COVID-19 and conjunctivitis: a meta-analysis

Ther Adv Ophthalmol
2021, Vol. 13: 1–10
DOI: 10.1177/25158414211003368

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Abstract

COVID-19 is a disease first identified in Wuhan City, Hubei Province, China, in December 2019, causes by a SARS-COV-2 virus infection. By 27 October 2020, 43,921,473 confirmed cases were reported worldwide, with 1,166,389 COVID-19 deaths. Conjunctivitis has been reported in adults and pediatric patients with COVID-19.

Objective: The aim of this meta-analysis is to estimate the odd Ratio (ORs) of conjunctivitis in patients with COVID-19.

Methods: A systematic review and meta-analysis have been performed using the PubMed and Google Scholar literature search. The ORs of conjunctivitis in adults and pediatric patients is the outcome of this meta-analysis.

Results: There have been 1041 articles published since the outbreak in December 2019, according to the latest literature. For the meta-analysis, 20 studies with a total of 3383 participants were included. The odds ratio (ORs) of conjunctivitis was 0.01 (95% confidence interval [CI]: 0.00–0.02). No bias has been reported.

Conclusion: Conjunctivitis is the most common ocular manifestations reported in adults. This comprehensive meta-analysis quantifies the existing evidence linking conjunctivitis with COVID-19 and highlights the high percentage of heterogeneity that is shown in the current studies. Finally, it offers a single review article which includes all the current articles available for COVID-19 and conjunctivitis in adults and children.

Keywords: COVID-19, meta-analysis, SARS-CoV-2, viral conjunctivitis

Received: 31 January 2021; revised manuscript accepted: 23 February 2021.

Introduction

COVID-19 is a disease first identified in Wuhan City, Hubei Province, China, in December 2019, caused by a SARS-COV-2 virus infection.[1] In February, COVID-19 was formally announced by the World Health Organization (WHO) as COVID-19, formerly recognized as 2019 Novel Coronavirus (2019-nCOV) respiratory disease. The ambiguity of COVID-19 as it infects patients can vary from asymptomatic infection to serious illness and mortality. The case report of COVID-19 patients on a cruise's ship (Diamond Princess ship) was one of the very early cases of a patient diagnosed with COVID-19 with viral conjunctivties.[2]

SARS-COV and SAR-COV-2 have been explained to have identical findings linked to the same coronavirus family. In addition, it was emphasized that the infection is spread by the tears.[3] Although the likelihood of coronavirus spreading through tears appears small, it may survive in the conjunctiva, even in the absence of signs of conjunctivitis, suggesting the importance of using eye protection to avoid infection from external droplets and aerosols.[4] The key components considered to understand the "Ocular Pathway" are angiotensin-converting-enzyme-2 (ACE2) receptors and TMPRSS2 protein.[4] By 27 October 2020, 43,921,473 confirmed cases were reported worldwide, with 1,166,389 COVID-19 deaths. In adults and pediatric patients with COVID-19, conjunctivitis has been identified. The aim of this meta-analysis is to update eye care physicians of the ORs of conjunctivitis in COVID-19 patients as a review of the current evidence.

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Methods

Trials identification and data consideration

The standards and guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) has been followed.[5,6] PubMed search and other search engines "Google Scholar" have been used from December 2019 to 27 October 2020. The key words used were "COVID-19," "Conjunctivitis" used individually or in combination. We selected randomized trials, observational studies, case series or case reports, and letters of research, letters to editors for confirmed cases of COVID-19 for the literature review, but only retrospective studies and observational studies for the meta-analysis. According to current scientific literature since the outbreak in December 2019 there have been 1041 papers written. The selected studies applied no language or other restrictions.

For bias detection, in each eligible study, a 7-point predefined quality control was used. The corresponding risk of bias was categorized as low (L), high (H), or unknown (U) to each quality item according to Higgins and colleagues[5,7] Unknown is used to judge insufficient information. The Complete outcome data were judged as "Low risk" or "high risk" or "unknown." The "low risk" is used when follow up percentage of participants lost was lower than 5% and "high risk" when follow up loss percentage was more than 20%.[8,9] For other potential sources of bias, including the bias source, including the funding source reported in each protocol, the term "other bias" was used.[5,10]

The overall treatment effect was calculated and the study weight for each study was calculated. Due to the larger sample size of some of the studies, the study weight was calculated and the "true effect" for each study is shown. The larger sample size provides more information than a small sample size.

