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Review Article

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

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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.

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.

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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).[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.[4, 5] Besides the polymerase chain reaction (PCR) test, other more sensitive and accurate methods have been proposed to detect the virus.[6] 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.[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.[9] However, ocular infections due to the SARS-CoV-2 virus are less common than adenovirus or influenza viruses. The prevalence of ocular abnormalities in COVID-19 patients may range from 2% to 60%.[10, 11] In a study on 103 clinically confirmed COVID-19 patients, 21% of the cases were reported to have ocular involvement.[9] 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.[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.[12] A previous study reported the presence of SARS-CoV-2 RNA in tears and ocular fluids of COVID-19 patients.[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.[14] However, the transmission of COVID-19 through ocular secretion is controversial and requires further research.[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 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.[16]

The quality of eligible studies was appraised independently by two of the authors (R. P and S. S) using the Newcastle-Ottawa Scale.[17] 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 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).

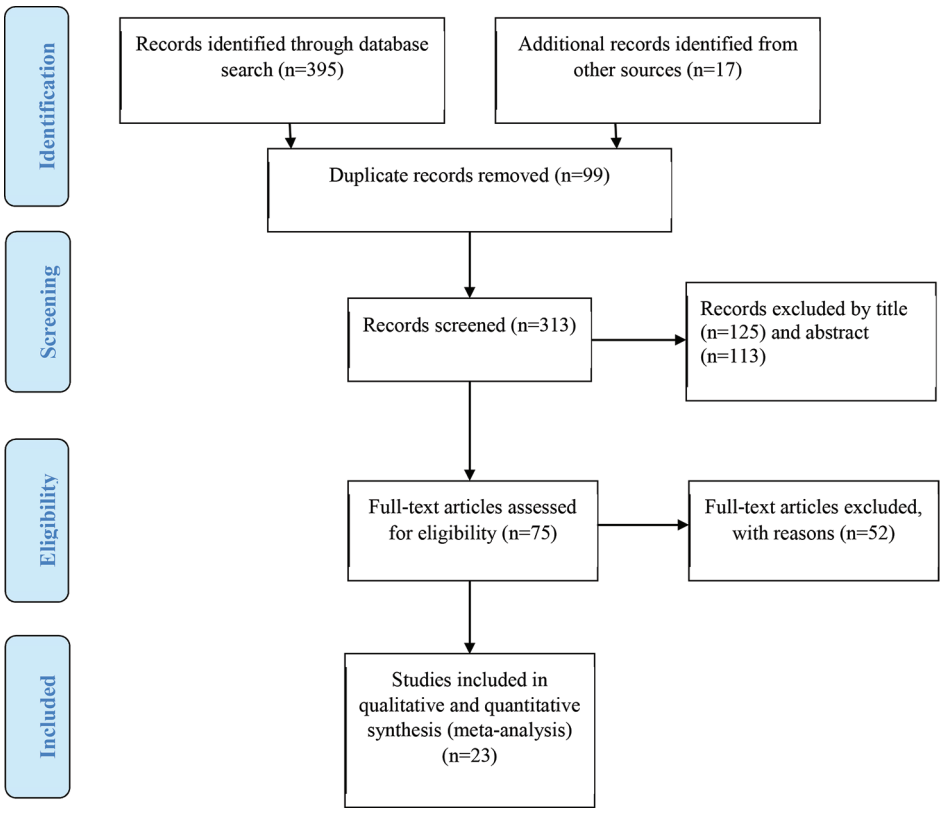

Figure 1: The flow diagram depicts the selection process of studies in accordance with the PRISMA guidelines.

