Review Article

Ophthalmic Manifestations of COVID-19 Disease: A Systematic Review and Meta-Analysis

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Abstract

Purpose: The COVID-19 pandemic has posed significant challenges for ophthalmologists. The aim of this manuscript is to provide general guidance for ophthalmologists to understand the prevalence of ocular manifestations in patients with COVID-19.
Materials and Methods: Relevant studies published between November 1, 2019, and July 15, 2020, regarding ocular manifestations of COVID-19 or the presence of SARS-CoV-2 in the cornea, conjunctiva, tear sac, and tears were identified from PubMed, Medline, Cochrane Library, Web of Science, and ClinicalKey. The search keywords included “COVID-19,” “ocular findings/symptoms/signs,” “eye/ophthalmology,” “2019-nCoV,” and “SARS-CoV-2." The PRISMA guideline was utilized for this systematic review. The reference list of all identified articles was manually searched by two authors independently. Relevant abstracts were reviewed, and if eligible, full texts and related reference lists were further assessed for eligibility. Subsequently, a snowballing method, applied to retrieval sources, was used for the search.
Results: The pooled prevalence of ocular manifestations among COVID-19 patients was estimated at 7 % (95 % confidence interval: 3 % - 10 %). Conjunctivitis was the most common ocular manifestation in COVID-19. Ocular manifestations in COVID-19 patients usually involve surface eye symptoms.
Conclusion: Ocular manifestations in COVID-19 patients typically include surface eye symptoms, such as conjunctival congestion, foreign body sensation, and, rarely, subepithelial involvement of the cornea. As demonstrated in our meta-analysis, the prevalence of ocular manifestations among COVID-19 patients is relatively high, and it is essential for ophthalmologists and all healthcare professionals to be aware of these occurrences.

Keywords: Coronavirus; Ocular; Manifestations; Ophthalmology; Review.

Article Notes: Received: Jul. 30, 2022; Received in revised form: Aug. 22, 2022; Accepted: Sep. 12, 2022; Available Online: Jan. 01, 2023.

How to cite this article: Jamalzehi M, Farhad Dadgar F. Ophthalmic Manifestations of COVID-19 Disease: A Systematic Review and Meta-Analysis. Journal of Ophthalmic and Optometric Sciences . 2023;7(1): 31-41.

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created a distinct medical reality and a continuously evolving global pandemic expected to infect tens of millions worldwide [1].

The COVID-19 pandemic presents major challenges for healthcare professionals in various fields. Given the need for continuous contact between ophthalmologists and their patients during clinical examinations, effective and safe mutual protection measures must be taken. This is of particular importance as COVID-19 is a highly contagious disease that can be transmitted through secretions and droplets from the nose or mouth [2, 3]. In particular cases, conjunctival swelling may be the first presenting symptom of COVID-19 infection [4].

Through this systematic review, we address important questions related to COVID-19 in ophthalmology, including the key ocular manifestations in patients infected with SARS-CoV-2, the efficacy of conjunctival swab testing for the virus, and the chance of SARS-CoV-2 spread through ocular mucosa or infected eye secretions.

Materials and Methods

Relevant studies published between November 1, 2019, and July 15, 2020, regarding ocular manifestations of COVID-19 or the presence of SARS-CoV-2 in the cornea, conjunctiva, tear sac, and tears were identified from PubMed, Medline, Cochrane Library, Web of Science, and ClinicalKey. The search keywords included "COVID-19," "ocular findings/symptoms/signs," "eye/ophthalmology," "2019-nCoV," and "SARS-CoV-2."

The criteria for studies included in this meta-analysis were articles reporting ocular signs and symptoms among COVID-19 patients and studies reporting diagnostic results from ocular tissue/conjunctival secretions. The PRISMA guideline was utilized for this systematic review. The reference list of all identified articles was manually searched by two authors independently. Relevant abstracts were reviewed, and if eligible, full texts and related reference lists were further assessed for eligibility. Subsequently, a snowballing method, applied to retrieval sources, was used for the search.

Risk of bias assessment and quality improvement

For assessing the risk of bias and improving the quality of studies chosen from the database search, we used the Newcastle–Ottawa Scale [5]. Subsequently, analysis was conducted to estimate the prevalence of ocular manifestations in COVID-19 patients. If significant heterogeneity existed among the studies, a random-effects model was employed. Heterogeneity was assessed using the I^2 statistic, where an I^2 value greater than 50 % was considered statistically significant heterogeneity.

