

# Evidence of SARS-CoV-2 Transmission Through the Ocular Route

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**Purpose:** Currently, the coronavirus disease 2019 (COVID-19) pandemic is raging around the world. However, the transmission of its pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is not fully clear. It is still controversial whether the ocular transmission of SARS-CoV-2 exists. This review aimed to summarize the evidence of SARS-CoV-2 ocular transmission.

**Methods:** Online articles were searched till October 23, 2020 in Pubmed, Embase, and websites of World Health Organization, Centers for Disease Control and Prevention COVID-19, American Academy of Ophthalmology, and American Society of Cataract and Refractive Surgery under the search strategy of (((("COVID-19"[Mesh]) OR ("SARS-CoV-2"[Mesh])) OR (2019 novel coronavirus)) OR (2019-nCoV)) AND (((("Conjunctivitis"[Mesh]) OR (Ocular Surface)) OR ("Eye"[Mesh])) OR ("Ophthalmology"[Mesh])). The language was not restricted. After screening, 1445 records were excluded and 168 references original articles were finally included.

**Results:** Cells of ocular surface express both the receptor of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), offering molecular bases for the ocular susceptibility to SARS-CoV-2. Accumulated COVID-19 patients presented conjunctivitis as the initial or the only symptom. Whether COVID-19 patients had ocular symptoms or not, SARS-CoV-2 was detectable on the ocular surface, and the isolated virus was infectious, proving that the ocular surface can not only be a reservoir but also a source of contagion. SARS-CoV-2 may reach the ocular surface by hand-eye contact and aerosols. Once SARS-CoV-2 reaches the ocular surface, it may transfer to other systems through the nasolacrimal system or hematogenous metastasis.

**Conclusion:** The ocular surface can serve as a reservoir and source of contagion for SARS-CoV-2. SARS-CoV-2 can be transmitted to the ocular surface through hand-eye contact and aerosols, and then transfer to other systems through nasolacrimal route and hematogenous metastasis. The possibility of ocular transmission of SARS-CoV-2 cannot be ignored.

**Keywords:** COVID-19, SARS-CoV-2, ocular transmission, conjunctivitis, ACE2, TMPRSS2

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## Introduction

In early December 2019, an unidentified pneumonia broke out in a seafood market in Wuhan, China. Subsequently, the disease was officially named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) on February 12, 2020.<sup>1</sup> Then, a new pathogen was isolated, and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV).<sup>2</sup> The number of infections increased sharply, and soon, on March 11, 2020, WHO announced that COVID-19 was characterized as a pandemic.<sup>3</sup>

A preponderance of evidence suggests natural hosts of the virus are bats.<sup>4-6</sup> The population of all ages is generally susceptible.<sup>7</sup> The current main transmission routes are respiratory droplets and close contact.<sup>8</sup> Indirect contact with the surface of contaminated objects may also cause infection, and such infected cases after contact with contaminated packaging of cold chain food have been reported in China.<sup>9</sup> COVID-19 has a wide range of symptoms, including fever, dry cough, fatigue, and shortness of breath, and asymptomatic infections are increasing, but severe cases can experience acute respiratory distress syndrome (ARDS) and may die.<sup>10</sup> The most common drug therapies are antiviral drugs, corticosteroid, and hydroxychloroquine, but all these drugs seem to have little effects.<sup>11</sup>

As there are no specific drugs for COVID-19, the pandemic is still spreading. As of January 8, 2021, there are more than 85,929 thousand confirmed cases and 1876 thousand confirmed deaths. More than 400,000 new cases occur every day worldwide.<sup>12</sup> Pfizer-BioNTech and Moderna COVID-19 vaccine developed in the US have been authorized for emergency use, and China has approved Sinopharm China National BiotecGroup's COVID-19 vaccine for marketing.<sup>13,14</sup> However, most people have not been vaccinated yet, and the safety and effectiveness of the vaccines still need time to prove. In order to effectively cut off the spread of the pandemic, we need to make it clear how it spreads. Although the main transmission routes are respiratory droplets and close contact, due to the rapid and broad spread of the virus, the other possible transmission routes cannot be ignored.

