Pooled Prevalence Estimate of Ocular Manifestations in COVID-19 Patients: A Systematic Review and Meta-Analysis

Saber Soltani1,2, PhD; Milad Zandi3,4, PhD; Seyed-Emansai Ahmad4, MSc; Bahman Zarandi5, MSc; Zeinab Hosseini4, MSc; Sara Akhavan Rezayat6, MSc; Morteza Abyadeh6, PhD; Reza Pakzad7,8, PhD; Pooneh Malekifar9, PhD; Iraj Pakzad7,8, PhD; Pooneh Malekifar9, PhD; Iraj Pakzad7,8, PhD; Pooneh Malekifar9, PhD; Hamidreza Mozhgani12,13, PhD

1Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; 2Research Center for Clinical Virology, Department of Virology, Tehran University of Medical Sciences, Tehran, Iran; 3Department of Hematology and Blood Banking, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran; 4Hepatitis Research Center, Lorestan University of Medical Sciences, Khoramabad, Iran; 5Department of Health Economics and Management, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; 6Cell Science Research Center, Department of Molecular Systems Biology, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran; 7Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran; 8Department of Epidemiology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran; 9Department of Epidemiology, School of Public Health, Tehran University Medical Sciences, Tehran, Iran; 10Research Center for Clinical Virology, Department of Virology, Tehran University of Medical Sciences, Tehran, Iran; 11Noor Eye Hospital, Tehran, Iran; 12Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran; 13Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

Correspondence: Reza Pakzad, PhD; Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Povohehsh Blvd., Banganjab, Postal code: 69318-51147, Ilam, Iran
Tel/Fax: +98 84 34222731
Email: rezapakzad2010@yahoo.com
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Abstract

Background: There are reports of ocular tropism due to respiratory viruses such as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Various studies have shown ocular manifestation in coronavirus disease-2019 (COVID-19) patients. We aimed to identify ophthalmic manifestations in COVID-19 patients and establish an association between ocular symptoms and SARS-CoV-2 infection.

Methods: A systematic search of Medline, Scopus, Web of Science, Embase, and Cochrane Library was conducted for publications from December 2019 to April 2021. The search included MeSH terms such as SARS-CoV-2 and ocular manifestations. The pooled prevalence estimate (PPE) with 95% confidence interval (CI) was calculated using binomial distribution and random effects. The meta-regression method was used to examine factors affecting heterogeneity between studies.

Results: Of the 412 retrieved articles, 23 studies with a total of 3,650 COVID-19 patients were analyzed. The PPE for any ocular manifestations was 23.77% (95% CI: 15.73-31.81). The most prevalent symptom was dry eyes with a PPE of 13.66% (95% CI: 5.01-25.51). The PPE with 95% CI for conjunctival hyperemia, conjunctival congestion/conjunctivitis, and ocular pain was 13.41% (4.65-25.51), 9.14% (6.13-12.15), and 10.34% (4.90-15.78), respectively. Only two studies reported ocular discomfort and diplopia. The results of meta-regression analysis showed that age and sample size had no significant effect on the prevalence of any ocular manifestations. There was no significant publication bias in our meta-analysis.

Conclusion: There is a high prevalence of ocular manifestations in COVID-19 patients. The most common symptoms are dry eyes, conjunctival hyperemia, conjunctival congestion/conjunctivitis, ocular pain, irritation/itching/burning sensation, and foreign body sensation.

What’s Known

- Several prevalence estimates of ocular manifestations in COVID-19 patients have been reported.
- To date, pooled data analysis has not been carried out.

What’s New

- The pooled prevalence of ocular manifestations was about 24%, i.e., 24 in 100 patients had at least one ocular symptom.
- The most prevalent ocular symptoms in COVID-19 patients were dry eyes and conjunctival hyperemia. Pterygium and diplopia have been rarely reported.