Results

Figure 1 depicts the flowchart of screening and study selection in this systematic review. The studies were published between November 1, 2019, and July 15, 2020. The initial screening yielded 234 citations, of which 208 were excluded based on criteria used to evaluate the titles and abstracts, such as irrelevant reports and inappropriate populations. Following the initial screening of titles, abstracts, and removal of duplicates, a total of 14 articles

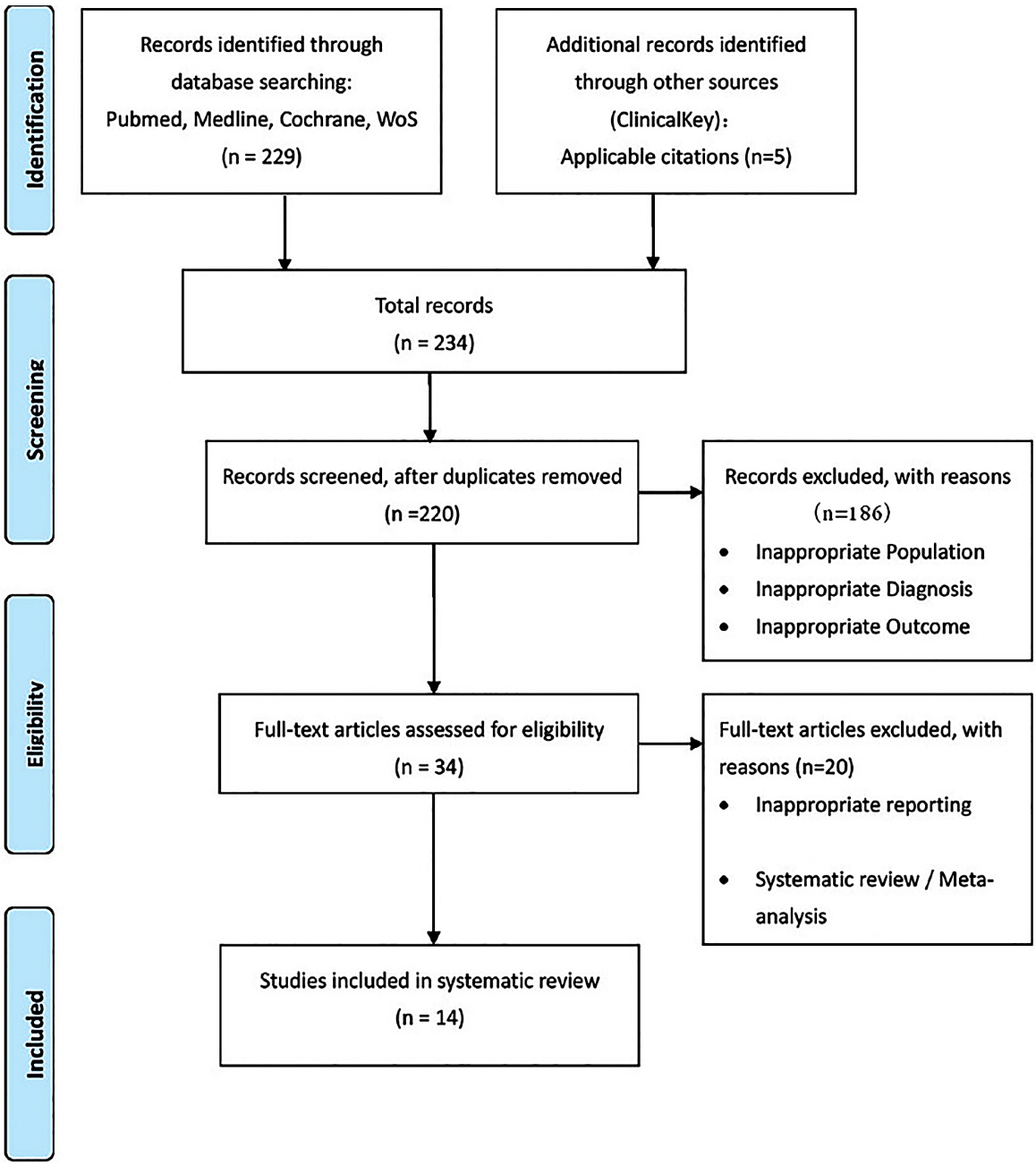


Figure 1: Flowchart of screening and study selection in the present systematic review

were included in our review.