On January 22, 2020, after an investigation in Wuhan, Guangfa Wang, a member of the pneumonia expert panel of China National Health Commission, was diagnosed with COVID-19 several days after the onset of red eyes. He speculated that he might infect with SARS-CoV-2 through conjunctiva without wearing goggles.<sup>15</sup> Immediately, the possibility of SARS-CoV-2 spreading through the route of ocular surface brought to global attention. With the development of the epidemic, numerous COVID-19 patients have begun to be reported conjunctivitis as the first symptoms or accompanying symptoms.<sup>16,17</sup> However, it is controversial whether SARS-CoV-2 can spread via the eye.<sup>18,19</sup> In the current severe epidemic situation, more evidence is urgently needed to better assess the possibility of ocular transmission and the need for protective measures.

This review summarized the evidence of SARS-CoV-2 transmission via the ocular route, aiming to draw attention to the necessity of eye protection and to help reduce further COVID-19 pandemic spread.

## Methods

An extensive search of literature was performed till October 23, 2020 in Pubmed and Embase under the following search strategy: (((("COVID-19"[Mesh]) OR ("SARS-CoV-2"[Mesh]) OR (2019 novel coronavirus)) OR (2019-nCoV)) AND (((("Conjunctivitis"[Mesh]) OR (Ocular Surface)) OR ("Eye"[Mesh]) OR ("Ophthalmology"[Mesh])). An electronic search was also conducted on websites of WHO (<https://www.who.int/>), Centers for Disease Control and Prevention COVID-19 (<https://www.cdc.gov/coronavirus/2019-ncov/>), American Academy of Ophthalmology (<https://www.aao.org/>), and American Society of Cataract and Refractive Surgery (<https://ascrs.org/>). The language was not restricted to reduce bias. The literature search and screening were conducted by two authors (J.-Y.Q. and H.-T.X.) independently. References were managed using EndNote X8 software.

In the above 6 databases, a total of 1613 records were identified. One hundred and eighty-one duplicate records were removed. The remained 1432 records were screened according to the following exclusion criteria: 1. Reviews, systematic reviews, and meta-analysis. 2. Records about medical education and clinical practice. 3. Studies about mental or psychological health. 4. Studies about SARS-CoV and Middle East respiratory syndrome (MERS). 5. Other irrelevant records. Only original articles were included. Finally, after screening titles, abstracts, and full texts, 168 references including case reports, case series, clinical studies, laboratory studies, and epidemiological surveys were included. All authors jointly participated in the following data analysis.

## Results

### The Expression of Cellular Receptors for SARS-CoV-2 in Ocular Tissues

The SARS-CoV-2 is an enveloped, pleomorphic, single-stranded RNA virus. One of the structural proteins of SARS-CoV-2 is the spike (S) protein.<sup>20</sup> Resembling SARS-CoV, SARS-CoV-2 enters into host cells depending on the binding of S protein to the receptor angiotensin-converting enzyme 2 (ACE2) on the host cell membrane. S protein priming is facilitated by the cellular

transmembrane serine protease 2 (TMPRSS2).<sup>21</sup> ACE2 and TMPRSS2 have been detected to be widely expressed throughout the human body with the highest expression of ACE2 presented in nasal secretory cells.<sup>22</sup> Several studies demonstrated the expression of ACE2 and TMPRSS2 in the eyes. Immunohistochemical analysis revealed the expression of ACE2 and TMPRSS2 in conjunctiva, limbus, and cornea.<sup>23,24</sup> Especially, the expression appeared to be higher in diseased conjunctival tissue.<sup>25</sup> Aqueous humor and retina were also identified as expressing ACE2.<sup>26,27</sup> Besides, porcine studies demonstrated that ACE2 was expressed in the ciliary body and vitreous.<sup>28</sup>

The expressions of ACE2 and TMPRSS2 on the ocular surface offer molecular bases for the ocular susceptibility to SARS-CoV-2. Therefore, the ocular surface is possible to serve as a portal of direct entry for SARS-CoV-2.