Data extraction

Inclusion criteria

(a) COVID-19 patients.
(b) Conjunctivitis was assessed, and the number of events was reported.

Exclusion criteria

a) If no data on ocular, manifestations neither conjunctivitis
b) Animal research
c) Case report, letter to the editorial or review

Quality of the comparative studies. Assessment of the quality characteristics used the following criteria: (1) random sequence generation (R), (2) allocation concealment (A), (3) blinding of participants and personnel (PB), 4) Blinding of outcome assessment (DB), (5) Incomplete outcome data (Attrition Bias) (AB), 6) Selective reporting (Reporting bias) (RB), and 7) Other bias (O). Each study was labeled with the right item either adequate (low risk of bias), unclear (unknown risk of bias), and inadequate (high risk of bias).

Literature screening and quality evaluation

One researcher independently screened the articles.

Statistical analyses

MedCalc 16.4.3 (Ostend, Belgium) software was used to statistically analyze the data and REV5. The ORs were calculated in each study. The study heterogeneity was assessed with the Cochran Q and I^2 statistics. For the heterogeneity qualitative interpretation, I^2 values of at least 50% were considered to reflect considerable heterogeneity, while values of at least 75% indicated large heterogeneity, as per the Cochrane Handbook.[5] Publication bias was evaluated using both graphical funnel plot[11] and Beggs statistical test. Random-effect model was used.

Results

Selection and characteristics of the study

PubMed and Google Scholar Searches of database resulted in 8681 articles; 1041 results were screened after duplicates removal. For the meta-analysis reviewer, 20 articles were analyzed with a total of 3383 participants. Eighteen articles were studied in adult patients with COVID-19 and two articles were studied in pediatric patients with COVID-19.[12,13] The flow chart presenting the selection of eligible studies is summarized (Figures 1 and 2). The characteristics of the included studies are summarized (Table 1). Table 1 includes first author's name, publication year, sample size, mean or median age or range of age reported and country of the study. Finally, the number of total COVID-19 patients and number of viral conjunctivitis patients (Table 1.)

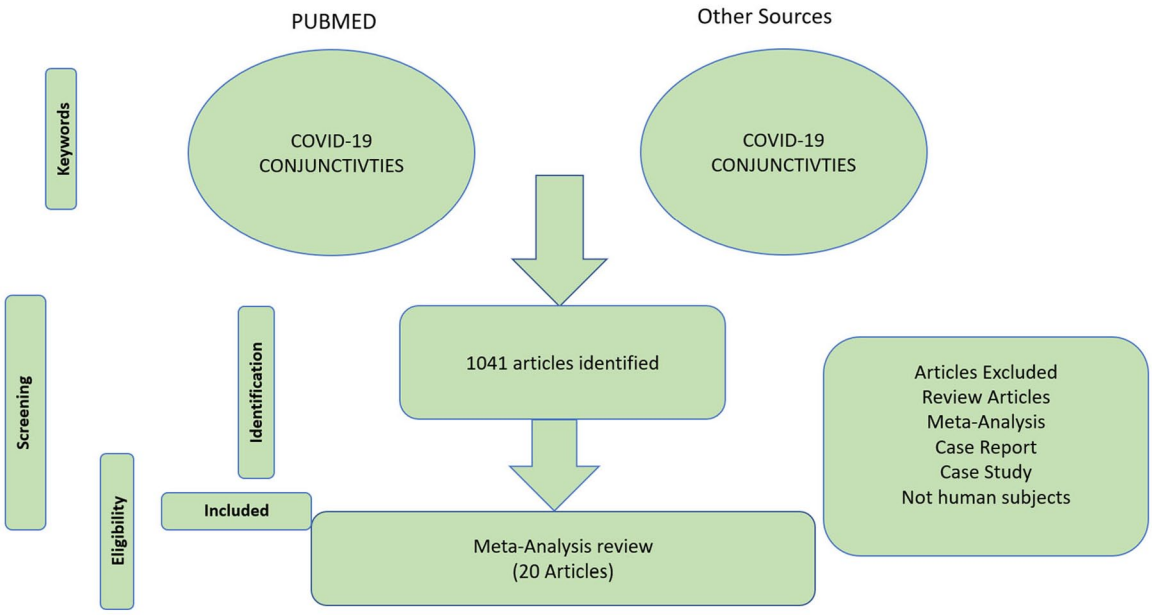

Figure 1. Flow PRISMA chart presenting the total number of articles and the number of the included studies. Adapted from Moher and colleagues.[6]

