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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.

Keywords ● COVID-19 ● SARS-CoV-2 ● Eye manifestations ● Systematic review ● Meta-analysis

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).\textsuperscript{3} 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.\textsuperscript{4, 5} Besides the polymerase
chain reaction (PCR) test, other more sensitive
and accurate methods have been proposed
to detect the virus.\textsuperscript{3} 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.\textsuperscript{7, 8}

Ocular complications caused by the SARS-
CoV-2 virus have been reported in both humans
and animals. Ocular symptoms in COVID-19 patients include conjunctivitis, anterior uveitis,
retinitis, redness, and optic neuritis.\textsuperscript{9} However,
ocular infections due to the SARS-CoV-2 virus
are less common compared to adenovirus or
influenza viruses. The prevalence of ocular
abnormalities in COVID-19 patients may range
from 2% to 60%.\textsuperscript{10, 11} In a study on 103 clinically
confirmed COVID-19 patients, 21% of the cases
were reported to have ocular involvement.\textsuperscript{5}
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.\textsuperscript{10}

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.\textsuperscript{12} A previous study reported
the presence of SARS-CoV-2 RNA in tears and
ocular fluids of COVID-19 patients.\textsuperscript{13} 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.\textsuperscript{14}
However, the transmission of COVID-19 through
ocular secretion is controversial and requires
further research.\textsuperscript{15}

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 1 December 2019 to 10 April 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.\textsuperscript{16}