## Accumulated Clinical Cases Were Reported Ocular Symptoms as the Initial or the Only Symptoms of COVID-19

A clinical study containing 172 COVID-19 patients showed that the most common ocular symptom of COVID-19 is conjunctivitis (23.3%), which manifested as conjunctival hyperemia, watery secretions, foreign body sensation, and itching.<sup>29</sup> Rare ocular symptoms including episcleritis, panuveitis, optic neuritis, retinal vascular diseases, cranial neuropathies, Miller Fisher syndrome, and Adie's syndrome have also been reported.<sup>30–34</sup>

If SARS-CoV-2 can transmit through the ocular transmission route, the initial symptoms should be ocular. Li et al and Zhang et al reported two cases of medical workers who developed conjunctivitis as the first symptom due to negligence in eye protection during clinical work, and subsequently was confirmed as COVID-19.<sup>35,36</sup> Similar COVID-19 cases with conjunctivitis as the initial symptom were also reported in Italy, the US, Malaysia, France, and Canada.<sup>16,17,37–39</sup>

In some cases of COVID-19, conjunctivitis was the only clinical manifestation. On the Diamond Princess ship, a 72-year-old patient presented no symptoms except severe viral conjunctivitis characterized by transparent serous secretions, conjunctival hyperemia, conjunctival chemosis, and pseudo-membranes on the tarsal conjunctiva accompanied by preauricular submaxillary lymph nodes enlarged.<sup>40</sup> Scalinci et al reported five COVID-19 cases with conjunctivitis as the only symptom throughout the entire illness.<sup>41</sup> Ying et al and Wu et al also reported cases confirmed COVID-19 with conjunctivitis as the sole presenting symptom.<sup>37,42</sup>

All these studies proved that SARS-CoV-2 conjunctivitis could be the initial symptom or the only symptom of COVID-19, supporting that the ocular transmission is possible with conjunctival mucosae as an entry point of SARS-CoV-2 under insufficient eye protection.

## SARS-CoV-2 Was Detected Through Conjunctival Swabs and Tears

Real-time reverse transcriptase polymerase chain reaction (RT-PCR) can detect viral nucleic acid to diagnose current infection, so it is widely used to diagnose COVID-19.<sup>43</sup> SARS-CoV-2 has been detected on the ocular surface by several clinical studies through RT-PCR. Table 1 summarizes these studies by the number of patients diagnosed with COVID-19, number of patients with ocular symptoms, number of patients with positive results in conjunctival secretions or tears (with ocular symptoms/without ocular symptoms), total ocular positive rate, and conjunctival secretions or tears sampling time.

COVID-19 with ocular manifestations ranges from 0% to 35.71% in different studies. Both in COVID-19 patients with and without ocular manifestations, SARS-CoV-2 nucleic acid was detected in conjunctival secretions or tears. The total ocular surface positive rate among COVID-19 patients was 0% to 28.57%. Positive rate ranges from 0% to 100% in patients with ocular symptoms, and 0% to 27.78% in those without ocular symptoms. The immense differences between studies may be caused by different districts, COVID-19 severities, sampling times, sampling methods, and sample sizes. All in all, the fact SARS-CoV-2 can reside on the ocular surface was proved.

Then here comes the question, whether SARS-CoV-2 detected in conjunctival secretions and tears is an infectious virus? Colavita et al inoculated Vero E6 cells with the first RNA positive ocular sample obtained from a COVID-19 patient. Cytopathic effect was observed 5 days post-inoculation, and viral replication was confirmed by real-time RT-PCR in spent cell medium.<sup>44</sup> Hui et al also isolated SARS-CoV-2 virus from a nasopharyngeal aspirate specimen and a throat swab of a COVID-19 patient. The isolated virus not only infected human conjunctival explants but also infected more extensively and reached higher infectious viral titers than SARS-CoV.<sup>45</sup> The above laboratory studies demonstrated that the virus in conjunctival swabs was infectious, and SARS-CoV-2 had stronger infectivity to ocular mucosa than SARS-CoV.