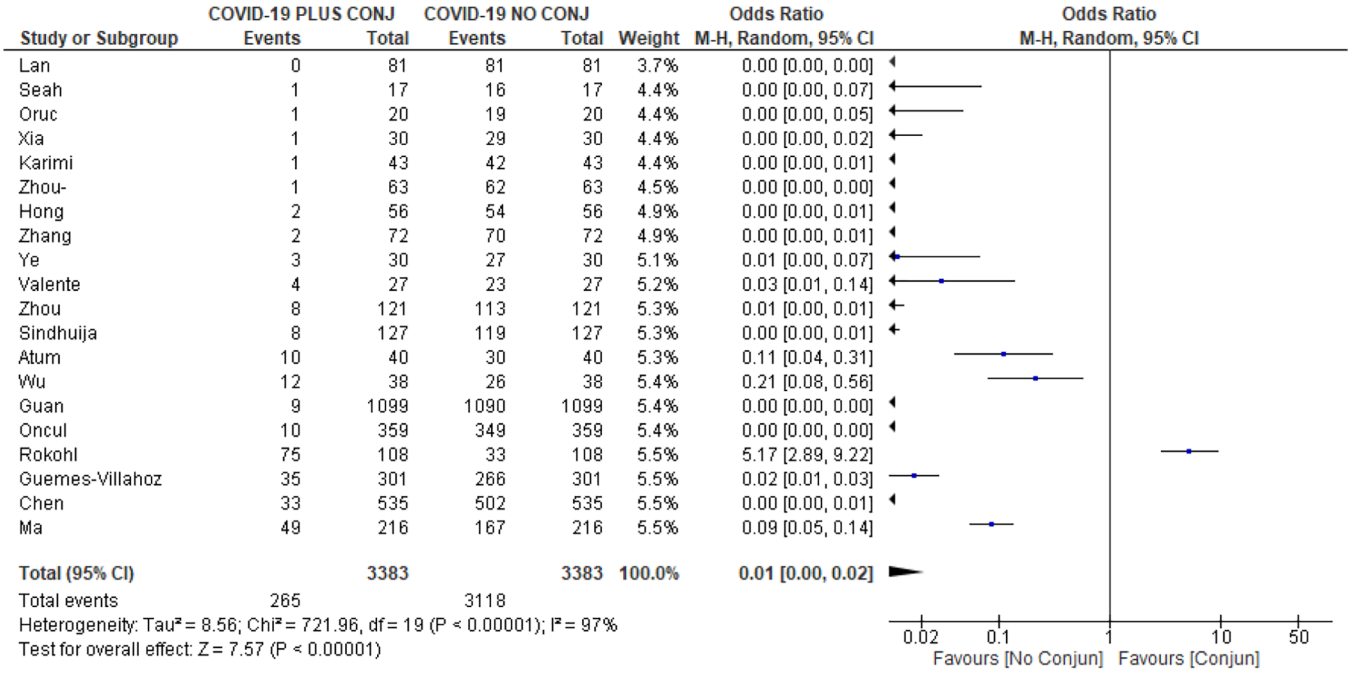

Figure 2. Forrest plot depicting pooled analysis.

The ORs ranged from 0.00 to 5.17, which reveals the high heterogeneity between individual studies. The sample size also varied between 17 and 1099 COVID-19 patients (Figure 2).

Independent studies bias risk

The risk of bias of the included studies has been reviewed and studied by the author (Supplemental Table 1). Random sequence

Table 1. Characteristics of included studies.

