mean of Age (years)	Data Collected	Analysis of Ocular Fluids
		Male	Female			
Karimi et al., 2020[24]	Cross-sectional	64.7	35.3	56.6	Eye examination	Conjunctival swab
Xu et al., 2020[25]	Cross-sectional	53.3	46.7	43	Eye examination	Conjunctival swab
Lan et al.,2020[26]	Cross-sectional	40.7	59.3	41.2	Eye examination	Conjunctival swab
Zhou et al.,2020[27]	Cross-sectional	22.2	77.8	35.8	Questionnaire	Conjunctival swab
Wu et al., 2020[28]	Cross-sectional	65.8	34.2	67.9	Eye examination	Conjunctival swab
Tostmann et al., 2020[29]	Cross-sectional	21.1	78.9	NR	Questionnaire	NR
Zhang et al., 2020[30]	Cross-sectional	55.4	44.6	48.3	Eye examination	Conjunctival swab
Hong et al., 2020[31]	Cross-sectional	47.1	52.9	57.9	Questionnaire	NR

Table 2. Risk of Bias Assessment

Study	Close representation of the national population	Sample frame	Random selection	Non-response bias	Data collected	Acceptable case definition	Reliability and validity of measurement instruments	Data collection	Denominator & Numerator	Total Score
Karimi et al., 2020[24]	-	-	-	+	+	+	+	+	-	4
Xu et al., 2020[25]	-	-	-	+	+	+	-	+	-	5
Lan et al.,2020[26]	-	+	-	+	+	-	-	+	-	5
Zhou et al.,2020[27]	-	+	-	+	+	-	-	+	-	5
Wu et al.,2020[28]	-	+	-	+	+	+	-	+	-	4
Tostmann et al.,2020[29]	-	+	-	-	+	-	+	+	-	5
Zhang et al.,2020[30]	-	+	-	+	+	+	+	+	-	3
Hong et al.,2020[31]	-	-	-	+	+	+	-	+	-	5

Characteristics

Eight Cross-sectional studies have been included in the present article. Of the number of patients, 46.25% were male and 53.75% were female. The mean age in patients with COVID-19 was 50.1 years. In six studies, data was collected by an eye examination, and in two studies, by questionnaire. Analysis of ocular fluids in six studies were conjunctival swabs (Table 1).

Bias Assessment

All studies had a moderate risk of bias, Except the Zhang et al., 2020 study, which had a low risk of bias (Table 2).

Prevalence of Ocular Symptoms in Patients with COVID-19

The prevalence of ocular symptoms in patients with COVID-19 was 13.82% (ES, 95% CI 3.92%, 23.73%), and heterogeneity was found (I^2 = 99.11%; p = 0.00) (High

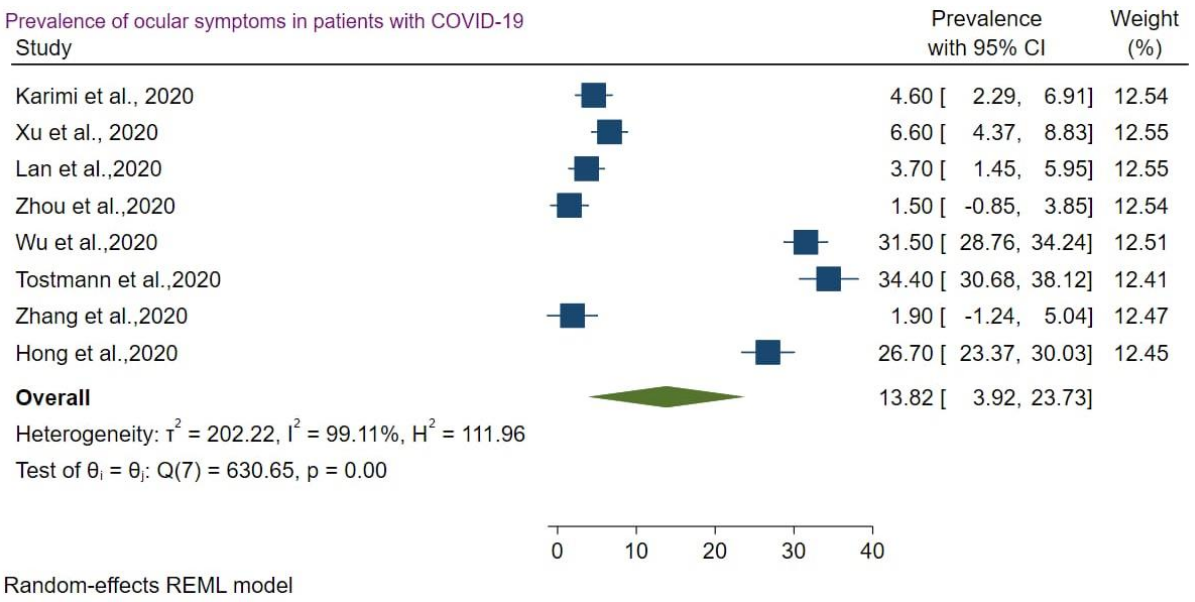

Figure 2. Forest Plot Showed the Prevalence of Ocular Symptoms in Patients with COVID-19.

heterogeneity) (Figure 2).

