Review Article

Exploring the Ocular Transmission Potential of Severe Acute Respiratory Syndrome Coronavirus 2 and the Assessment of Conjunctival Swab Test Results: A Concise Review

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Abstract

Purpose: To evaluate the possibility of coronavirus disease 2019 (COVID-19) transmission through the eyes, particularly through the ocular surface and conjunctival route, as well as the positivity of conjunctival swab test.

Methods: A narrative review was conducted to assess the possibility of COVID-19 transmission and the role of conjunctival swabs in diagnosing COVID-19 patients. Several studies were analyzed to compare the positivity rates and sensitivities of conjunctival swabs versus nasopharyngeal swabs.

Results: Despite the fact that respiratory droplets are the major route of severe acute respiratory syndrome coronavirus 2 transmission, the eyes can potentially serve as an active (via tears) or passive route (via the nasolacrimal duct) of infection. Besides, conjunctival swabs exhibited a low positive rate and sensitivity for detecting COVID-19 compared to nasopharyngeal swabs. While nasopharyngeal swabs typically showed positivity rates between 60% and 100%, conjunctival swabs ranged from showing no detectable evidence to a 57% positivity rate.

Conclusions: Despite the low transmission rate through the eyes, thorough consideration is necessary as ocular transmission cannot be entirely ruled out. Further research and vigilance are warranted to better understand and mitigate potential ocular routes of COVID-19 transmission.

Keywords: Conjunctivitis, Coronavirus, Eye, Ocular surface, Tears

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Submitted: 29-Jan-2024; **Revised:** 26-Feb-2024; **Accepted:** 10-Mar-2024; **Published:** 18-Jan-2025

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) was presented in December 2019 in Wuhan, China, where ophthalmologists reported the first.[1] It is a highly contagious infection with significant mortality and economic morbidity implications.[2] Although the infection primarily manifests as fever, headache, cough, shortness of breath, diarrhea, anosmia, and malaise, and numerous clinical studies of this virus have focused on its common respiratory manifestations, there is growing concern regarding ocular complications.[3] The virus can lead to ocular manifestations such as conjunctivitis, keratitis, uveitis, retinal pathologies, and neuro-ophthalmologic involvement.[4-7] These clinical manifestations often occur in patients with more severe disease who require mechanical ventilation.[8]

It has been speculated that there are potentially four routes for ocular transmission, including direct exposure to

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joco

DOI: 10.4103/joco.joco_35_24

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How to cite this article: Mirzaei A, Djalilian A, Baharnoori SM, Bohrani Sefidan B, Shahriari M, Cheraqpour K, *et al*. Exploring the ocular transmission potential of severe acute respiratory syndrome coronavirus 2 and the assessment of conjunctival swab test results: A concise review. J Curr Ophthalmol 2024;36:122-8.

virus-containing infectious droplets, contaminated hands, dense vascularity due to the spread of viremia to the lacrimal gland and ocular tissues, and spread from the upper respiratory tract to the lacrimal sac.[9]

Viral diagnosis plays a critical role in the control of communicable diseases such as COVID-19.[10] The real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay is the current reference standard for the diagnosis of COVID-19.[11] In addition to biological samples from the respiratory tract, researchers have also presented feces,[12] saliva, urine,[13] and semen[14] as likely samples for COVID-19. While transmission through the eyes is reportedly less common than through the nose or mouth, it should still be considered, despite the controversy surrounding the presence of this virus in tears.

There are several methods for detecting viruses on the ocular surface, and the most commonly used method for detecting COVID-19 is conjunctival swabbing by PCR or RT-PCR. These samples are obtained from tears, cells, and fluids that spread in the conjunctival sac.[15] Tears play an important role in innate defense against microorganisms.[16] They contain antibodies that help the body identify and bind harmful antigens such as bacteria and viruses.[17] Xia *et al*. found that among 30 patients with positive COVID-19, only one patient with conjunctivitis had COVID-19 in the tear film, using RT-PCR testing.[18] However, Seah *et al*. indicated a low risk of ocular transmission because viral culture and reverse transcription were unable to detect viral particles in their samples.[19]

Due to the novelty of COVID-19, comprehensive investigation across all aspects of this virus is imperative, including the exploration of potential modes of transmission. The controversy surrounding the role of the ocular surface as a transmission route[20] and the uncertainty among clinicians regarding the eyes' potential as an entry point for the novel virus into human ocular tissues[21] emphasizes the need for a closer look. With this in mind, our aim was to evaluate studies addressing the plausibility of ocular transmission of COVID-19, as well as studies examining the positivity of conjunctival swab tests.