Study ID	Country	Conjunctivitis	Mean ± STD or median/range age (years)	Study iD	Country	Conjunctivitis	Average years
Guan and colleagues[14]	China	9/1099	Median: 47 (range: 35.0–58.0)	Wu and colleagues[15]	China	12/38	65.8 ± 16.6
Xia and colleagues[16]	China	1/30	54.5 ± 14.2	Zhou and colleagues[17]	China	8/121	Median: 48 (range: 22–89)
Zhou and colleagues[18]	China	1/63	Range: 18–60	Zhang and colleagues[19]	China	2/72	58.7 ± 14.8
Sindhuja and colleagues[20]	India	8/127	Median 38.8	Guemes-Villahoz and colleagues[21]	Spain	35/301	Median: 72
Chen and colleagues[22,23]	China	33/535	Median: 44 (range: 16–68)	Lan and colleagues[24]	China	0/81	41.69 ± 18.6
Seah and colleagues[25]	Singapore	1/17	Range: 18–50	Atum and colleagues[26]	Turkey	10/40	41.38 ± 23.72 (range: 1–82)
Hong and colleagues[27]	China	2/56	48 ± 12.1	Oruc and colleagues[28]	Turkey	1/20	[b]
Valente and colleagues[13]	Italy	4/27	96.26 ± 76.10 (months) range (1–216 months)	Ye and colleagues[29]	China	3/30	38.33 ± 23.33[a]
Ma and colleagues[12]	China	49/216	Median: 7.25, (range: 2.6–11.6)	Öncül and colleagues[30]	Turkey	10/359	Median: 58.5 (range:20–91)
Rokohl and colleagues[31]	Germany	75/108	37.9 ± 13.7	Karimi and colleagues[32]	Iran	1/43	56 ± 13

[a]The age of the 3 conjunctivitis ages was listed, rather than the average of the 30 patients.
[b]Not listed.

was low in 6 studies.[12,14,19,20,22,27] Allocation concealment was low in five studies.[12,14,20,22,27] The blinding participants and personnel (PB) is low in 10 articles.[12,20–22,26–28,30–32] The blinding of outcome assessment (DB) is low in 12 articles.[12,20–22,24–28,30–32]

The incomplete outcome data (Attrition Bias) (AB) is low in 19 articles.[12–18,20–22,24–32]

Selective reporting (Reporting bias (RB) is 16 articles.[12–14,16–18,20,21,24,26–32] All other bias is low in all 20 articles[12–22,24–33] (Supplemental Table 1).

Overall final analyses. The systematic review of the selected 20 articles estimated the ORs of conjunctivitis of a total of 3383 COVD-19 patients. The ORs = 0.01; 95% confidence interval (CI): [0.00, 0.02] (Figure 2). Heterogeneity was statistically significant using the I^2 value of 97% and $p < 0.0001$. In addition, no publication bias was detected using the funnel plot inspection.

Discussion

Conjunctivitis may be the first manifestation of the COVID-19 infection.[15,23,34]

Most patients in the 20 articles were hospitalized with COVID-19 (Table 2). Each article had at least two groups of patients, both non-severe and severe. Other articles were grouped into three classes, moderate, severe, and critical according to the PC-NCP guidelines[35] (Table 2).

The majority of patients with viral conjunctivitis were male patients (Table 3). Other ocular manifestations have been documented, such as conjunctival hyperemia[25,29,31] and secretion,[25,30] conjunctival discharge,[29,31] eye rubbing, subconjunctival bleeding,

Table 2. Characteristics of COVID-19 patients that included in each study.

	No. of patients	Female	Male
Guan and colleagues[14]	1099 hospitalized Only laboratory-confirmed cases	459	640
Wu and colleagues[15]	38 hospitalized patients with NCP	13	25
Xia and colleagues[16]	30 hospitalized patients with NCP	9	21
Karimi and colleagues[32]	43 severe COVID-19 9 patients were admitted to ICU because of respiratory failure	14	29
Sindhuja and colleagues[20]	127 patients	14	113
Zhang and colleagues[19]	72 confirmed laboratory diagnosis SARS-COV2-RT-PCR	36	36
Zhou and colleagues[17]	67 63 confirmed laboratories confirmed NCP 4 suspected cases of NCP	42	25
Zhou and colleagues[18]	121 patients	68	53
Guemes-Villahoz and colleagues[21]	301 patients from COVID admission unit with laboratory-confirmed SARS-COV2 infection 41 patients admitted to the intensive care unit. Age: 72 (59–82)	121	180
Chen and colleagues[22,23]	A total of 535 COVID-19 patients (27 with conjunctival congestion) were enrolled in the study	267	268
Lan and colleagues[24]	Hospitalized 81 patients	48	33
Seah and colleagues[25]	17 patients 20–75 (37) Age of patients (range, median)	6	11
Atum and colleagues[26]	40 patients tested positive Rt-PCR of nasopharyngeal and oropharyngeal swabs. 41.38 ± 23.72 years Range: 1–82 years	15	25
Hong and colleagues[27]	56 hospitalized patients who were discharged from the isolation ward and recovered well enough to return home. 48 (24–68, 12.1) Mean (range, SD), years	25	31
Oruc and colleagues[28]	20 patients COVID-19 patients	x	x
Valente and colleagues[13]	27 patients Nasopharyngeal swabs were positive for COVID-19 in all patients. Mean age: 84 months. Age range: 8 days to 210 months Children	7	20
Ye and colleagues[29]	30 COVID-19 patients	x	x
Ma and colleagues[12]	216 pediatric patients Laboratory-confirmed children with COVID-19 A median (interquartile range) age of 7.25 (2.6–11.6) years.	82	134
Öncül and colleagues[30]	359 COVID-19 patients Mean age of the patients was 58.5 years (20–91). 294 (81.9%) patients were treated in the inpatient clinic 65 (18.1%) patients were treated in the ICU. 11 (16.9%) of the 65 patients treated in the ICU received respiratory support with a mechanical ventilator.	162	197
Rokohl and colleagues[31]	108 Mean age of 37.9 ± 13.7 years (range: 18–87 years).	57	51