Table 1: Detailed characteristic of studies on the prevalence of ocular manifestations in COVID-19 patients

Author	Country	Study design	Sample size			Age (years)*	Ocular findings	
			Total	Male	Female		Manifestation	Percent
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%
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%
							Swollen eyelid	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%
Atum et al.[15]	Turkey	Case series	40	62.50%	37.50%	41.38±23.72 (1–82)	Ocular symptoms	25%
							Conjunctivitis	25 %
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%
Rokohl et al.[23]	Germany	Cohort	108	47.22%	52.78%	37.90±13.70	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%

Cavalleri et al.[24]	Italy	Cross-sectional	172	68.03%	31.97%	64.2±13.4	Ocular symptoms	26.20%
							Conjunctival hyperemia	15.12%
							Epiphora	13.37%
							Eye secretion	2.33%
							Swollen eyelid	2.91%
							Foreign body sensation	9.89%
							Itching sensation	6.98%
Zhou et al.[14]	China	Cross-sectional	121	43.80%	56.2%	48 (22-89)	Ocular symptoms	6.60%
							Itching sensation	4.13%
							Conjunctival hyperemia	2.48%
							Epiphora	2.48%
							Foreign body sensation	1.65%
Oncul et al.[25]	Turkey	Cross-sectional	359	54.90%	45.10%	58.50 (20-91)	Ocular symptoms	4.50%
							Conjunctival hyperemia	0.58%
							Epiphora	1.39%
							Eye secretion	1.67%
							Photophobia	1.11%
							Conjunctivitis	1.95%
Chen et al.[26]	China	Cross-sectional	535	50.10%	49.90%	44.0 (34.0–54.2)	Ocular symptoms	23.74%
							Dry eyes	20.94%
							Conjunctival congestion	4.67%
							Blurred vision	12.71%
							Foreign body sensation	11.78%
							Eye secretion	9.72%
							Ocular pain	4.11%
							Epiphora	10.28%
							Itching sensation	9.91%
Valente et al.[27]	Italy	Case series	27	74.10%	25.90%	7 (1-17.50)	Ocular symptoms	14.80%
							Conjunctivitis	14.80%
Bostanci et al.[28]	Turkey	Cross-sectional	93	58.10%	41.90%	39.40±21.90 (7-88)	Ocular symptoms	21.50%
							Conjunctival hyperemia	21.51%
							Epiphora	9.68%
							Eye secretion	6.45%
							Conjunctivitis	8.60%
							Photophobia	16.13%
							Itching sensation	13.98%
							Burning sensation	7.53%
							Foreign body sensation	3.22%
							Blurred vision	4.30%
Abrishami et al.[10]	Iran	Cross-sectional	142	54.20%	45.77%	62.60±15 (23–96)	Ocular symptoms	64.80%
							Conjunctival hyperemia	30.98%
							Keratitis	2.11%
							Cataract	7.75%
							Diabetic retinopathy	6.34%
							Epiphora	23.24%
							Hyperemia	16.20%
							Eye irritation	13.38%
							Itching sensation	8.45%
							Foreign body sensation	2.82%
							Ocular pain	3.52%
							Photophobia	0.70%
							Blurred vision	0.70%
Invernizzi et al.[29]	Italy	Cross-sectional	54	70.30%	29.60%	49.90±15.60 (23–82)	Ocular symptoms	27.70%
							Vision difficulties	1.80%
							Hyperemia	3.60%
							Burning sensation	22.20%
							Photophobia	1.80%
Tostmann et al.[30]	Netherlands	Cross-sectional	90	21.10%	78.90%	39.01	Ocular symptoms	34.40%
							Ocular pain	34.40%

Bourdon et al.[31]	France	Cohort	500	60.60%	39.40%	40.60±20.30 (1-92)	Ocular symptoms	64.20%
							Pterygium	0.20%
							Diplopia	1%
							Hordeolum	21.80%
							Corneal abscess	2%
							Recurrent corneal erosion	1.20%
							Optic neuritis	0.60%
							Macular disorder	0.60%
							Angle-closure	0.20%
							Vitreoretinal disorder	11.80%
							Blepharitis	9.20%
							Uveitis	8.20%
							Conjunctivitis	4.20%
							Foreign body sensation	3.20%
							Subconjunctival hemorrhage	3%
Xu et al.[32]	China	Cross-sectional	15	50%	50%	48±13.40	Ocular symptoms	6.67%
							Itching sensation	6.67%
Lan et al.[33]	China	Case series	81	40.70%	59.30%	41.69±18.60	Ocular symptoms	3.70%
							Itching sensation	3.70%
							Swollen eyelid	2.47%
							Dry eyes	1.24%
							Conjunctivitis	2.47%
Perlman et al.[34]	USA	Cohort	433	62.40%	37.60%	37.50±13.80	Ocular symptoms	29.10%
							Dry eyes	29.10%
							Ocular pain	19.17%