Methods

This is a narrative review of articles evaluating the positivity of conjunctival PCR in patients with COVID-19. A thorough search of the literature was performed to identify quantitative studies. This review incorporated articles indexed under this topic in ISI Web of Science, PubMed, and Google Scholar. We rigorously and critically evaluated relevant and accessible articles published from December 2019 to July 2023. The keywords used for the search included "COVID-19", "conjunctivitis", "conjunctiva", "polymerase chain reaction", "PCR", "viruses", "ocular transmission", "ocular surface", "tears", "tear film", and "coronavirus". We included original/research articles published in the abovementioned indexing databases and we excluded narrative and systematic reviews as well as short communications.

Results

Ocular transmission of coronavirus disease 2019

Respiratory droplets are the major route of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission, with droplets from a patient being transmitted to a healthy person.[22] However, there is also consideration that the virus can spread indirectly through mucosal membranes, such as the eyes.[23] The eyes can potentially serve as an active route of infection (via tears) or passive route (via the nasolacrimal duct).[24-26]

To date, numerous studies have examined the association between SARS-CoV-2 infection and its ocular manifestations; however, the topic remains controversial.[27-29] The presence of the COVID-19 virus on the ocular surface and in tears has been noted in patients with and without ocular manifestations.[27-31] Studies have estimated that the percentage of results in ocular secretions ranges from 0% to 57%,[32-36] and the virus demonstrates high transmissibility in patients with moderate-to-severe infections.[37] Consequently, there is concern that staff in ophthalmology wards could be at risk during ophthalmologic examinations due to possible exposure.[38]

As laboratory findings in previous investigations showed the rarity of conjunctival infection by COVID-19,[39] these findings not only imply the conjunctiva as an unfavorable tissue for this virus but also not a suitable entry pathway for the virus to infect the respiratory tract.[40] Conversely, there exists an anatomical connection in the nasolacrimal system that establishes a link between the ocular surface and the upper respiratory tract. When a drop enters the eye, regardless of whether it is absorbed by the cornea and conjunctiva, it primarily exits through the nasolacrimal duct, emptying into the nasal cavity. Thus, it gains access to the upper respiratory tract or gastrointestinal tract.[27] Furthermore, COVID-19 can be detected in tears, allowing the virus to traverse from the eyes to the nasopharynx through the open nasolacrimal duct without the need for angiotensin-converting enzyme 2 (ACE-2) receptors in the cornea and conjunctiva.[41]

Notably, the tear film acts as a natural protective barrier against pathogens due to its antimicrobial proteins (e.g., lactoferrin, lysozyme, lipocalin, and beta-lysine) and immunoglobulins.[42] Although Colavita *et al*. were among the first authors to report ocular involvement of SARS-CoV-2 in a 65-year-old woman with a protracted infection, they described this as an unusual occurrence, linking it to the higher prevalence of dry eye in Chinese women over 60 years of age.[43]

Conjunctivitis or keratoconjunctivitis may serve as an early indicator of COVID-19 before the onset of respiratory symptoms[44,45] or the sole manifestation of infection.[46] This suggests that the ocular surface could potentially act as both a gateway and a source of infection. However, in contrast, the risk of isolated conjunctival viral activity in patients with negative nasopharyngeal swab RT-PCR is absent or extremely low, suggesting that additional conjunctival swabs are unnecessary for patients with negative nasopharyngeal

swabs.[47,48] Therefore, studies support the notion that the presence of conjunctivitis is a systemic response rather than local activity of COVID-19 on the ocular surface.[32,49,50]

Ozturker reported a patient with conjunctivitis as the sole symptom of COVID-19 in a medical emergency department. The patient exhibited no typical clinical symptoms and was initially referred to the eye clinic due to redness, burning, tearing, and photophobia. Despite negative results from conjunctival swabs, both nasopharyngeal swabs and blood tests confirmed the diagnosis of COVID-19, highlighting the importance of considering COVID-19 in cases where conjunctivitis is the only manifestation of the virus, regardless of the ultimate outcome.[2]