Introduction

In late 2019, the first cases of coronavirus disease-2019 (COVID-19) were detected in Wuhan (China) and subsequently became a major global pandemic.1 Within a year, more than 1.4 million deaths were reported worldwide.2 The severe acute respiratory
syndrome-coronavirus-2 (SARS-CoV-2) is an enveloped beta coronavirus with positive-sense, single-stranded ribonucleic acid (RNA). The primary route of SARS-CoV-2 transmission is through respiratory droplets and close contact, while other routes are being investigated. In comparison with other members of the coronavirus family (SARS-CoV and MERS-CoV), SARS-CoV-2 has multiple modes of transmission, a higher transmission rate, and is highly infectious. Besides the polymerase chain reaction (PCR) test, other more sensitive and accurate methods have been proposed to detect the virus. COVID-19 symptoms usually appear 2-14 days after exposure and may include fever, cough, fatigue, shortness of breath, headache, psychological distress, and gastrointestinal disorders. The prevalence of ocular abnormalities in COVID-19 patients may range from 2% to 60%. In a study on 103 clinically confirmed COVID-19 patients, 21% of the cases were reported to have ocular involvement. Another study reported that 64.8% of COVID-19 patients had at least one ocular manifestation and the prevalence was associated with the severity of the disease.

In addition to the mouth and nose, coronavirus, can enter the body through the eyes. The presence of angiotensin-converting enzyme 2 (ACE2) on the cornea and conjunctival epithelium facilitates the entry of the virus into the host cell membrane. A previous study reported the presence of SARS-CoV-2 RNA in tears and ocular fluids of COVID-19 patients. Therefore, ocular route transmission should not be ignored and hand-eye contact should be avoided. Healthcare workers are thus required to wear eye protection, especially the ophthalmologists who may come into contact with tears or conjunctival secretions of COVID-19 patients. However, the transmission of COVID-19 through ocular secretion is controversial and requires further research.

The present study aimed to identify ophthalmic symptoms of COVID-19 patients and establish an association between these symptoms and SARS-CoV-2 infection. Our findings complement the known symptoms of COVID-19 and contribute to appropriate and timely intervention in these patients.

Materials and Methods
A systematic search of Medline, Scopus, Web of Science, Embase, and Cochrane Library was conducted for studies on the prevalence of SARS-CoV-2 related ocular manifestations. Without any language restrictions, publications from December 1st, 2019 to April 10th, 2021 were considered. To identify preprint papers, servers such as medRxiv and Social Science Research Network (SSRN) were also searched. The search strategy included a combination of medical subject headings (MeSH) terms and text words such as COVID-19, Coronavirus, SARS-CoV-2, Feature, Manifestation, Characteristic, Symptoms, Sign, Ocular, Eye, and Vision. The PICOTS (population, intervention, comparison, outcome, time, study design) components were COVID-19 patient, none, none, ocular manifestations/signs, none, and observational studies, respectively. Additionally, Google Scholar was searched to identify gray literature, and a virologist was consulted in the selection of important articles. The reference list of all articles was scanned manually to identify additional relevant studies.

Identified citations were uploaded into Endnote X6 (Clarivate Analytics, United State) and duplicate citations were excluded. The remaining articles were initially screened for title relevancy, and then the abstract and full text were independently screened by two reviewers (R. P and S. S). Inter-rater disagreements were resolved after consultations with the third author (I. P). Blinding and a clear division of tasks were implemented in the article selection process. The inter-rater agreement was 92%. Inclusion criteria were all observational epidemiological studies (cohort, cross-sectional, and case series) on the prevalence of at least one ocular manifestation in patients with confirmed COVID-19. The exclusion criteria were case reports and case series with a sample size <5 and studies in the form of editorials, commentaries, letters to editors, and reviews. The assessment was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

The quality of eligible studies was appraised independently by two of the authors (R. P and S. S) using the Newcastle-Ottawa Scale. The scale consists of three parts, namely selection (four items), confounder (one item), and exposure (two items) with a maximum score of four, one, and two points, respectively. Based on the scoring system, studies were categorized as very good (6 or 7 points), good (4 or 5 points), satisfactory (2 or 3 points), and unsatisfactory (0 or 1 point).
The extracted data from the selected studies were the name of authors, publication year, country, study design, sample size, the age and sex of COVID-19 patients, type of ocular manifestation, the prevalence of the most common ocular symptoms, and other ocular symptoms.

**Statistical Analysis**

Data were analyzed using Stata software, version 14.0 (StataCorp LLC, College Station, Texas, USA). Heterogeneity between the studies was examined using Cochran’s Q test and the I² index. Based on the Higgins classification approach, I² >0.7 was considered high heterogeneity. The pooled prevalence with a 95% confidence interval (CI) was calculated using the Stata command “metaprop”, and the pooled prevalence was estimated using the random-effects model. The meta-regression analysis was used to examine the effect of age and sample size on heterogeneity between the studies. The Stata command “metabias” was used to check publication bias. In case of any publication bias, the prevalence rate was adjusted with the Stata command “metatrim” using the trim-and-fill method. P values less than 5% were considered statistically significant.