Study characteristics

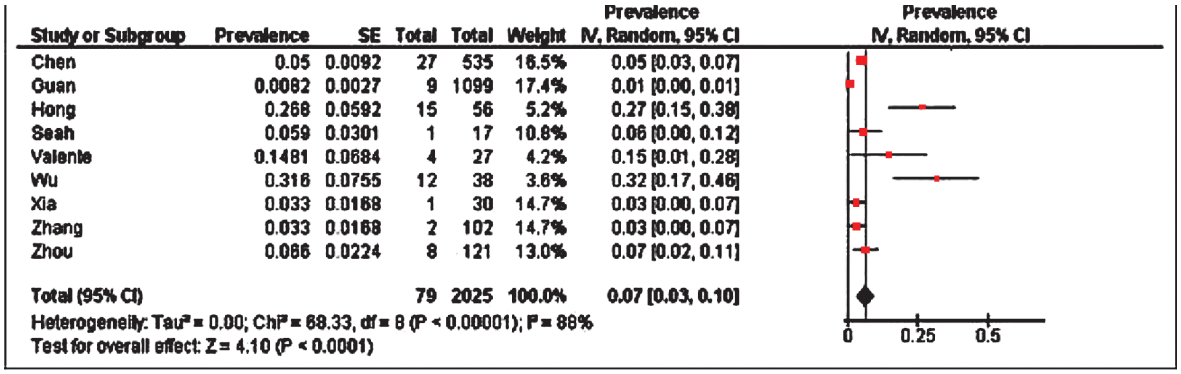
All studies reviewed which included reports of ocular manifestations in patients infected with SARS-CoV-2, are listed alphabetically in table 1. From these selected studies, nine were original articles (comprising prospective and retrospective studies) or case sereis [6-14], three were case reports [15-17], and two were letters to the editor [18, 19].

The overall systematic review of studies showed that the prevalence of ocular manifestations among COVID-19 patients ranged from 1 % to 32 % (Table 2). All

Table 1: List of selected articles reporting ocular manifestations of COVID-19 included in metha-analysis

Article	Article Category	Number of Patients	Number of patients with ophthalmic manifestations	Percentage of patients with ophthalmic manifestations	Risk of Bias	The form of ophthalmic involvement
Cheema et al., [15]	Case Report	1	1	NA	High	Keratoconjunctivitis
Chen et al., [8]	Original Article	535	27	5	High	Conjunctival congestion, Increased secretion, eye pain, foreign body sensation, photophobia
Chen et al., [17]	Case report	1	1	NA	High	Follicular conjunctivitis
Guan et al., [6]	Original Article	1099	9	0.8	Low	Conjunctival congestion
Hong et al., [9]	Original Article r	56	15	26.8	High	Conjunctivitis, dry eye, foreign body sensation
Khavandi et al., [19]	Letter to Editor	1	1	NA	High	Follicular conjunctivitis
Navel et al., [16]	Case report	1	1	NA	High	Hemorrhagic conjunctival swelling, pseudomembrane Top of Form
Seah et al., [10]	Original Article	17	1	5.9	High	Conjunctival discharge and hemorrhage
Wu et al., [11]	Original Article	38	12	31.6	Low	Conjunctival hemorrhage, chemosis, epithelial defect
Wu et al., [18]	Letter to Editor	1	1	NA	High	Blepharitis, conjunctival swelling
Valente et al., [12]	Original Article	27	4	4	Low	Mild conjunctival hemorrhage, slight discharge
Xia et al., [7]	Original Article	30	1	3.3	Low	Conjunctivitis
Zhang et al., [13]	Original Article	102	2	2	High	Conjunctivitis
Zhou et al., [14]	Original Article	121	8	6.6	Low	Conjunctivitis, foreign body sensation Top of Form

Table 2: Forest plot of nine original or case series studies estimating the combined prevalence of ocular manifestations among patients with COVID-19



reported ocular manifestations were associated with patients confirmed to have COVID-19 through laboratory testing (nasopharyngeal or tears PCR). Risk of bias assessments were assigned to all included studies according to PRISMA guidelines.

