COVID-19 and conjunctivitis: a meta-analysis

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Abstract

COVID-19 is a disease first identified in Wuhan City, Hubei Province, China, in December 2019, caused 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
**Methods**

**Trials identification and data consideration**

The standards and guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) have 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.)
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
was low in 6 studies. Allocation concealment was low in five studies. Allocation concealment was low in five studies. The blinding participants and personnel (PB) is low in 10 articles. The blinding participants and personnel (PB) is low in 10 articles. The blinding of outcome assessment (DB) is low in 12 articles. The blinding of outcome assessment (DB) is low in 12 articles. The incomplete outcome data (Attrition Bias) (AB) is low in 19 articles. The incomplete outcome data (Attrition Bias) (AB) is low in 19 articles. Selective reporting (Reporting bias (RB) is 16 articles. Selective reporting (Reporting bias (RB) is 16 articles. All other bias is low in all 20 articles (Supplemental Table 1).

Overall final analyses. The systematic review of the selected 20 articles estimated the ORs of conjunctivitis of a total of 3383 COVID-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. 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 (Table 2).

The majority of patients with viral conjunctivitis were male patients (Table 3). Other ocular manifestations have been documented, such as conjunctival hyperemia and secretion, conjunctival discharge, eye rubbing, subconjunctival bleeding,
Table 2. Characteristics of COVID-19 patients that included in each study.

| 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               | 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.
| 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    | 5      | 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\(^{12}\) | 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      |                        |          |              | + NPS, −CS         |        |
| Zhou and colleagues\(^{17}\)  | 1/63 Adults     |      |        |                        |          |              |                    |        |
| 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, 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 | | | | |
| Study ID                  | No. of patients | Male | Female | Age (years) mean ± STD | Severity | ICU or death | Tests and comments | B or U |
|--------------------------|----------------|------|--------|------------------------|----------|--------------|--------------------|--------|
| Lan and colleagues⁵⁴     | 0/81 Adults    |      |        |                        |          |              |                    |        |
| Seah and colleagues²⁷    | 1/17 Adults    |      |        |                        |          |              |                    |        |
| Atum and colleagues⁵⁶    | 10/ 40 Adults  | 7    | 3      | 43.33 ± 20.79          |          |              |                    |        |
| Hong and colleagues²⁷    | 2/56 Adults    | 1    | 1      | 49.5 ± 4.95            |          |              |                    |        |
| Oruc and colleagues²⁸    | 1/20 Adults    |      |        |                        |          |              |                    |        |
| Valente and colleagues¹³ | 4/27 children  |      |        | 115.75 (months) ± 51.05|          |              |                    |        |
| Ye and colleagues²⁹      | 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 colleagues¹²      | 49/216 Children| 35   | 14     | M                      |          |              | 9 had ocular complaints being the initial manifestations of COVID-19. |        |
| Öncül and colleagues³⁰   | 10/359 Adults  | 6    | 4      | 51.7 ± 11.95           | 3 CR     | 6 M          | 1 S                |        |
| Rokohl and colleagues²¹  | 75/108 Adults  |      |        |                        |          |              | 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. |        |

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 conjunctivitis21 and chronic conjunctivitis22 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 colleagues21 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.

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