**Ethics Approval and Consent to Participate**

This study was approved by the Ethics Committee of Ilam University of Medical Sciences (Ethical code: IR.MEDILAM.REC.1400.034).

**Results**

A total of 412 articles were retrieved from various databases, of which 99 duplicate studies were removed. The remaining 313 articles were screened for eligibility and 290 articles failed to meet one or more inclusion criteria. Eventually, 23 articles were selected in the systematic review (figure 1). Of the 23 included articles, 9 (39.13%) were case series, 3 (13.04%) cohort, and 11 (47.83%) cross-sectional studies. The studies included a total of 3,650 COVID-19 patients aged one to 96 years with ocular manifestation (table 1). The studies were primarily conducted in China (30.43%), Italy (13.04%), and Turkey (13.04%).

**Clinical Presentations and Pooled Prevalence**

The extracted data from the 23 included studies on ocular manifestations are listed in table 1. The forest plots for the prevalence of any ocular manifestations in each study and the pooled prevalence estimate (PPE) of a specific ocular symptom are shown in figure 2. Additionally, the forest plot for the prevalence of each ocular symptom is presented in supplementary figures S1 to S4. As listed in table 2, the PPE for any ocular manifestations was 23.77% (95% CI: 15.73-31.81).

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**Figure 1:** The flow diagram depicts the selection process of studies in accordance with the PRISMA guidelines.
| Author, Year | Country | Study design | Sample size | Age (years)* | Ocular findings |
|--------------|---------|--------------|-------------|--------------|----------------|
| Lee et al.9 | Korea   | Case series  | 103         | 13.60% 86.36% 53±12 | Ocular symptoms 21% Epiphora 1.94% Itching sensation 3.88% Visual disturbance 5.82% Conjunctival congestion 6.79% Ocular discomfort 4.85% Ocular pain 2.91% |
| Liu et al.17 | China   | Case series  | 142         | 50.70% 49.30% 48 (14-83) | Ocular symptoms 2.80% Ocular discomfort 2.80% Ocular symptoms 8.66% Conjunctival congestion 6.30% Burning sensation 0.79% Epiphora 0.79% |
| Sindhuja et al.18 | India | Case series  | 127         | 11.02% 88.98% 38.80 (5–73) | Ocular symptoms 8.66% Conjunctival congestion 6.30% Burning sensation 0.79% Epiphora 0.79% |
| Guemes-Villahoz et al.19 | Spain  | Case series  | 301         | 59.80% 40.19% 72 (59–82) | Ocular symptoms 11.60% Conjunctivitis 11.63% Foreign body sensation 3.99% Subconjunctival hemorrhage 0.99% Pterygium 1.33% Hordeolum 0.66% Epiphora 4.98% |
| Guemes-Villahoz et al.20 | Spain  | Case series  | 36          | 39% 61% 67.90 (28–92) | Ocular symptoms 50% Conjunctivitis 50% Subconjunctival hemorrhage 8.33% Pterygium 5.55% Conjunctival hyperemia 50% Hordeolum 2.78% |
| Karimi et al.21 | Iran    | Case series  | 43          | 67.50% 32.50% 56.60±13.70 | Ocular symptoms 4.65% Conjunctivitis 2.33% Foreign body sensation 2.33% Ocular symptoms 25% Conjunctivitis 25 % |
| Atum et al.15 | Turkey  | Case series  | 40          | 62.50% 37.50% 41.38±23.72 (1–82) | Ocular symptoms 27% Conjunctivitis 3.57% Ocular pain 5.36% Itching sensation 5.36% Foreign body sensation 7.14% Conjunctival hyperemia 3.57% Dry eyes 8.93% Eye secretions 3.57% |
| Hong et al.22 | China   | Cross-sectional  | 56          | 55.40% 44.60% 48 (24–68) | Ocular symptoms 27% Conjunctivitis 3.57% Ocular pain 5.36% Itching sensation 5.36% Foreign body sensation 7.14% Conjunctival hyperemia 3.57% Dry eyes 8.93% Eye secretions 3.57% |
| Zhang et al.11 | China   | Cross-sectional  | 72          | 50% 50% 58.68±14.81 | Ocular symptoms 2.78% Conjunctivitis 2.78% Ocular symptoms 69.40% Burning sensations 34.26% Itching sensations 16.67% Epiphora 31.48% Photophobia 20.37% Foreign body sensations 6.48% Conjunctivitis 7.41% Swollen eyelid 13.89% Diplopia 1.85% Conjunctival hyperemia 24.07% Reduced visual acuity 8.33% Ocular pain 10.19% |