Eyelids

The only reported case of eyelid dermatitis related to COVID-19 was described by Wo et al., [18] reporting a 2-year-old boy with a history of contact with infected family members. Initially, the child presented with mild eyelid dermatitis and conjunctival inflammation [18]. COVID-19 infection was confirmed in the patient using reverse transcription-polymerase chain reaction (RT-PCR).

Conjunctivitis

Conjunctivitis as well as conjunctival hemorrhage and congestion are the main ophthalmic signs of COVID-19 reported in a majurity of studies. In a study by Chen et al.,[8] a total of 27 patients (5.0 %) out of 535 COVID-19 patients had conjunctival congestion or hemorrhage. Four of these 27 patients presented with conjunctival inflammation as the initial symptom. In this study, no tears or conjunctival swabs were collected. Ocular symptoms accompanying conjunctival congestion were eye pain, photophobia, dry eyes, and tearing [8].

In the largest cohort of COVID-19 patients to date included in this study (n = 1099), Guan et al.,[6] reported only 9 patients (0.8 %) with conjunctival congestion. No conjunctival PCR was collected in their study. Out of the 9 patients with conjunctival congestion, 5 and 4 patients were classified as having mild and severe COVID-19, respectively.

Xia et al.,[7] conducted an interventional future-oriented study on COVID-19 patients. Tears and conjunctival secretions were collected from all patients for PCR. Only one patient presented with conjunctivitis symptoms, and the result for COVID-19 in tears/conjunctival swab was positive for this patient. On the other hand, no virus was observed in conjunctival secretions and tears in patients without conjunctivitis.

Wu et al., [11] reported that a total of 12 patients out of 38 patients with Covid-19 (31.6 %) showed conjunctival symptoms, including conjunctival hemorrhage, chemosis, epiphora, or increased secretion. This study also suggested higher white blood cells and neutrophils count as well as an increase in

levels of procalcitonin, C-reactive protein, and lactate dehydrogenase are associated with the occurrence of ocular symptoms in the associated group.

Hong et al.,[9] investigated 56 discharged COVID-19 patients. Assessment of ocular surface status before and after the onset of COVID-19 was performed using ocular surface disease index (OSDI) and sjogren's syndrome-evaluation questionnaire (SEEQ). Pre-COVID-19 symptoms were assessed by asking patients about ocular symptoms before COVID-19. Fifteen patients (27 %) reported ocular symptoms during COVID-19, including eye pain, itching, foreign body sensation, tearing, redness, dry eyes, and conjunctival secretions. Worsening of the ocular surface manifestastions among patients was indicated by a significant increase in mean SEEEQ and OSDI scores after the onset of COVID-19. Among participants, six patients (11 %) showed ocular symptoms before the onset of fever or respiratory symptoms.

Zhang et al.,[13] conducted a retrospective study of 102 clinically diagnosed COVID-19 patients (based on clinical symptoms and CT scans). Seventy-two percent of the 102 patients were confirmed by the RT-PCR method, among which only two patients (2.78 %) had conjunctival inflammation. Only one patient with conjunctival symptoms had a positive RT-PCR result in the nasopharyngeal swab.

A prospective study in Singapore by Seah et al.,[10] including 17 COVID-19 patients reported that one patient (9.5 %) hospitalized with COVID-19 developed bilateral follicular conjunctivitis. This study also compared the presence of the virus in tears with nasopharyngeal swabs, which were collected simultaneously for each patient. All tears samples were negative for the virus, even in the patient with conjunctivitis symptoms.

Case reports of patients diagnosed with COVID-19 and presenting ocular symptoms were also reviewed. Cheema et al.,[15] described a case of a young woman who initially presented with signs of hyperemic conjunctival bleeding, tearing, and photophobia. Follicular changes and conjunctival congestion were observed during the physical examination. Considering the progressing conjunctival congestion and her report of recent travel, COVID-19 nasopharyngeal swab testing testing was ordered for the patient, which returned positive. Furthermore, retrospective testing of the eye swab, initially sent for PCR for Zika or Chlamydia, was also positive for SARS-CoV-2. This case highlights the importance of considering COVID-19 as a differential diagnosis for patients with acute conjunctivitis symptoms who have a recent travel history.