*Data presented as mean (range), mean±SD (range), or mean

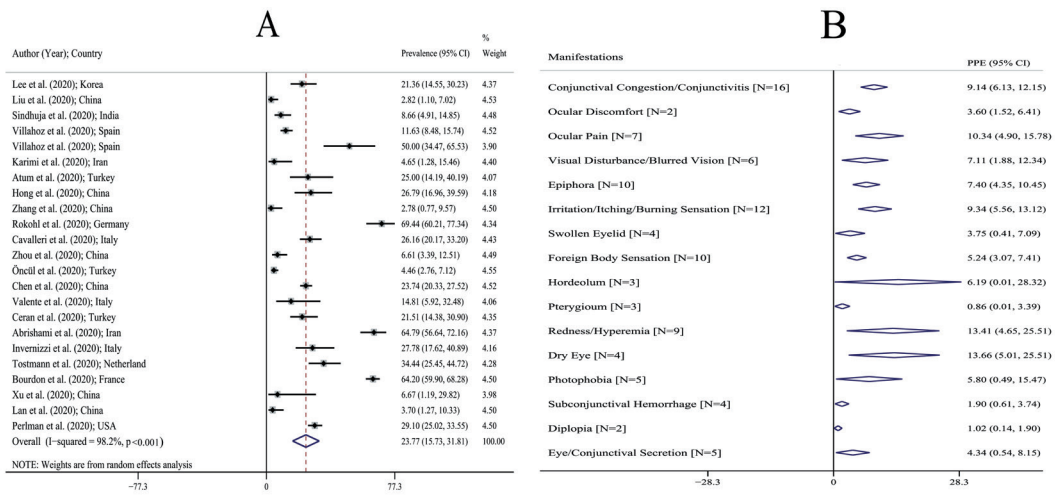

Figure 2: The forest plots for the pooled prevalence estimate (PPE) of any ocular manifestations (A) and specific ocular symptom (B) in patients with COVID-19 based on a random-effects model. A: Each study is labeled with the name of the first author, year, and country. The midpoint of each line segment shows the prevalence estimate, the length of the line segment indicates a 95% confidence interval (CI) in each study, and the diamond mark illustrates the PPE. B: The diamond mark illustrates PPE and the length of the diamond indicates 95% CI.

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 for diplopia and ocular discomfort (only two studies on this subgroup) (table 2).

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

Symptom	NS	Pooled data			Publication bias	
		Heterogeneity	PPE (%)	95% CI	Coefficient	P value
Any ocular manifestations	23	I^2=98.20%, Tau^2=0.001, P<0.001	23.77	15.73 to 31.81	-1.12	0.417
Conjunctival congestion / conjunctivitis	16	I^2=89.66%, Tau^2=0.001, P<0.001	9.14	6.13 to 12.15	0.70	0.289
Ocular discomfort	2	I^2=10.14%, Tau^2<0.001, P=0.875	3.60	1.52 to 6.41	---	---
Ocular pain	7	I^2=93.59%, Tau^2=0.001, P<0.001	10.34	4.90 to 15.78	0.31	0.845
Visual disturbance/blurred vision	6	I^2=93.56%%, Tau^2=0.001, P<0.001	7.11	1.88 to 12.34	-0.96	0.336
Epiphora	10	I^2=92.25%, Tau^2=0.001, P<0.001	7.40	4.35 to 10.45	0.40	0.716
Irritation/itching/burning sensation	12	I^2=90.04%, Tau^2=0.001, P<0.001	9.34	5.56 to 13.12	0.15	0.850
Swollen eyelid	4	I^2=80.91%, Tau^2=0.001, P=:0.030	3.75	0.41 to 7.09	0.99	0.756
Foreign body sensation	10	I^2=80.26%, Tau^2=0.001, P<0.001	5.24	3.07 to 7.41	-0.40	0.432
Hordeolum	3	I^2=98.34%, Tau^2=0.28, P=0.001	6.19	0.01 to 28.32	-1.92	0.698
Pterygium	3	I^2=75.41%, Tau^2=0.010, P=0.020	0.86	0.01 to 3.39	0.45	0.150
Conjunctival hyperemia	9	I^2=96.04%, Tau^2=0.201, P=0.001	13.41	4.65 to 25.51	2.29	0.168
Dry eyes	4	I^2=94.95%, Tau^2=0.080, P<0.001	13.66	5.01 to 25.51	-2.41	0.228
Photophobia	5	I^2=94.01%, Tau^2=0.120, P<0.001	5.80	0.49 to 15.47	1.55	0.370
Subconjunctival hemorrhage	4	I^2=74.25%, Tau^2=0.010, P=0.041	1.90	0.61 to 3.74	0.40	0.410
Diplopia	2	I^2=5.04%, Tau^2<0.001, P=0.917	1.02	0.14 to 1.90	---	---
Eye/conjunctival secretion	5	I^2=88.07%, Tau^2=0.040, P=0.001	4.34	0.54 to 8.15	-0.59	0.530