| Rokohl et al.23 | Germany | Cohort  | 108         | 47.22% 52.78% 37.90±13.70 | Ocular symptoms 2.78% Conjunctivitis 2.78% Ocular symptoms 69.40% Burning sensations 34.26% Itching sensations 16.67% Epiphora 31.48% Photophobia 20.37% Foreign body sensations 6.48% Conjunctivitis 7.41% Swollen eyelid 13.89% Diplopia 1.85% Conjunctival hyperemia 24.07% Reduced visual acuity 8.33% Ocular pain 10.19% |
| Study                  | Country | Study Design | Sample Size | Age Range | Ocular Symptoms | Conjunctival Hyperemia | Epiphora | Eye Secretion | Swollen Eyelid | Foreign Body Sensation | Itching Sensation |
|-----------------------|---------|--------------|-------------|-----------|----------------|------------------------|----------|---------------|------------------|----------------------|------------------|
| Cavalleri et al.24     | Italy   | Cross-sectional | 172         | 68.03%    | 31.97%         | 64.2±13.4              |          |               |                  |                      |                  |
| Zhou et al.14          | China   | Cross-sectional | 121         | 68.03%    | 31.97%         | 64.2±13.4              |          |               |                  |                      |                  |
| Oncul et al.25         | Turkey  | Cross-sectional | 359         | 54.90%    | 45.10%         | 58.50 (20-91)          |          |               |                  |                      |                  |
| Chen et al.26          | China   | Cross-sectional | 535         | 50.10%    | 49.90%         | 44.0 (34.0–54.2)       |          |               |                  |                      |                  |
| Valente et al.27       | Italy   | Case series   | 27          | 74.10%    | 25.90%         | 7 (1-17.50)            |          |               |                  |                      |                  |
| Bostanci et al.28      | Turkey  | Cross-sectional | 93          | 58.10%    | 41.90%         | 39.40±21.90 (7-88)     |          |               |                  |                      |                  |
| Abrishami et al.10     | Iran    | Cross-sectional | 142         | 54.20%    | 45.77%         | 62.60±15 (23–96)       |          |               |                  |                      |                  |
| Invernizzi et al.29    | Italy   | Cross-sectional | 54          | 70.30%    | 29.60%         | 49.90±15.60 (23–82)    |          |               |                  |                      |                  |
| Tostmann et al.20      | Netherlands | Cross-sectional | 90          | 21.10%    | 78.90%         | 39.01                  |          |               |                  |                      |                  |
The most prevalent symptom was dry eyes (in four studies) with a PPE of 13.66% (95% CI: 5.01-25.51). Only two studies reported ocular discomfort and diplopia with a PPE of 3.60% (95% CI: 1.52-6.41) and 1.02% (95% CI: 0.14-1.90), respectively. The PPE with 95% CI for conjunctival hyperemia, conjunctival congestion/conjunctivitis, ocular pain, irritation/itching/burning sensation, and foreign body sensation was 13.41% (4.65-25.51), 9.14% (6.13-12.15), 10.34% (4.90-15.78), 9.34% (5.56-13.12), and 5.24% (3.07-7.41), respectively.

**Heterogeneity and Meta-regression**

The results of Cochran’s Q test showed significant heterogeneity between the studies for all symptoms except diplopia and ocular discomfort (only two studies on this subgroup) (table 2).
The I² index for most symptoms (any ocular manifestations, conjunctival congestion/conjunctivitis, ocular pain, visual disturbance/blurred vision, epiphora, irritation/itching/burning sensation, swollen eyelid, foreign body sensation, hordeolum, conjunctival hyperemia, dry eye, photophobia, and eye/conjunctival secretion) was above 80%. The results of meta-regression analysis showed that age (coefficient: -0.029, 95% CI: -0.717 to 0.658, P: 0.930) and sample size (coefficient: 0.025, 95% CI: -0.339 to 0.084, P: 0.385) had no significant effect on the prevalence of any ocular manifestations (figure 3).