The quality of eligible studies was appraised
independently by two of the authors (R. P and
S. S) using the Newcastle-Ottawa Scale.\textsuperscript{17} The
scale consists of three parts, namely selection
(four items), confounder (one item), and
exposure (two items) with a maximum score of
4, 1, and 2 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 $I^2$ index. Based on the Higgins classification approach, $I^2 > 0.7$ 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.
### Table 1: Detailed characteristic of studies on the prevalence of ocular manifestations in COVID-19 patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Age (years)*</th>
<th>Ocular findings</th>
<th>Manifestation</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.⁹</td>
<td>Korea</td>
<td>Case series</td>
<td>103</td>
<td>53±12</td>
<td>Ocular symptoms</td>
<td>21%</td>
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<td></td>
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<td></td>
<td></td>
<td>Epiphora</td>
<td>1.94%</td>
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<td>Itching sensation</td>
<td>3.88%</td>
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<td>Visual disturbance</td>
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<td></td>
<td></td>
<td>Conjunctival congestion</td>
<td>6.79%</td>
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<td></td>
<td></td>
<td>Ocular discomfort</td>
<td>4.85%</td>
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<td></td>
<td>Ocular pain</td>
<td>2.91%</td>
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<tr>
<td>Liu et al.¹⁷</td>
<td>China</td>
<td>Case series</td>
<td>142</td>
<td>48 (14-83)</td>
<td>Ocular symptoms</td>
<td>2.80%</td>
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<td>Ocular discomfort</td>
<td>2.80%</td>
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<tr>
<td>Sindhuja et al.¹⁸</td>
<td>India</td>
<td>Case series</td>
<td>127</td>
<td>38.80 (5–73)</td>
<td>Ocular symptoms</td>
<td>8.66%</td>
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<td>Burning sensation</td>
<td>0.79%</td>
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<td></td>
<td>Epiphora</td>
<td>0.79%</td>
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<td></td>
<td>Swollen eyelid</td>
<td>0.79%</td>
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<tr>
<td>Guemes-Villahoz et al.¹⁹</td>
<td>Spain</td>
<td>Case series</td>
<td>301</td>
<td>72 (59–82)</td>
<td>Ocular symptoms</td>
<td>11.60%</td>
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<td>Foreign body sensation</td>
<td>3.99%</td>
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<td>Pterygium</td>
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<td>Hordeolum</td>
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<td></td>
<td></td>
<td>Epiphora</td>
<td>4.98%</td>
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<tr>
<td>Guemes-Villahoz et al.²⁰</td>
<td>Spain</td>
<td>Case series</td>
<td>36</td>
<td>67.90 (28–92)</td>
<td>Ocular symptoms</td>
<td>50%</td>
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<td>Subconjunctival hemorrhage</td>
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<td>Conjunctival hyperemia</td>
<td>50%</td>
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<td>Hordeolum</td>
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<td>Karimi et al.²¹</td>
<td>Iran</td>
<td>Case series</td>
<td>43</td>
<td>56.60±13.70</td>
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<td>Conjunctivitis</td>
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<td>Atum et al.¹⁵</td>
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<td>Case series</td>
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<tr>
<td>Hong et al.²²</td>
<td>China</td>
<td>Cross-sectional</td>
<td>56</td>
<td>48 (24–68)</td>
<td>Ocular symptoms</td>
<td>27%</td>
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<td>Eye secretions</td>
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<td>Zhang et al.¹¹</td>
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<td>Cross-sectional</td>
<td>72</td>
<td>58.68±14.81</td>
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<td>2.78%</td>
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<td>Conjunctivitis</td>
<td>2.78%</td>
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<td>Rokohl et al.²³</td>
<td>Germany</td>
<td>Cohort</td>
<td>108</td>
<td>37.90±13.70</td>
<td>Ocular symptoms</td>
<td>69.40%</td>
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<td>Burning sensations</td>
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<td>Itching sensations</td>
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<td>Photophobia</td>
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<td>Diplopia</td>
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<td>Reduced visual acuity</td>
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<td>Ocular pain</td>
<td>10.19%</td>
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<td>Author(s)</td>
<td>Country</td>
<td>Study Design</td>
<td>N</td>
<td>Age Range</td>
<td>Prevalence (%)</td>
<td>Most Common Symptoms</td>
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<tr>
<td>Cavalleri et al.24</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>172</td>
<td>68.03%</td>
<td>31.97%</td>
<td>Ocular symptoms: 26.20%</td>
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<td>64.2±13.4</td>
<td>Conjunctival hyperemia: 15.12%</td>
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<td>121</td>
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<td>Ocular symptoms: 6.60%</td>
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<td></td>
<td>48 (22-89)</td>
<td>Conjunctival hyperemia: 4.13%</td>
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<tr>
<td>Oncul et al.25</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>359</td>
<td>54.90%</td>
<td>45.10%</td>
<td>Ocular symptoms: 16.50%</td>
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<td></td>
<td>58.50 (20-91)</td>
<td>Conjunctival hyperemia: 4.50%</td>
<td></td>
</tr>
<tr>
<td>Chen et al.26</td>
<td>China</td>
<td>Cross-sectional</td>
<td>535</td>
<td>50.10%</td>
<td>49.90%</td>
<td>Ocular symptoms: 16.20%</td>
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<td></td>
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<td></td>
<td>44.0 (34.0–54.2)</td>
<td>Conjunctival congestion: 23.74%</td>
<td></td>
</tr>
<tr>
<td>Valente et al.27</td>
<td>Italy</td>
<td>Case series</td>
<td>27</td>
<td>74.10%</td>
<td>25.90%</td>
<td>Ocular symptoms: 14.80%</td>
<td></td>
</tr>
<tr>
<td>Bostanci et al.28</td>
<td>Turkey</td>
<td>Cross-sectional</td>
<td>93</td>
<td>58.10%</td>
<td>41.90%</td>
<td>Ocular symptoms: 27.70%</td>
<td></td>
</tr>
<tr>
<td>Abrishami et al.10</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>142</td>
<td>54.20%</td>
<td>45.77%</td>
<td>Ocular symptoms: 27.70%</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>62.60±15 (23–96)</td>
<td>Conjunctival hyperemia: 21.51%</td>
<td></td>
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<tr>
<td>Invernizzi et al.29</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>54</td>
<td>70.30%</td>
<td>29.60%</td>
<td>Ocular symptoms: 27.70%</td>
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<td></td>
<td></td>
<td></td>
<td>49.90±15.60 (23–82)</td>
<td>Vision difficulties: 1.80%</td>
<td></td>
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<tr>
<td>Tostmann et al.30</td>
<td>Netherlands</td>
<td>Cross-sectional</td>
<td>90</td>
<td>21.10%</td>
<td>78.90%</td>
<td>Ocular symptoms: 27.70%</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>39.01</td>
<td>Ocular pain: 34.40%</td>
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</tbody>
</table>