**Table 1** Clinical Studies of SARS-CoV-2 Detected on Ocular Surface

No.	Reference Detail	Patients, n	With Ocular Symptoms	Positive in Conjunctival Secretions or Tears		Total Ocular Positive Rate	Conjunctival Secretions or Tears Sampling Time
				With Ocular Symptoms	Without Ocular Symptoms		
1	Arora et al <sup>74</sup>	78	0(0.00%)	0	18(23.08%)	23.08%	Within 48 hours after laboratory confirmation of COVID-19
2	Atum et al <sup>75</sup>	40	10(25.00%)	1(10.00%)	2(6.67%)	7.50%	Within 3 days after admission
3	Deng et al <sup>76</sup>	90	NA	0	0	0.00%	NA
4	Güemes-Villahoz et al <sup>77</sup>	36 <sup>a</sup>	18	1(5.56%)	1(5.56%)	5.56%	Within 24 hours after suspected conjunctivitis
5	Karimi et al <sup>78</sup>	43	2(4.65%)	1(50.00%)	2(4.88%)	6.98%	On the first day of hospitalization
6	Kaya et al <sup>79</sup>	32	0(0.00%)	0	5(15.60%)	15.60%	6.84 ± 6.81 days (1–35 days) after onset
7	Kumar et al <sup>80</sup>	45	0(0.00%)	0	1(2.22%)	2.22%	Within 2–5 days after onset of 32/45 patients, and NA of 13/45 patients
8	Li et al <sup>81</sup>	92	5(5.43%)	1(20.00%)	4(4.60%)	5.43%	NA
9	Li et al <sup>82</sup>	49 <sup>b</sup>	0	0	4(8.16%)	8.16%	Within 2–27 days of onset or first positive nasopharyngeal specimen
10	Liang et al <sup>83</sup>	37	3(8.10%)	0(0.00%)	1(2.94%)	2.70%	NA
11	Mahmoud et al <sup>84</sup>	28	10(35.71%)	3(30.00%)	5(27.78%)	28.57%	3 days after admission
12	Valente et al <sup>67</sup>	27	4(14.81%)	1(25.00%)	2(8.70%)	11.11%	On the day of admission and repeated every 2–3 days before discharge
13	Wu et al <sup>85</sup>	38	12(31.58%)	2(16.67%)	0(0.00%)	5.26%	NA
14	Xia et al <sup>86</sup>	30	1(3.33%)	1(100.00%)	0(0.00%)	2.78%	7.33±3.82 days (1–16 days) after onset
15	Xie et al <sup>87</sup>	33 <sup>b</sup>	0	0	2(6.06%)	6.06%	Within 7 days after the diagnosis of COVID-19
16	Zhang et al <sup>36</sup>	72	2(2.78%)	1(50.00%)	0(0.00%)	1.39%	18.15±7.57 days (6–46 days) after onset
17	Zhou et al <sup>88</sup>	121	8(6.61%)	1(12.50%)	2(1.77%)	2.48%	Samples from all patients were collected on the same day
18	Dutescu et al <sup>89</sup>	18	5(27.78%)	5 <sup>c</sup>		27.78%	NA
19	Fang et al <sup>90</sup>	32	NA	5 <sup>c</sup>		15.63%	NA
20	Huang et al <sup>91</sup>	15	NA	1 <sup>c</sup>		6.67%	Within 1 week of admission to ICU

**Notes:** <sup>a</sup>A half of COVID-19 patients with ocular symptoms and a half of without ocular symptoms were included. <sup>b</sup>COVID-19 patients without any ocular manifestation were included. <sup>c</sup>Does not describe whether patients with positive conjunctival swabs or tears have eye symptoms.