Khavandi et al., [19] reported a 65-year-old Caucasian male who had no history of travel or common COVID-19 symptoms but initially presented with mucoid discharge and follicular conjunctival inflammation. Two days later, he developed sudden fever and respiratory distress, and was diagnosed with COVID-19. Conjunctival swab RT-PCR test for SARS-CoV-2 was positive twice during admission.

Chen et al., [17] reported a 30-year-old male who, on the 13th day after the onset of COVID-19, presented with bilateral follicular conjunctivitis. Conjunctival swabs were immediately collected after the onset of conjunctivitis (day 13) and tested positive for SARS-CoV-2. Subsequently, conjunctival swabs remained positive on days 14, 17, and 19, albeit with decreasing titers. The diagnosis of SARS-CoV-2 in a conjunctival sample in this patient for several days indicates a potential source of transmission, especially considering the high viral titers during the acute phase of ocular manifestations.

In addition to the common appearance of conjunctival inflammation, its severity has also raised concerns. For example, Navel et al.,[16] reported a case of profuse hemorrhagic conjunctivitis and pseudomembrane formation in a patient being treated for severe COVID-19. The patient's ocular symptoms started around day 17 after admission, and subsequently, despite treatment with saline solution and artificial tears, there was an increase in follicles, chemosis, pseudomembrane, and tarsal hemorrhages. No abnormal inflammation was observed in the posterior segment and retina. Conjunctival cultures to investigate bacterial or viral causes as well as conjunctival swabs for SARS-CoV-2 testing were negative. This case highlights the importance for all physicians to be aware of potential late (>14 days) ocular complications in severe COVID-19 patients.

Cornea and anterior segment

Compared to conjunctival congestion, corneal involvement in COVID-19 is relatively rare. In a case reported by Cheema et al.,[15] besides conjunctivitis, corneal pathological symptoms were also observed. These included small pseudo-dendrites appearing simultaneously with conjunctivitis, before transforming into small sub-epithelial infiltrates. This case shows that without proper care, ophthalmic manifestations of COVID-19 can be variable and may progress. To date, there is no published evidence indicating anterior segment involvement in COVID-19. However, for a comprehensive understanding of the complete clinical spectrum of COVID-19 in the eye, further research is needed.

Retina and Vitreous

Hong et al., [9] reported a patient with floaters in the right eye after hospitalization for COVID-19. However, it could not be directly attributed to COVID-19, and no other cases of COVID-19-related posterior segment involvement were reported in their study.

Prevalence of concurrent ocular manifestations in COVID-19

Considering the prevalence of ocular manifestations among COVID-19 patients, the reported range of prevalence was between 1 % and 32 % in different articles included in this study. A meta-analysis of 9 studies involving 2025 patients was conducted. Overall, the prevalence of ocular manifestations among COVID-19 patients was 7 % (95 % confidence interval: 3 % - 10 %). Due to heterogeneity (88 % I^2) among the studies, a random-effects model was used.

The rate of diagnosing COVID-19 from tears samples and conjunctival secretions among a total of 391 patients in 7 studies was calculated. The positive rate from collected eye tissue or eye secretions was very low at 1 % (95 % confidence interval: 0 % - 3 %). This suggests that the diagnosis of SARS-CoV-2 with the help of tears and conjunctival samples is not a viable uption.

Ocular manifestations caused by treatment of COVID 19

During the initial outbreak of COVID-19, experimental treatment with chloroquine and hydroxychloroquine at a dose of 1000 milligrams per day for 10 days of chloroquine, followed by 800 milligrams per day, then 400 milligrams per day for 5 days of hydroxychloroquine was suggested. However, the above doses were significantly higher than the maximum safe doses for retinal toxicity.

In a report by Ruamviboonsuk et al.,[20] macular abnormalities in retinal imaging and mERG were observed in two out of every seven patients (28 %) who received high-dose hydroxychloroquine treatment for COVID-19. A review of the medical history revealed that these patients had no known risk factors such as renal failure, concurrent use of other retinotoxic drugs, or retinal disease. Based on these findings the risks of irreversible retinal toxicity and vision loss may outweigh the unproven benefits of both drugs in specific patients, especially those with a previous history of retinal or macular diseases.