Polymerase chain reaction analysis of tear film from ocular surface in patients with coronavirus disease 2019

Despite the low transmission rate of COVID-19, conjunctival swab testing using PCR or RT-PCR remains the most commonly used method for pathogen detection.[15] Notably, studies examining conjunctival PCR positivity in patients have yielded varied results. While certain previous studies reported very low positivity rates, others presented significantly higher outcomes, which necessitates careful consideration [Table 1].

Studies conducted by Ranzenigo *et al*.,[5] Granstam *et al*.,[33] and Sonmez *et al*.[32] showed that none of the patients with ocular symptoms yielded positive results in conjunctival smears. Similarly, Deng *et al*. reported the absence of detectable SARS-CoV-2 through PCR testing of conjunctival swabs in a cohort of 114 patients with clinically confirmed COVID-19 pneumonia.[51] However, one of the first studies published in 2020 showed that only one patient (2.23%) among 45 patients exhibited positive results.[27] In addition, Dora *et al*. investigated 113 patients with COVID-19, finding that only three patients (2.65%) showed positive conjunctival smears.[52]

Table 1: Studies evaluating conjunctival polymerase chain reaction in patients with coronavirus disease 2019

Study reference	Study design	Sample size	Time of sampling	Samplings' interval	Positive conjunctival swabs	Positive nasopharyngeal swab
Ranzenigo *et al*.[5]	Cross-sectional	53 patients	Within 3 days	At the same time	0%	86.7%
Karabela *et al*.[6]	Cross-sectional	83 patients	Within 3 days	At the same time (within 3 h)	First swab: 6.02% of clinically-confirmed and 15.15% of laboratory-confirmed patients. Second swab: 0%	First swab: 37.35% Second swab: 22.89%
Kumar *et al*.[27]	Prospective interventional	45 patients	N/A	N/A	2.23%	100%
Wu *et al*.[31]	Case series	38 patients	N/A	N/A	73.7%	5.2%
Sonmez *et al*.[32]	Cross-sectional	40 patients	N/A	Within 24 h	2.5%	100%
Granstam *et al*.[33]	Cross-sectional	68 patients and 70 staff	N/A	N/A	0%	Just one patient
Kaushik *et al*.[34]	prospective interventional	30 patients	N/A	At the same time	6.7%	100%
Karakus *et al*.[35]	Cross-sectional	25 patients	N/A	Within 24 h	36%	N/A
Azzolini *et al*.[36]	Cross-sectional	91 patients	N/A	Within 2 days	57.1%	63.7%
Ozturk *et al*.[49]	Cross-sectional	70 patients	Nasopharynx swabs: Within the last 24 h in outpatient clinic conjunctival swabs: Immediately after hospitalization	N/A	11.42%	68.57%
Hadrawi *et al*.[50]	Cross-sectional	171 patients	N/A	N/A	4.9%	100%
Deng *et al*.[51]	Cross-sectional	114 patients	N/A	At the same time	0%	79%
Dora *et al*.[52]	Cross-sectional	113 samples	N/A	N/A	2.65%	63.8%
Ernawati *et al*.[53]	Cross-sectional	47 patients	N/A	Within 1-4 days	4.3%	N/A
Susiyanti *et al*.[54]	Cross-sectional	42 patients	N/A	At the same time	4.76%	100%
Gijs *et al*.[55]	Cross-sectional	243 symptomatic laboratory-confirmed COVID-19 patients	N/A	N/A	7.0%	N/A
Misawa *et al*.[56]	Cross-sectional	50 patients	N/A	Within 24 h	10%	68%
Islam *et al*.[57]	Case report	1 patient	N/A	At the same time	100%	100%
Furdova *et al*.[58]	Cross-sectional	484 patients	N/A	Within 24 h	12%	N/A
Sabage *et al*.[59]	Cross-sectional	61 patients	N/A	N/A	18.2%	54.1%