**Abbreviations:** NA, not available; ICU, intensive care unit.

Considering that SARS-CoV-2 genomes can be detected in COVID-19 patients’ conjunctiva and tears, and the virus detected was of infectibility, it is worth noting that ocular surface is not only a reservoir of SARS-CoV-2 but may also be a source of contagion.

## Was Hand-Eye Contact Related to COVID-19?

If SARS-CoV-2 can transmit through the ocular route, hand-eye contact should undoubtedly increase the risk of infection. Guo et al reported a 53-year-old man developed

viral conjunctivitis in the left eye 8 days after confirmed with COVID-19. The conjunctival swab was positive for SARS-CoV-2 in the left eye and negative in the right eye. The patient tended to rub his eyes without washing his hands.<sup>46</sup> The difference between the two eyes may be caused by hand-eye transmission.

Although a retrospective cross-sectional study involving 127 COVID-19 patients conducted by Sindhuja et al showed no significant association between conjunctival congestion and hand-eye contact, another study enrolled 535 COVID-19 patients showed the difference.<sup>47,48</sup> Through searching the electronic medical records and collecting questionnaires, 46 of 535 COVID-19 patients with a history of frequent hand-eye contact were identified, and 286 cases reported an occasional hand-eye contact history. A total of 27 cases presented with conjunctival congestion, of which 13 cases had a history of occasional hand-eye contact, and 6 cases had a history of frequent hand-eye contact. Multivariate regression analysis showed that frequent hand-eye contact was closely correlated with the occurrence of conjunctival congestion. Their research supported that hand-eye contact is an independent risk factor for SARS-CoV-2 infection on the ocular surface. Patients may touch contaminated objects with their hands and transferred the virus to the ocular surface through hand-eye contact. The virus then invaded the conjunctiva resulting in conjunctivitis.

## Aerosols Increase the Risk of Ocular Surface Exposure

Droplets are produced when people are speaking, sneezing, and coughing.<sup>49</sup> The droplets with a diameter  $\leq 5 \mu\text{m}$  are defined as aerosols, which can be suspended in the air for long distances transmission.<sup>50</sup> During the SARS-CoV epidemic in 2003 and the MERS-CoV epidemic in 2012, the transmission route of aerosols was reported.<sup>51</sup> SARS-CoV-2 is 79% homologous to SARS-CoV and 50% consistent with MERS-CoV,<sup>6</sup> so it may also be transmitted through aerosols.

Several researchers studied whether aerosols are produced during surgery. There was no detectable aerosol generation during microkeratome-assisted LASIK and vitrectomy.<sup>52-54</sup> However, experiments on porcine eyes and models of human cadaveric corneoscleral rim mounted on an artificial anterior chamber showed visible aerosol produced during phacoemulsification.<sup>55,56</sup> Besides, the studies of Workman et al on human cadaver heads

demonstrated that cold instrument and microdebrider use did not generate visible aerosols, but endoscopic endonasal surgery using a high-speed drill and cautery use generated large amounts of aerosols.<sup>49,57,58</sup> The above studies remind ophthalmologists that ocular transmission of SARS-CoV-2 may occur when performing aerosol-generating operations such as phacoemulsification, drill, and cautery, and eye protection is indispensable during these high-risk operations.

In addition to the aerosols produced by surgery, it also deserves attention from ophthalmologists whether outpatients produce aerosols, because outpatients may not have been tested for SARS-CoV-2 virus nucleic acid. The study of Tang et al showed that aerosols were generated while using a noncontact tonometer to measure intraocular pressure (IOP), and aerosols and IOP were positively correlated.<sup>59</sup> Aytogan et al reported that SARS-CoV-2 was detectable on the surface of slit-lamp shield and phoropter.<sup>60</sup> Even if the slit-lamp shield was used, it cannot completely block infectious aerosols. Aerosols can suspend in the air, flow beyond the shield, and then arrive at the ophthalmologists' neck and clothing.<sup>61,62</sup> SARS-CoV-2 can remain viable in aerosols for at least 3 hours.<sup>63</sup> Once aerosols form, SARS-CoV-2 can bind to the ACE2 on the exposed ocular mucosa to cause infection. In order to prevent aerosols from contacting the eye surface, eye protection cannot be ignored.