CI: Confidence interval; PPE: Pooled prevalence estimate; NS: Number of studies

The I^2 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.[2] In addition to affecting the respiratory tract, complications associated with ocular involvement have been reported.[23] 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

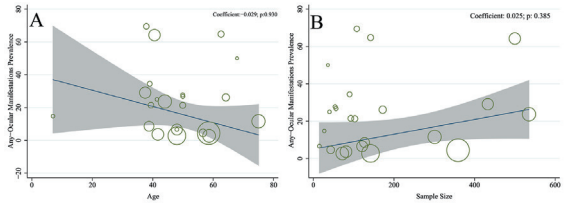

Figure 3: The results of meta-regression analysis show no significant association between age (A) or sample size (B) and the prevalence of any ocular manifestations. The size of the circles indicates the precision of each study.

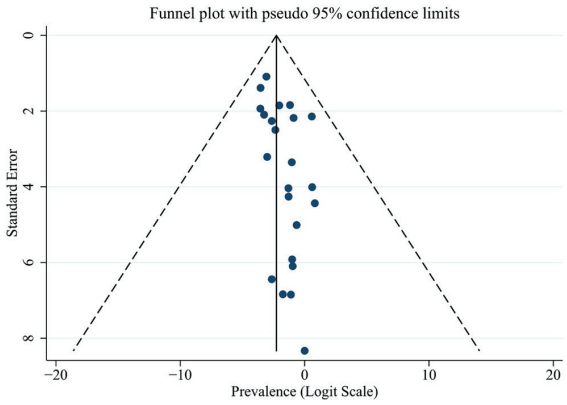

Figure 4: The funnel plot indicates the publication bias assessment. The horizontal and vertical axes represent the prevalence of any ocular manifestations (in logit scale) and the standard error of the prevalence, respectively.

was 11.64%.[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%).[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%).[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.[9, 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,[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.[39] Another study reported a previously healthy patient developed diplopia following SARS-CoV-2 infection, which was associated with acute abducens nerve palsy.[40] Belghmaidi and colleagues reported cranial nerve palsy in a patient with SARS-CoV-2 infection.[41] Ocular discomfort, as a rare symptom of COVID-19, has been associated with dry eye disease.[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.[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.[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.[43, 44] Zhou and colleagues stated that ACE2 and TMPRSS2 could potentially be up-regulated due to inflammatory responses.[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.[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.[44] 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.[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.[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.[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 procalcitonin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms.[47] However, two other studies reported inconsistencies in data that associated severe COVID-19 with ocular involvement.[48, 49] Nonetheless, one should consider ocular involvement among the various risk factors for the severity of COVID-19.[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),[51] even though ACE2 receptors are expressed in the retina.[12] 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.[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.[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 strips[55] and corneal scrapings[56, 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, 59]

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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