Various Ocular Symptoms

Subgroup meta-analysis:

The prevalence of Redness in patients with COVID-19 was 12.37% (ES, 95% CI 1.11%, 25.85%), and heterogeneity was found (I^2 = 99.37%; p = 0.00) (High heterogeneity) (Figure 3). The prevalence of Dryness in patients with COVID-19 was 26.70% (ES, 95% CI 23.17%, 30.23%). The prevalence of Ocular pain in patients with COVID-19 was 30.64% (ES, 95% CI 23.16%, 38.12%), and heterogeneity was found (I^2 = 92.02.11%; p = 0.00) (High heterogeneity) (Figure 3).

The prevalence of foreign body sensation in patients with COVID-19 was 14.47% (ES, 95% CI 9.42%, 38.36%), and heterogeneity was found (I^2 = 99.25%; p = 0.00) (High heterogeneity). Prevalence of Discharge in patients with COVID-19 was 19.93% (ES, 95% CI 1.69%, 38.18%), and heterogeneity was found (I^2 = 99.32%; p = 0.00) (High heterogeneity) (Figure 3). The prevalence of Itching in patients with COVID-19 was 8.77% (ES, 95% CI 2.87%, 20.40%), and heterogeneity was found (I^2 = 98.82%; p = 0.00) (High heterogeneity) (Figure 3).

The prevalence of Follicular conjunctivitis in patients with COVID-19 was 12.77% (ES, 95% CI 0.40%, 25.93%), and heterogeneity was found (I^2 = 99.34%; p = 0.00) (High heterogeneity). The prevalence of Watering in patients with COVID-19 was 1.023% (ES, 95% CI 1%, 46.30%), and heterogeneity was found (I^2 = 99.73%; p = 0.00) (High heterogeneity) (Figure 3).

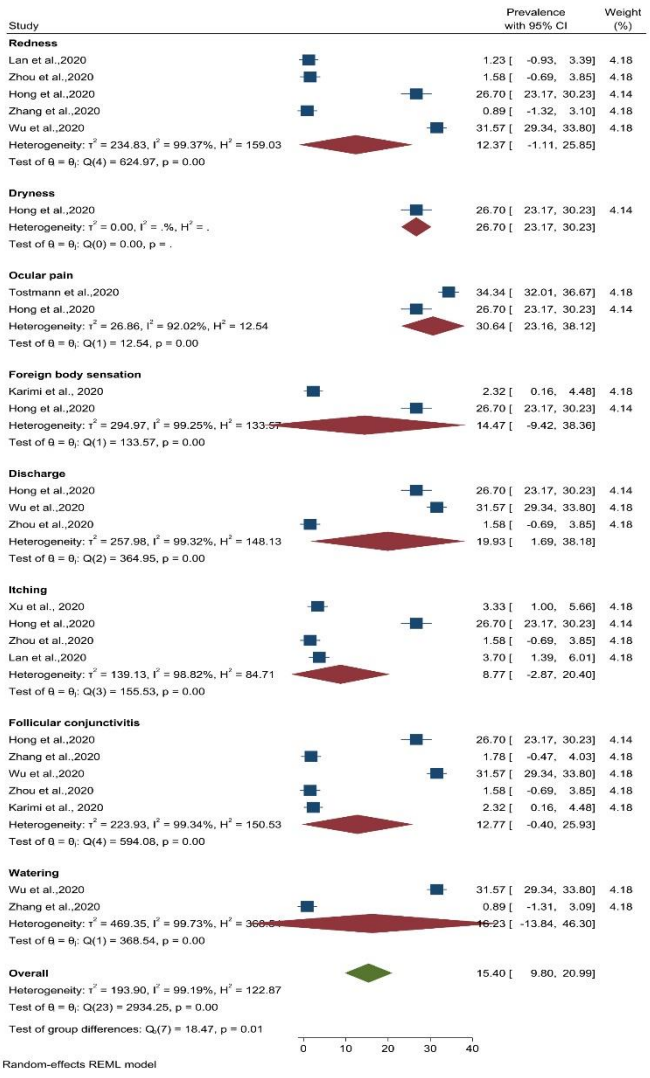

Figure 3. Forest Plot Showed the Prevalence of Various Ocular Symptoms in Patients with COVID-19.