COVID-19: Coronavirus disease 2019, N/A: Not available

Ernawati *et al*. conducted tests on 47 patients diagnosed with COVID-19 using nasopharyngeal and conjunctival swabs through RT-PCR. Their results showed that 95.7% of patients yielded negative results in conjunctival swab PCR, demonstrating a low sensitivity for detecting this virus. In addition, no significant correlation was observed between COVID-19 severity and conjunctival swab results ($P = 0.589$). Notably, only two patients (4.3%) exhibiting ocular signs and symptoms tested positive on PCR ($P > 0.05$).[53] This aligns with the observations of Wu *et al*. who identified positive conjunctival swabs in 2 out of 38 COVID-19 cases (5.26%). The authors suggested that the low positivity rate in conjunctival swabs could be attributed to the sampling from just one eye of the patients.[31]

Notably, Hadrawi *et al*. examined patients who tested positive for COVID-19 through PCR from nasopharyngeal swabs and subsequently collected conjunctival swabs for RT-PCR testing. The study revealed that 4.9% of patients yielded positive results for COVID-19 through conjunctival swabs, with a sensitivity of 4.8%. Despite the limited positive rate and sensitivity, tears have been suggested as a potential route of disease transmission.[50]

In a recent study involving 53 patients with COVID-19, 46 (86.79%) tested positive using either a rapid antibody test or naso-oropharyngeal swab. Among 42 patients with positive naso-oropharyngeal swab results, 14 (33.33%) exhibited symptoms of eye infection, including redness, epiphora, itching, and discharge. The study also identified two positive conjunctival swabs (4.76%) among patients with positive naso-oropharyngeal swabs, despite these patients not presenting any ocular symptoms. The conclusion of the study was that the presence of ocular symptoms in patients with COVID-19 did not necessarily correlate with a positive conjunctival swab result. In contrast, the study suggested that the SARS-CoV-2 virus might be present on the ocular surface in patients even in patients without ocular symptoms.[54]

Kaushik *et al*. showed that two out of 30 patients (6.7%) had a positive result in RT-PCR conjunctival swab. They argued that despite the lower positivity rate in conjunctival swabs compared to nasopharyngeal and pharyngeal swabs, meticulous care should be given to ophthalmological examinations.[34] In addition, Gijs *et al*., examining 243 symptomatic and laboratory-confirmed COVID-19 patients, showed that only 17 patients (7.0%) had positive results in conjunctival swabs.[55] In a separate study, Végh *et al*. reported 8 positive conjunctival swabs (8.25%) among 97 patients.[60]

Misawa *et al*. also conducted a comparison of 50 conjunctival swab specimens collected within 24 h of naso/oropharyngeal swabs in patients with severe/critical illness. Their findings showed that, despite 34 (68%) positive naso/oropharyngeal swabs RT-PCR results, only five (10%) positive conjunctival swabs were detected and none of the patients exhibited ocular symptoms. The authors concluded that there might be a higher viral presence in the tears of severe cases, irrespective of the presence of conjunctivitis.[56] Furthermore, a case report documented the first patient in Bangladesh with a positive conjunctival swab.[57]

Despite the previously mentioned studies indicating low positivity rates for conjunctival swabs, the following studies yielded slightly higher values. In a recent study conducted by Ozturk *et al*., which examined 70 patients, eight patients with either no symptoms or conjunctivitis (11.42%) exhibited positive conjunctival samples.[49] Similar outcomes were reported in an earlier and more extensive study involving 484 patients. In this study, 58 patients (12%) recorded positive results in conjunctival swab PCR tests.[58] In addition, Sabage *et al*. found that SARS-CoV-2 RNA was detected in conjunctival swabs from 6 out of 47 patients (18.2%). They also found that the Schimer strip only detected four patients (12.1%).[59]

Furthermore, Karabela *et al*. observed a higher positivity of SARS-CoV-2 (15.15%) in the tear and conjunctival secretions of patients with laboratory-confirmed COVID-19 pneumonia. Despite this higher rate, it was found that the positivity (6.02%) in tear and conjunctival secretions from patients with clinically confirmed COVID-19 pneumonia was comparable to, or slightly higher than, rates reported in previous studies. The authors noted that these results might be attributed to the potentially higher viral load in nasopharyngeal secretions compared to ocular secretions, as well as to the possibility of virus clearance in ocular secretions over an extended period.[6]