- Ocular symptoms include: Conjunctival hyperemia, Epiphora, Eye secretion, Swollen eyelid, Foreign body sensation, Itching sensation, and Other.
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) 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

<table>
<thead>
<tr>
<th>Table 2: Pooled prevalence estimate and corresponding 95% confidence interval of ocular manifestations in COVID-19 patients. The results of publication bias using Egger’s test are also presented</th>
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</thead>
<tbody>
<tr>
<td>Symptom</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Any ocular manifestations</td>
</tr>
<tr>
<td>Conjunctival congestion / conjunctivitis</td>
</tr>
<tr>
<td>Ocular discomfort</td>
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<tr>
<td>Ocular pain</td>
</tr>
<tr>
<td>Visual disturbance/blurred vision</td>
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<tr>
<td>Epiphora</td>
</tr>
<tr>
<td>Irritation/itching/burning sensation</td>
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<tr>
<td>Swollen eyelid</td>
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<tr>
<td>Foreign body sensation</td>
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<tr>
<td>Hordeolum</td>
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<tr>
<td>Ptterygium</td>
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<tr>
<td>Conjunctival hyperemia</td>
</tr>
<tr>
<td>Dry eyes</td>
</tr>
<tr>
<td>Photophobia</td>
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<tr>
<td>Subconjunctival hemorrhage</td>
</tr>
<tr>
<td>Diplopia</td>
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<tr>
<td>Eye/conjunctival secretion</td>
</tr>
</tbody>
</table>

CI: Confidence interval; PPE: Pooled prevalence estimate; NS: Number of studies
was 11.64%. 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 11.1%). 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%). Compared to our results, the difference could be due to fewer detailed studies and/or a lower number of patients. However, 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. Compared to our results, the difference could be due to fewer detailed studies and/or a lower number of patients. However, 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.

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, 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 has been reported to have developed diplopia associated with acetylcholine receptor antibodies. Another study reported a previously healthy patient developed diplopia following SARS-CoV-2 infection, which was associated with acute abducens nerve palsy. Belghmaidi and colleagues reported cranial nerve palsy in a patient with SARS-CoV-2 infection. Ocular discomfort, as a rare symptom of COVID-19, has been associated with dry eye disease. We found that subconjunctival hemorrhage was a less common COVID-19 related ocular manifestation. However, some studies have associated this symptom with COVID-19, and patients with SARS-CoV-2 infection in the ICU might be prone to a higher risk of subconjunctival hemorrhage. 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. Zhou and colleagues stated that ACE2 and TMPRSS2 could potentially be up-regulated due to inflammatory responses. 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. 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. 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. 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.

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. 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 procalcitonin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms. However, two other studies reported inconsistencies in data that associated severe COVID-19 with ocular involvement. Nonetheless, one should consider ocular involvement among the various risk factors for the severity of COVID-19.

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), even though ACE2 receptors are expressed in the retina. 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. 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.53 If SARS-CoV-2 could invade retinal ganglion cells, it could also lead to neurologic symptoms.54 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.44 The tear fluid sampling method is an important factor, and various techniques such as Schirmer strips55 and corneal scrapings56, 57 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.58, 59 In this process, the tear sampling method, day of sample collection, and amount of collected sample could affect the real-time PCR positivity.60

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.48 Cavalleri and colleagues assessed ocular symptoms in COVID-19 patients before and during hospitalization.24 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.15, 26 Ocular diseases increase the possibility of SARS-CoV-2 infection due to increased rate of hand-ocular surface contact.15 Therefore, exposure to ocular secretions could be a mechanism for viral transmission.54, 55

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.

**Acknowledgment**

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**Conflict of Interest:** None declared.

**References**


Ocular symptoms in COVID-19 patients


21 Karimi S, Arabi A, Shahraki T, Safi S.


Ocular symptoms in COVID-19 patients