**Publication Bias**

The results of Egger’s test showed no significant publication bias in our meta-analysis (figure 4).

**Discussion**

In a systematic review, 23 studies comprising a total of 3,650 clinically confirmed COVID-19 patients were analyzed. The PPE of any ocular manifestations was 23.77%, i.e., 24 in 100 patients had at least one ocular symptom. The most prevalent symptom was dry eyes with a PPE of 13.66% (95% CI: 5.01-25.51). The PPE for conjunctival hyperemia, conjunctival congestion/conjunctivitis, ocular pain, irritation/itching/burning sensation, and foreign body sensation was 13.41%, 9.14%, 10.34%, 9.34%, and 5.24%, respectively.

The coronavirus SARS-CoV-2, which can cause COVID-19, is globally responsible for more than 1.4 million deaths. In addition to affecting the respiratory tract, complications associated with ocular involvement have been reported. In a systematic review and meta-analysis of 16 studies (2,347 COVID-19 patients), Aggarwal and colleagues reported that the PPE for ocular surface manifestation...
was 11.64%.\textsuperscript{35} Similarly, Cheong analyzed 17 studies (483 COVID-19 patients) and reported a low prevalence of ocular manifestations (from 0 to 31.58%) and a low rate of SARS-CoV-2 detection in ocular swab samples (from 0 to 11.11%).\textsuperscript{36} Evidently, the number of patients in this study was much lower than in ours. Nasiri and colleagues also analyzed 38 studies (8,219 COVID-19 patients) and reported a low prevalence of ocular manifestations (11.03%).\textsuperscript{37} Compared to our results, the difference could be due to fewer detailed studies and/or a lower number of patients. Moreover, our results showed no significant association between age or sample size and the prevalence of any ocular manifestations. Other studies, despite a low sample size and exclusion of cohort studies, also reported no association between age and ocular manifestations.\textsuperscript{5, 19, 38}

The results of our study showed significant heterogeneity between studies for all symptoms except for diplopia and ocular discomfort. However, other studies have reported diplopia (i.e., double vision) as a complication of SARS-CoV-2 infection.\textsuperscript{23, 31} whereas in our study it was only a sporadic complication. Several studies have also reported the development of diplopia due to various conditions. For example, a patient with confirmed SARS-CoV-2 infection was reported to have developed diplopia associated with acetylcholine receptor antibodies.\textsuperscript{39} Another study reported a previously healthy patient developed diplopia following SARS-CoV-2 infection, which was associated with acute abducens nerve palsy.\textsuperscript{40} Belghmaidi and colleagues reported cranial nerve palsy in a patient with SARS-CoV-2 infection.\textsuperscript{41} Ocular discomfort, as a rare symptom of COVID-19, has been associated with dry eye disease.\textsuperscript{9, 17} We found that subconjunctival hemorrhage was a less common COVID-19 related ocular manifestation. However, some studies have associated this symptom with COVID-19.\textsuperscript{19, 20, 31} Schwarz and colleagues stated that patients with SARS-CoV-2 infection in the ICU might be prone to a higher risk of subconjunctival hemorrhage.\textsuperscript{42} However, because of the small sample size, further studies are required to substantiate their findings.

The ocular surface may serve as another entry gateway for SARS-CoV-2 since angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), as a mechanism for infection, are present in the conjunctiva and cornea.\textsuperscript{43, 44} Zhou and colleagues stated that ACE2 and TMPRSS2 could potentially be up-regulated due to inflammatory responses.\textsuperscript{43} Our results showed that the most common ocular manifestation in COVID-19 patients were dry eyes and conjunctival hyperemia. However, Hu and colleagues did not observe these symptoms, but detected SARS-CoV-2 in the tears of an asymptomatic patient.\textsuperscript{44} In their case report, the patient had nasolacrimal duct obstruction, and the eye swabs had been reported weak positive for the virus despite earlier negative nasopharyngeal swabs.\textsuperscript{45} These findings were in line with another study that reported the presence of SARS-CoV-2 in the tears of pediatric patients without ocular manifestations.\textsuperscript{27} Three possibilities are conceivable for these findings. First, respiratory viruses can enter the body through the nasolacrimal duct. Second, those, who only have ocular symptoms may also be COVID-19 patients, but misdiagnosed as non-COVID. Third, if the virus can cause infection through the eyes, then ocular manifestations could be considered early symptoms of COVID-19. Interestingly, a previous study suggested the possibility of viral transmission through the nasopharynx in individuals wearing N95 masks but no eye protection equipment.\textsuperscript{45}

