

LETTER TO THE EDITOR

SARS-CoV-2 may be related to conjunctivitis but not necessarily spread through the conjunctiva SARS-CoV-2 and conjunctiva

To the Editor,

We appreciate the comments of Liu et al¹ and Peng et al² in relation to our previous study. Currently, the controversy on the relationship among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the ocular surface and conjunctivitis are reflected in two aspects as follows: (a) can SARS-CoV-2 infection cause conjunctivitis? (b) can SARS-CoV-2 be transmitted through the ocular surface?

With regard to the correlation between SARS-CoV-2 infection and conjunctivitis, one large clinical study has reported a low incidence of conjunctivitis (<1.0%), namely conjunctival congestion, in patients with COVID-19.³ Therefore, many experts maintain that conjunctivitis in patients with COVID-19 is purely a concurrent disease unrelated to SARS-CoV-2 infection. However, we believe that this number is an underestimation, because a diagnosis of conjunctivitis requires an examination by an ophthalmologist. In a study on the ocular manifestations of patients with COVID-19 conducted by ophthalmologists,⁴ which involved 534 confirmed COVID-19 cases, it was reported that 4.68% of patients suffered from conjunctival congestion and 11.8% suffered from ocular foreign body sensation. Meanwhile, based on the findings of Zhou et al,⁵ Sun et al,⁶ and us,⁷ there were two COVID-19 patients with viral conjunctivitis among three patients with positive reverse transcription polymerase chain reaction (RT-PCR) results and two with suspected conjunctival sac infection. Although there are few cases of SARS-CoV-2 infection in the eyes, which makes statistical analysis impossible, we believe that there is a correlation between SARS-CoV-2 infection and conjunctivitis. We also tested conjunctival sac secretions from the patient for herpes simplex virus, adenovirus and other common viruses of viral conjunctivitis. The results were all negative, which indicated that the viral conjunctivitis of the patient may be related to SARS-CoV-2.

The careful observation of patients failed to support the local invasion and replication of SARS-CoV-2, but this may have been due to the short positive detection window of the virus on the ocular surface. Given that conjunctivitis can last for more than a week, the pathological mechanism of SARS-CoV-2 infection as it relates to conjunctivitis is unclear. In a study on feline infectious peritonitis caused by feline CoV (FCoV), researchers found that 90% of sick cats suffered from conjunctivitis, and the FCoV antigen could be detected in the conjunctiva. The authors suspected that monocytes and macrophages were infected by FCoV, thereby causing endothelial barrier dysfunction and vasculitis.⁸ In addition, we contend that conjunctivitis caused

by SARS-CoV-2 may also involve an abnormal autoimmune response. Further studies are needed to confirm these findings.

It is worth mentioning that SARS-CoV-2 variants have been described. During the SARS-CoV outbreak in 2003-2004, the human coronavirus NL63 (HCoV-NL63) variant showed strong conjunctival susceptibility. It was reported that 17% of patients with HCoV-NL63 had conjunctivitis.⁹ Therefore, we consider it important to isolate and culture the virus and to conduct further virological studies in SARS-CoV-2 patients with conjunctivitis or other rare symptoms.



With regard to whether SARS-CoV-2 is transmitted through the conjunctiva, we have to clarify several issues as follows: (a) does SARS-CoV-2 exist in the conjunctival sac? (b) can SARS-CoV-2 replicate in the conjunctiva? (c) can SARS-CoV-2 enter the systemic circulation to cause pneumonia?