Ocular Manifestations as the First Symptom of COVID-19

Prevalence of Ocular manifestations as the first symptom of

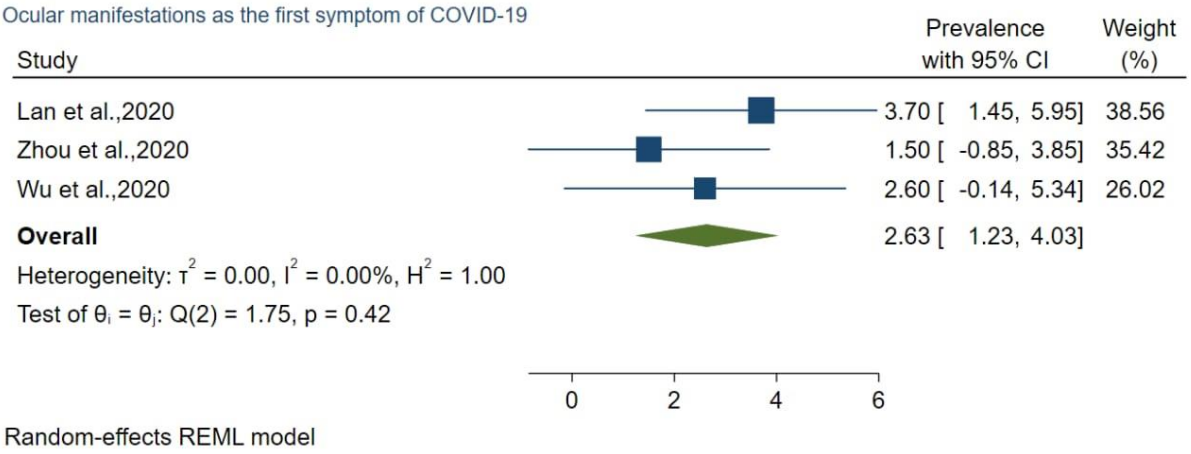

Figure 4. Forest Plot Showed Ocular Manifestations as the First Symptom of COVID-19 in Patients.

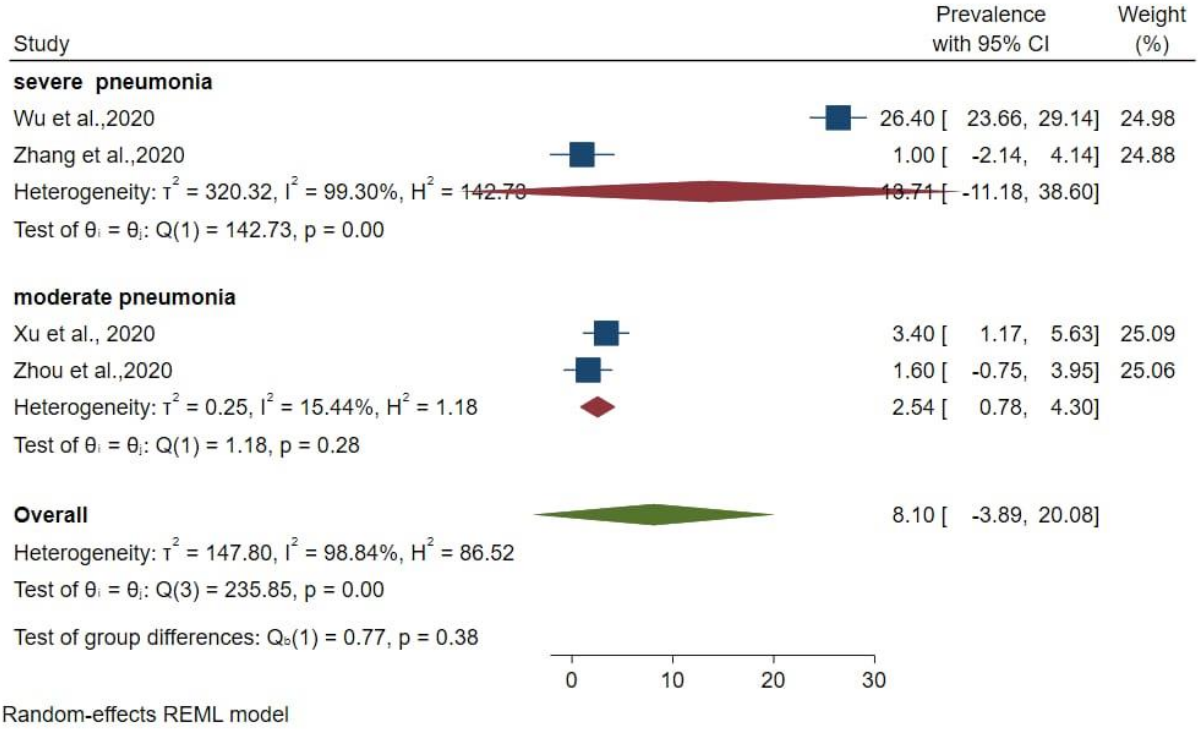

Figure 5. Severe or Moderate Pneumonia in Patients with COVID-19

COVID-19 in patients was 2.63% (ES, 95% CI 1.23%, 4.03%), and heterogeneity was found (I^2 = 0.00%; p = 0.42) (low heterogeneity) (Figure 4).