The present study was instigated to examine an association between severe COVID-19 illness and ocular involvement. We found that conjunctivitis was prevalent in COVID-19 patients with ocular manifestations. In a meta-analysis of three studies, Loffredo and colleagues reported that conjunctivitis in COVID-19 patients was significantly correlated with disease severity.\textsuperscript{46} Another study on ocular findings in COVID-19 patients reported that those with ocular manifestations were more likely to have higher white blood cell counts and higher levels of procalcitronin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms.\textsuperscript{47} However, two other studies reported inconsistencies in data that associated severe COVID-19 with ocular involvement.\textsuperscript{48, 49} Nonetheless, one should consider ocular involvement among the various risk factors for the severity of COVID-19.\textsuperscript{50} In the present systematic review, we found that most of the included studies reported symptoms related to the ocular surface. In a study on 43 hospitalized COVID-19 patients, Pirraglia and colleagues did not detect any effect on the ocular posterior segments (the retina and retinal vessels),\textsuperscript{51} even though ACE2 receptors are expressed in the retina.\textsuperscript{52} However, a real-time PCR test of the retinal biopsy of 14 deceased COVID-19 patients showed weak positive COVID-19 results in three retinal specimens.\textsuperscript{52} Using optical coherence tomography (OCT) imaging technique, Marinho and colleagues
also reported retinal involvement in 12 COVID-19 patients showing lesions at the level of ganglion cells and inner plexiform layers. If SARS-CoV-2 could invade retinal ganglion cells, it could also lead to neurologic symptoms. Overall, in case of even subtle alterations in OCT findings, ophthalmologists should suspect an asymptomatic COVID-19 patient.

The outcome of our study strongly suggests various ocular manifestations are indicative of SARS-CoV-2 infection, as eye swabs could be positive for SARS-CoV-2 RNA despite earlier negative nasopharyngeal swabs. The tear fluid sampling method is an important factor, and various techniques such as Schirmer strips and corneal scrapings have been proposed. Regardless of the method, the main goal is to obtain as many cells as possible to have a proper viral load. Since there is no baseline to determine an adequate level of tear fluid, it is recommended to take as much fluid as possible. In this process, the tear sampling method, day of sample collection, and amount of collected sample could affect the real-time PCR positivity.

Our results showed that dry eyes and conjunctival hyperemia were the most prevalent ocular manifestations of SARS-CoV-2 infection. It has been suggested that any admitted COVID-19 patient with conjunctival hyperemia should be treated as having an ophthalmic manifestation of suspected COVID-19 unless proven otherwise. Cavalleri and colleagues assessed ocular symptoms in COVID-19 patients before and during hospitalization. They reported ocular manifestations (conjunctival hyperemia, epiphora, foreign body sensation) in a greater number of patients before admission than those during hospitalization. Some COVID-19 patients may have a history of concomitant ocular diseases, such as refractive disorders, allergic conjunctivitis, dry eye syndrome, keratitis, cataracts, and diabetic retinopathy. Ocular diseases increase the possibility of SARS-CoV-2 infection due to increased rate of hand-ocular surface contact. Therefore, exposure to ocular secretions could be a mechanism for viral transmission. As the main strength of the present study, for the first time, we conducted a comprehensive review of studies on ocular manifestations and the prevalence estimation of each ocular symptom. As a limitation, we were unable to perform gender-specific estimates due to insufficient data in the included studies. We also would have liked to estimate the pooled prevalence of ocular manifestations in different geographical regions, but the limited number of studies would have undermined the accuracy of the estimate. To deal with high heterogeneity and its effect on the interpretation of pooled data, we used a random-effects model.

**Conclusion**

The SARS-CoV-2 infection could cause ocular manifestations. However, these symptoms ameliorate without further complications. These manifestations could also be indicative of infection with the virus. The most common ocular findings in COVID-19 patients were dry eyes and conjunctival hyperemia. Attention should be paid to COVID-19 patients with ocular complications, especially those, who already suffer from eye disorders, to delay the development of common eye diseases. Given the anticipated worldwide increase in studies on COVID-19, it is strongly recommended to estimate the regional prevalence of ocular manifestation in COVID-19 patients.

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**Conflict of Interest:** None declared.

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