Recent studies have confirmed that SARS-CoV-2 is found in the conjunctival sac of patients with SARS-CoV-2. In addition to our study,⁷ Zhou et al,⁵ Sun et al⁶ have reported that SARS-CoV-2 is detected in the conjunctival sac; however, conjunctival sac infection rates were not high at 1/30, 3/67 (two of them were suspiciously positive) and 1/72, respectively. Considering the relatively high specificity and low sensitivity (approximately 50%) of the RT-PCR method, the actual positive rates may be slightly higher than these reported values.¹⁰ In a positive case, we demonstrated that the window for SARS-CoV-2 detection in the conjunctival sac was within 3 days. In addition, isolates were negative for SARS-CoV-2, consistent with the results of Sun et al⁶ Moreover, SARS-CoV-2 was detected in respiratory tract and fecal specimens. Although the patient consistently wore a mask, the upper edge of the mask did not completely cover the nose root. It is very likely that, respiratory droplets entered the ocular surface. In addition, the patient had a habit of eye rubbing. Therefore, we agree with Liu et al,¹ who concluded that exogenous factors may have contributed to the detection of SARS-CoV-2 in the conjunctival sac. Interestingly, the patient tested negative for the virus after education. Thus far, there is no evidence to suggest that SARS-CoV-2 can replicate on the ocular surface.

To determine whether SARS-CoV-2 in the conjunctiva can cause systemic disease, Deng et al¹¹ carried out an interesting study. The authors vaccinated the conjunctiva of rhesus monkeys with a 50% tissue culture infective dose (TCID₅₀)—of SARS-CoV-2, and 1 day later, the virus was detected in the respiratory tract. The virus was also detected in the lungs and digestive tract of rhesus macaques at autopsy,

suggesting that SARS-CoV-2 transmission may occur through the conjunctiva in theory. However, there is still no evidence on how SARS-CoV-2 can enter the body from conjunctiva till now. Deng et al.¹¹ reported that SARS-CoV-2 failed to be detected in the conjunctival sac 2 days after conjunctival vaccination, which indicating that the chances of SARS-CoV-2 replication in the conjunctiva and the release of virus into the bloodstream were very small. Because the ocular surface is connected to the respiratory tract through the nasolacrimal duct, the virus may have entered the respiratory tract through the ocular surface. The low expression of angiotensin-converting enzyme 2 in epithelial cells of the conjunctiva compared to those of the respiratory system may have played a role; however, further studies are needed.¹²

Thus, although conjunctivitis caused by SARS-CoV-2 may be expected, we still agree with Liu et al.¹ and Peng et al.,² which state that eyes are not the main transmission routes of SARS-CoV-2. We arrive at this conclusion because the positive SARS-CoV-2 detection rate and the viral load in conjunctival sac is very low. In addition, there is no evidence that SARS-CoV-2 can replicate locally until now.

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REFERENCES

- Liu Z, Sun CB. Conjunctiva is not a preferred gateway of entry for SARS-CoV-2 to infect respiratory tract. *J Med Virol*. 2020. <https://doi.org/10.1002/jmv.25859>
- Peng Y, Zhou Y. Is novel coronavirus disease (COVID-19) transmitted through conjunctiva? *J Med Virol*. 2020. <https://doi.org/10.1002/jmv.25753>
- Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *New Engl J Med*. 2020. <https://doi.org/10.1056/NEJMoa2002032>
- Chen L, Deng C, Chen X, et al. Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: a cross-sectional study. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.03.12.20034678>
- Zhou Y, Zeng Y, Tong Y, et al. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.02.11.20021956>
- Sun X, Zhang X, Chen X, et al. The infection evidence of SARS-COV-2 in ocular surface: a single-center cross-sectional study. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.02.26.20027938>
- Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol*. 2020. <https://doi.org/10.1002/jmv.25725>
- Hok K. Morbidity, mortality and coronavirus antigen in previously coronavirus free kittens placed in two catteries with feline infectious peritonitis. *Acta Vet Scand*. 1993;34:203-210.
- van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med*. 2004;10(4):368-373. <https://doi.org/10.1038/nm1024>
- Sun C, Wang Y, Liu G, et al. Role of the eye in transmitting human coronavirus: what we know and what we do not know. *Preprints*. 2020. <https://doi.org/10.20944/preprints202003.0271.v1>
- Deng W, Bao L, Xiang Z, et al. Rhesus macaques can be effectively infected with SARS-CoV-2 via ocular conjunctival route. *BioRxiv*. 2020. <https://doi.org/10.1101/2020.03.13.990036>
- Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270-273. <https://doi.org/10.1038/s41586-020-2012-7>