In contrast, Karakus *et al*. reported that 9 out of 25 patients (36%) exhibited positive results on the day of their study visit to a tertiary center. They hypothesized that the timing of the smear test plays an important role in the confirmation rate of adenoviral conjunctivitis. They suggested that by the time the swabs were taken, the patients were likely at a more advanced stage of viral conjunctivitis, leading to potentially negative results in the swabs. Notably, some patients had not used preservative topical anesthetic drops before sample collection, while others had used topical eye drops in the days leading up to the study; the actual effects of these eye drops remained unclear.[35] Interestingly, Azzolini *et al*. reported the highest positivity rate for conjunctival swabs (57.1%, 52 out of 91 hospitalized patients with COVID-19). However, as in other studies, they observed lower conjunctival positivity tests in comparison to nasopharyngeal swabs.[36]

Discussion

Regarding the unknown aspects of the emerging virus, we comprehensively reviewed the recent investigations on the ocular transmission potential of SARS-CoV-2 and the positivity of conjunctival swab test. To date, limited research has addressed the controversy surrounding whether the ocular surface can transmit viral infections.[24-26] It is assumed that the virus enters host cells through ACE-2 receptors found in various body organs. Since the eye has an intraocular renin–angiotensin system, these receptors can be identified

on the ocular surface, trabecular meshwork, aqueous humor, iris, ciliary body, and retina.[39,61] Similar to other body organs, the presence of ACE-2 and TMPRSS2 (Transmembrane Protease, Serine 2) is important for cellular entry into the ocular surface. ACE-2 has been primarily detected in ocular surface epithelial cells.[39] However, it has been shown that ACE-2 expression is comparatively lower in conjunctival and corneal cells, which are potential points of entry for the virus[49,62,63] than in liver and kidney cells.[39] Consequently, clinical and laboratory findings suggest that conjunctival infection by COVID-19 is rare.[39]

According to our unpublished data of 50 COVID-19 patients in a referral center, we found no positive conjunctival swabs in the tears, conjunctival secretion as well as conjunctival cells. This is consistent with the previous study by Sugita *et al*. who used conjunctival swabs to collect not only tears but also conjunctival secretions and conjunctival cells and found two positive RT-PCR results.[64] Thus, the low positive rates for conjunctival PCR testing observed in several of the aforementioned studies can be attributed to a variety of factors, including small sample size, initiation of systemic antiviral therapy before testing, or the timing of sample collection.[28] Indeed, the timing of sample collection plays a significant role due to the limited duration of the existence of the virus's presence and its genetic material in ocular fluids. In addition, we must take into account the lower sensitivity of the RT-PCR tests and the potential impact of the small quantity of tears and conjunctival secretions collected.[9] While the positivity of nasopharyngeal swabs is mostly between 60% and 100%, the positivity rate of conjunctival swabs varies between 0% and 57%. This means that the positivity of nasopharyngeal swabs is much higher even in patients with negative conjunctival swabs, which underlines the different sensitivity depending on the site of sampling. Furthermore, Sabage *et al*. reported lower sensitivity of Schirmer's strip versus conjunctival swabs.[59] We also advise taking conjunctival swab samples without the use of analgesic drops or Schirmer's strip.

Further, evidence regarding the necessary amount of viral load or receptor expression for causing infection remains absent. However, the eye is generally not regarded as a high-risk tissue because of low expression of ACE-2 and TMPRSS2.[65] It is notable that we have collected articles from the onset of the pandemic through its conclusion, as confirmed by the CDC's announcement on May 11, 2023.[66] This collection positions us to curate a comprehensive review, offering a complete perspective on the situation. Collectively, given these considerations, healthcare providers are advised to use protective eyewear, face shields, and other safety equipment, regardless of whether patients' clinical, ocular manifestations or laboratory results are available.

Drawing from the findings of numerous studies that have evaluated the role of conjunctival swabs in diagnosing patients with COVID-19, it becomes evident that this method holds a low positivity and sensitivity for detecting the virus. While COVID-19 itself presents a low ocular transmission rate by tear film, these results should not entirely dismiss the potential for this transmission. Thus, a comprehensive consideration of this aspect remains essential.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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