Severe or Moderate Pneumonia in Patients with COVID-19 and Had Ocular Symptoms

The prevalence of Severe pneumonia in patients was 10.71% (ES, 95% CI 1%, 38.60%), and heterogeneity was found (I^2 = 99.30%; p = 0.00) (High heterogeneity) (Figure 5). The prevalence of moderate pneumonia in patients was 2.54% (ES, 95% CI 0.78%, 4.30%), and heterogeneity was found (I^2 = 15.44%; p = 0.28) (Low heterogeneity) (Figure 5). Overall prevalence was 8.10% (ES, 95% CI 3.89%, 20.08%), and the test of group differences showed that no significant differences were observed between Severe or moderate pneumonia in patients with COVID-19 and ocular symptoms (p = 0.38) (Figure 5).

Discussion

The current systematic review and meta-analysis study focused on ocular signs and symptoms related to ocular surface manifestations among patients with laboratory-confirmed COVID-19. Age distribution and geographical location can affect ocular manifestations in patients with

COVID-19. However, the number of studies is insufficient, and further studies are needed to confirm these results. Most studies focusing on ocular manifestations describe ocular effusions as part of the initial presentation of COVID-19.

In 2022, Daryabari et al. confirmed the presence of the COVID-19 virus in the tears of patients admitted to the ICU.[10] In the study by Zhou et al., one out of 63 patients had conjunctivitis, and three other patients were positively diagnosed with the virus on conjunctival swabs[32] in a study by Sun et al. Two of the 72 patients with COVID-19 had conjunctivitis[33] in a study by Xia et al. Conjunctivitis was reported as a symptom with a positive diagnosis of the virus.[15] Atum et al. said ten out of 40 patients with COVID-19 had conjunctival examination.[34] People with coronary artery disease usually show conjunctiva and eye surface pathology. However, Optical Coherence Tomography (OCT) and imaging of the retinal fundus have demonstrated the presence of cotton wool stains (CWS).[35] According to the results of the present study, the prevalence of eye pain, redness, discharge, and follicular conjunctiva is high. Other studies have reported similar ocular manifestations.[9,36,37] On the one hand, there was a high heterogeneity between the results. On the other hand, it is not clear whether eye diseases existed before the patient was exposed to Quaid-19. The prevalence of dry eye, pruritus, and foreign body sensation is expected in the general population and cannot be associated with COVID-19.[38] Also, studies conducted on healthcare workers provide better results, and to achieve comprehensive results and provide sufficient evidence, more studies should be performed on healthcare workers.

Due to the high prevalence of the disease and the transmission from person to person, direct slit-lamp examination has been performed only in some studies. The location, nature, duration, extent, and severity of redness should be further investigated. Studies reporting ocular features do not provide information on potential drugs to control these manifestations. Several antiviral drugs such as RamedSivir, Favipiravir, and GalidCivir are being studied against coronavirus.[28] It may also cause ocular manifestations due to the hospitalization of patients with COVID-19 in the intensive care unit.[39,40] Studies have also not shown whether viral RNA in ocular fluids has infectious potential or leads to transmission of COVID-19. More laboratory studies are needed to provide sufficient evidence.[41,42]

On the other hand, studies found that ocular manifestations (especially follicular conjunctivitis) could be the first or sometimes only manifestation of COVID-19.[27,31] Non-uniformity in collecting and reporting study data is a limitation in the present study. Case report studies were omitted in the present study to provide more substantial evidence. However, high heterogeneity was observed between the results. Ocular manifestations such as pain, redness, and conjunctivitis may be seen in people with COVID-19. Transmission of the disease from ocular fluid remains unclear, and the rate of viral RNA detection from conjunctival swab/tear fluid using RT-PCR is low. It is suggested that more studies be done in this field. High-quality studies and larger sample sizes can help to provide more substantial evidence.

Conclusion

The present systematic review and meta-analysis study showed the prevalence of ocular symptoms in patients with COVID-19 was 13.82%. Prevalence of redness, dryness, ocular pain, foreign body sensation, discharge, itching, follicular conjunctivitis, and watering was 12.37%, 26.70%, 30.64%, 14.47%, 19.93%, 8.77%, 12.77%, and 1.23%, respectively.

Authors' Contributions

All the authors participated equally in this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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