ICU, intensive care unit; NCP, Novel Coronavirus Pneumonia; RT-PCR, reverse transcriptase-polymerase chain reaction; SD, standard deviation; x, no data.

Table 3. Characteristics of conjunctivitis patients that included in each study.

Study iD	No. of patients	Male	Female	Age (years) mean ± STD	Severity	ICU or death	Tests and comments	B or U
Guan and colleagues[14]	9/1099 Adults				5: N, 4: S		CC	
Wu and colleagues[15]	12/38 Adults	7 2 70's 2 60's 1 50's 1 40's 1 30's	5 3 80's 1 70's 1 60's		4: M, 2: S 6: CR		+NPS 11 +CS 2	
Xia and colleagues[16]	1/30 Adults	1					+Sputum RT-PCR +CS	
Karimi and colleagues[32]	1/43 Adults						+Tear RT-PCR 3	B
Sindhuja and colleagues[20]	8/127 Adults			*N*=8 41.13 ± 16.64			2/8 CC with no systemic symptoms 1/8 CC before COVID-19 symptoms. 5/8 had only CC without any associated ocular complaints	
Zhang and colleagues[19]	2/72 Adults	1	1					
Zhou and colleagues[17]	1/63 Adults		1				+NPS, –CS	
Zhou and colleagues[18]	8/121 Adults				7 S or CR 1 MD or M		1 + SAR-CoV-2 in CS	
Guemes-Villahoz and colleagues[21]	35/301 Adults				Male S1 1, S2 12 S3 8 Female S1 9, S2 3 S3 2		Acute conjunctivitis 13 before admission, 12 in the time interval between admission and evaluation 10 at the time of evaluation. 11.6% prevalence of conjunctivitis among hospitalized patients with COVID-19	54.29% U
Chen and colleagues[22,23]	33/535 Adults						Chronic conjunctivitis 30 /508 – CC 3/27 + CC *N* = 27 with CC Median age (IQR) – years 44(28–53.5) Female: 12	

(Continued)

Table 3. (Continued)

Study iD	No. of patients	Male	Female	Age (years) mean ± STD	Severity	ICU or death	Tests and comments	B or U
Lan and colleagues[24]	0/81 Adults						$N = 3$ eye discomfort, F 65 (DES) M 63 Allergic conjunctivitis F 47 (unexplained conjunctivitis, self-resolved) All three cases negative CS	
Seah and colleagues[27]	1/17 Adults						Conjunctival injection and chemosis during the stay in the hospital	
Atum and colleagues[26]	10/ 40 Adults	7	3	43.33 ± 20.79			+CS Only one tested positive using CS	
Hong and colleagues[27]	2/56 Adults	1	1	49.5 ± 4.95			9/56 showed ocular symptoms after the onset of COVID-19	U
Oruc and colleagues[28]	1/20 Adults						5% conjunctivitis and 5% diplopia developed in patients diagnosed with COVID-19	
Valente and colleagues[13]	4/27 children			115.75 (months) ± 51.05			1 +CS	
Ye and colleagues[29]	3/30 Adults	2	1	38.33 ± 26.08	3 MD to M	1 Death	Clinical symptoms: hyperemia, eye pain, foreign body sensation, stickiness, or increased watery exudation.	B
Ma and colleagues[12]	49/216 Children	35	14		M		9 had ocular complaints being the initial manifestations of COVID-19.	
Öncül and colleagues[30]	10/359 Adults	6	4	51.7 ± 11.95	3 CR 6 M 1 S		+NPS (10) The rate of ocular disease 4/65 in intensive care patients. Conjunctival chemosis developed in two (0.56%) patients in the ICU	
Rokohl and colleagues[31]	75/108 Adults				75 M		115 non-hospitalized individuals with COVID-19 were called and 109 of them responded 75/108 (69.4%) had at least one ocular symptom during COVID-19 Burning sensations in 39 (36.1%), Epiphora in 37 (34.3%), and Redness in 28 (25.9%), compatible with conjunctivitis. These symptoms occurred 1.96 ± 3.17 days after the beginning of COVID-19	