## The Possible Routes of SARS-CoV-2 Transfer from Ocular Surface

If the ocular surface is the portal for SARS-CoV-2 to enter, where does the virus transfer after entering? An animal experiment reveals the possible nasolacrimal routes of SARS-CoV-2 transfer from the ocular surface.<sup>64</sup> Five rhesus macaques were inoculated with  $1 \times 10^6$  50% tissue-culture infectious doses of SARS-CoV-2. Only in the conjunctival swabs of rhesus macaques inoculated via conjunctival route could the SARS-CoV-2 be detected. Conjunctival swabs of the rhesus macaques that were inoculated via intragastric or intratracheal route were negative. Three days post conjunctival inoculation, rhesus macaques presented mild interstitial pneumonia. Autopsies showed that SARS-CoV-2 was detectable in the nasolacrimal system tissues, including the lacrimal gland, conjunctiva, nasal cavity, and throat, which connected the eyes and respiratory tract on anatomy. Tears and secretions can be drained into the respiratory tract tissues or swallowed into the digestive system, and the microvilli of

lacrimal duct epithelium cells can facilitate tear absorption.<sup>65</sup> Thus, SARS-CoV-2 on the ocular surface can be transferred to different systems along with tears through the nasolacrimal route.

A case reported by Hu et al also supported that SARS-CoV-2 could be transferred through the nasolacrimal system.<sup>66</sup> A patient with obstruction of the left common lacrimal duct was hospitalized after being confirmed with COVID-19. The nasopharyngeal swab became negative after 22 days of continuous positive. On the 25th day of hospitalization, the nasopharyngeal swab was negative, but the left eye conjunctival swab presented a positive result. Subsequently, the left eye conjunctival swab continued to be positive for 2 weeks. During this period, neither the nasopharyngeal swab nor the conjunctival swab of the right eye showed positive results. The continuous negative result of nasopharyngeal swab may be caused by the obstruction of the left eye's lacrimal duct, which prevented the virus from entering the nasolacrimal system with tears from the left eye. Besides, the ocular surface virus shedding time was up to two weeks, longer than the 3 to 6 days in other cases.<sup>67</sup> It may own to the inability of tears to flush the virus on the ocular surface into the nasolacrimal duct because of the obstruction.

Another possible route is hematogenous metastasis. Based on the detection of SARS-CoV-2 nucleic acid in the retina of deceased COVID-19 patients, the possibility of blood transmission is worth considering.<sup>68</sup> Once reaches the ocular surface, SARS-CoV-2 could invade the conjunctiva and iris under the mediation of ACE2 and CD147, another possible receptor for SARS-CoV-2 on host cells.<sup>69</sup> De Figueiredo et al described the following possible pathways.<sup>70</sup> After reaching blood capillaries and then choroid plexus, the virus reaches the blood-retinal barrier (BRB), which expresses both ACE2 and CD147 in retinal pigment epithelial cells and blood vessel endothelial cells. Since CD147 mediates the breakdown of neurovascular blood barriers, the virus can cross the BRB and enter into blood. Although the hematogenous metastasis of SARS-CoV-2 from the ocular surface may exist theoretically, more clinical or experimental evidence is needed to verify.

The above nasolacrimal route and blood metastasis explain the possible paths of virus transfer from ocular surface, indicating that SARS-CoV-2 may not be localized to the eyes after its invasion into the conjunctiva.