Discussion

In total, 2025 patients from 14 studies were analyzed in this review. The overall prevalence of ocular manifestations in COVID-19 in our meta-analysis was estimated at 7 % (95 % confidence interval: 3 % - 10 %). Conjunctival symptoms, including conjunctival hyperemia, increased secretion, pain, and foreign body sensation, were the most common ocular manifestations in COVID-19. All available studies in the systematic review reported patients with conjunctivitis. Rare cases of corneal symptoms such as pseudo-dendrites, epithelial defects, and superficial complications like pseudo-membranes were also reported in the studies.

Currently, no significant clinical involvement has been reported in the cornea, iris, vitreous, or retina. Potential accompanying conditions, including orbital cellulitis and retinal toxicity due to the use of chloroquine/ hydroxychloroquine above the recommended daily dose, were among the possible serious ocular complications after COVID-19.

Diagnosis of COVID-19 from tears or conjunctival secretions samples

Although the most common ocular sign presented by COVID-19 patients is conjunctivitis, the positive detection rate of SARS-CoV-2 virus by RT-PCR through tears or conjunctival secretions is low. The combined positive rate of PCR in swabs from tears and conjunctival secretions in our meta-analysis was low at 1 % (95 % confidence interval 0.0 % - 3 %). The reasons for the low positive rate could be that the virus shedding period in ocular tissues may be very short, and it is uncertain at which stage of COVID-19 it occurs. Wu et al., [11] showed that ocular manifestations in severe COVID-19 were more common, and a higher percentage of patients with ocular manifestations were positive for SARS-CoV-2 in conjunctival swabs. Xia et al., [7] also demonstrated that no virus was detected in tears or conjunctival secretions swabs from patients without conjunctivitis, whereas a positive diagnosis was found in tears of a patient with conjunctival swelling.

Overall, these findings indicate that although patients with conjunctival symptoms are more likely to have a positive diagnosis than those without conjunctival symptoms swabs from tears or conjunctival secretions are not suitable for definitive diagnosis of COVID-19.

Ocular manifestations of COVID-19 in children

In the studies used in this review, the occurrence of ocular symptoms in COVID-19 patients was more frequently reported in adults. Valente et al., [12] reported conjunctival symptoms in 3 out of 27 children with mild clinical symptoms of coronavirus. It is hypothesized that the

systemic manifestations of COVID-19 in children may be milder compared to adults. Consequently, the positive rate of conjunctival swabs in children with conjunctivitis was low.

The risk of transmitting the coronavirus via conjunctiva or tears

The detection of viral genomes in tears indicates that SARS-CoV-2 has the potential to cause ocular disease or even viral transmission through the eye as a gateway of entry. HCoVs are typically transmitted through respiratory droplets or direct contact with an infected individual. Conjunctiva, as a mucosal structure, is exposed to infectious secretions from close contact with infected patients. It is a known fact that respiratory viruses, such as human adenovirus (species D) and avian influenza virus (H7), can cause keratoconjunctivitis or conjunctivitis. Tears and conjunctival secretions may also harbor the virus and spread it. Currently, there are no collective clinical or population-based studies to statistically evaluate the risk of COVID-19 transmission from conjunctival tissues or tears [21,22].

Preventive strategies by ophthalmologists in managing patients with COVID-19

Our systematic review showed that patients with COVID-19 may initially present with ocular manifestations. Therefore, all ophthalmologists should adhere to infection control protocols and personal protective measures, including face masks, PPE, and gloves, when examining all patients, regardless of travel or contact history. Essential and non-essential ophthalmic services can also be discussed in temporary guidelines to guide ophthalmologists in balancing the risks and necessities of providing essential ophthalmic services [23].

Limitations

This was a systematic review and meta-analysis of the published reports up to the date of conducting the review. Most studies used in this review were retrospective in nature or case reports, and some of them had a high chance of bias. However, given the scarcity of available evidence at the time of conducting the review, these studies were included in the meta-analysis.

Conclusion

Ocular manifestations in COVID-19 patients typically include surface eye symptoms, such as conjunctival congestion, foreign body sensation, and, rarely, subepithelial involvement of the cornea. As demonstrated in our meta-analysis, the prevalence of ocular manifestations among COVID-19 patients is relatively high, and it is essential for ophthalmologists and all healthcare professionals to be aware of these occurrences. Further experimental and clinical research is needed to investigate the significance of ocular manifestations and their underlying mechanisms in the progression or transmission of COVID-19.

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Footnotes and Financial Disclosures

Conflict of Interest:

The authors have no conflict of interest with the subject matter of the present study.