B, bilateral; CC, conjunctival congestion; CR, critical; CS, conjunctival swab; DES, dry eye syndrome; ICU, intensive care unit; M, moderate; MD, mild; N, non-severe; NPS, nasopharyngeal swab; RT-PCR, reverse transcriptase-polymerase chain reaction; S, severe; U, unilateral.

keratitis, and vitreous hemorrhages. Oruc and colleagues, recorded that 5% of COVID-19 patients had conjunctivitis and 5% had diplopia.[28] Acute conjunctivitis[21] and chronic conjunctivitis[22] were reported. Some studies reported conjunctivitis following the onset of COVID-19,[13–20,22,24–27,29,30,32] while one study reported the diagnosis of conjunctivitis as the initial manifestation of COVID-19.[12] Guemes-Villahoz and colleagues[21] reported acute conjunctivitis in 13 patients prior to hospital admission, 12 patients between hospital admission and evaluation, and 10 patients at the time of evaluation. All of the included studies were hospitalized by COVID-19, except for one study included non-hospitalized patients.[31] All patients were laboratory-confirmed SARS-COV2.

One study confirms that conjunctivitis can be a symptom of COVID-19 infection related with more serious type of disease, which confirms previous study.[36]

Furthermore, unilateral conjunctivitis in a 27-year-old COVID-19 male patient, has been reported as a first manifestation.[37] Only two patients with conjunctivitis had been reported in 72 laboratory-confirmed COVID-19 cases.[19] In addition, only one patient had conjunctivitis and foreign body sensation (2.3%) and tears in the 43 COVID-19 patients.[32] In contrast, other reports showed no ocular conjunctivitis which could be due to the very low sample size.[38]

The prevalence rate of acute conjunctivitis in COVID-19 was reported ranging from 1.1 to 15.9.[15,39] Other studies reported acute conjunctivitis in 31.6% of patients.[23,39,40]

One meta-analysis study showed that the probability of conjunctivitis in patients with non-severe COVID-19 was 4 out of 173, and severe COVID-19 was 5 of 926.[40] Wu et al.[15] showed that only one patient had the first symptoms of conjunctivitis.

There is certainly a difference in the percentage of conjunctivitis in COVID-19 patients that contributes to the aim of this meta-analysis. In our study, we found that 1% of COVID-19 patients are likely to have conjunctivitis with a total of 3383 COVID-patients.[12–22,24–32]

A related point to consider is that these findings have been reviewed retrospectively, and second, clinical symptoms have not been confirmed by clinical tests, but only have been subjectively reported by patients. In addition, because conjunctival mucosa can be a point of entry of COVID-19 infection due to overexpression of ACE2 receptors in epithelium from congested conjunctiva,[41] careful attention should also be given to protective measures such as the face shields and goggles.

This meta-analysis is consistent with the meta-analysis that showed that the incidence of ocular manifestations in COVID-19 patients ranged from 2% to 32%.[42] This meta-analysis review studied ORs of conjunctivitis and showed that the ORs ranged from 0.00 to 0.02.

The limitation of this study is (1) pediatric COVID-patients studies are needed, only 2 of the 20 studies in which the pediatric study was conducted, (2) only one reviewer performed the meta-analysis which may lead to bias, and (3) a greater sample size is needed.

Conclusion

Viral conjunctivitis is the most common ocular manifestations reported in adults. This comprehensive meta-analysis quantifies the existing evidence linking conjunctivitis with COVID-19 and highlights the high percentage of heterogeneity that is shown in the current studies. Viral conjunctivitis has been reported in males more than females. Finally, it offers a single review article which includes all the current articles available for COVID-19 and conjunctivitis.

Author contributions

Conceived and designed the literature review: M.A. performed the article assessment, analyzed the data and wrote the paper.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

This study was a review, and no ethical approval is required.

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Supplemental material

Supplemental material for this article is available online.

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