## Discussion

Our review summarized current experimental and clinical evidence and highlighted the possibility of the ocular transmission of SARS-CoV-2. The expression of ACE2 and TMPRSS2 on the ocular surface provides molecular bases for SARS-CoV-2 to enter cells. Accumulated COVID-19 patients presented conjunctivitis as the initial symptom or the only symptom, indicating that the ocular surface may serve as a portal of entry for the SARS-CoV-2. SARS-CoV-2 virus was detectable on the ocular surface of COVID-19 patients, and the isolated virus was also infectious, proving that the ocular surface can not only be a reservoir but also can serve as a source of contagion. In addition to the droplet transmission and direct contact transmission of common respiratory viruses, SARS-CoV-2 may reach the ocular surface by hand-eye contact and aerosols. Once SARS-CoV-2 reaches the ocular surface, it may transfer to other systems through the nasolacrimal system or hematogenous metastasis. All in all, ocular involvement and transmission of SARS-CoV-2 cannot be ignored during the COVID-19 pandemic.

Previous studies have shown that respiratory viruses such as adenovirus and influenza viruses can infect the ocular surface. Adenovirus can cause typical epidemic keratoconjunctivitis.<sup>71</sup> Although the ocular and systemic manifestations are different from SARS-CoV-2, the fact that respiratory viruses have eye-tissue tropism can provide a reference for evaluating the possibility of SARS-CoV-2 ocular transmission. SARS-CoV-2 belongs to the  $\beta$  coronavirus family, highly homologous to SARS-CoV. SARS-CoV has been confirmed to cause systematic infection after ocular inoculation in multiple animal models.<sup>72</sup> With a stronger conjunctival invasion ability than SARS-CoV,<sup>45</sup> the ocular tropism of SARS-CoV-2 is considerable. The conjunctival inoculation on rhesus macaques proved that SARS-CoV-2 infection through ocular route is possible. More direct evidence is needed to further confirm ocular transmission.

As a respiratory virus, the main transmission routes of SARS-CoV-2 are droplet transmission and direct contact transmission like other respiratory viruses. In general, the incidence of ocular manifestations and the positive rate of conjunctival swabs in COVID-19 patients are relatively low (0 to 35.71% and 0 to 28.57% in our review, respectively). This may owe to the ocular defense mechanisms. The mechanical barriers of the eyelids and eyelashes can prevent foreign bodies from entering into eyes.<sup>73</sup> The innate protection system on the ocular surface, including

tear renewal and antibacterial components in tears, such as lactoferrin, IgA, and lysozyme, can eliminate viruses.<sup>19</sup> Besides, the expression of ACE2 and TMSSPR2 appeared to be higher in diseased conjunctival tissue, which can also explain the limited eye involvement of healthy eyes.

However, because of the high infectivity and pathogenicity of SARS-CoV-2, ocular transmission cannot be ignored. To lower the possibility of ocular transmission, it is recommended to wear goggles or use a protective mask, wash hands frequently, avoid hand-eye contact, and wear a mask to avoid droplets and aerosols for both health care workers and the general population. Hospitals should also be disinfected, especially in areas prone to aerosols. Besides, ophthalmologists should be on alert for patients with conjunctivitis who could present ocular symptoms as the initial sign of COVID-19 but have not been identified.

## Conclusion

In conclusion, our review outlined the evidence of SARS-CoV-2 transmission through the ocular route. SARS-CoV-2 can have a variety of ocular symptoms, the most common of which is conjunctivitis. The ocular surface can serve as a reservoir and source of contagion for SARS-CoV-2. There is a risk that ocular surface can be infected with SARS-CoV-2 through hand-eye contact and aerosols, and transfer SARS-CoV-2 to other systems through nasolacrimal route and hematogenous metastasis. Further studies are needed to more directly confirm the existence of ocular transmission and to assess the proportion of ocular transmission in the population.

## Data Sharing Statement

The data supporting the findings of this study are available from the corresponding authors Ming-Chang Zhang and Hua-Tao Xie on request.

## Ethics Approval and Informed Consent

This article do not contain any studies with human participants or animals.

## Consent for Publication

This article does not contain any studies with human participants.

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## Disclosure

The authors have no conflicts of interest to declare for this work.

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