

Ocular involvement of coronavirus disease (COVID-19): A systematic review of conjunctival swab results

Indra Tri Mahayana,¹ Natalia Christina Angsana,² Muhammad Zhafran Ayyasy,² Anastasya Sondang Hutajulu,² and Suhardjo¹

¹Department of Ophthalmology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

²Ophthalmology Research Unit, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

SUBMITTED: 20 April 2020

REVISED: 29 April 2020

ACCEPTED: 31 Mei 2020

KEYWORDS

COVID-19

Coronavirus

Conjunctivitis

Ocular manifestation

ABSTRACT Coronavirus disease (COVID-19) is a pandemic disease which is caused by the latest discovered coronavirus. Conjunctivitis is allegedly the first presentation of COVID-19 since it can spread by aerosol contact with the conjunctiva. The present study aimed to systematically review the employment of conjunctival swab with Real-time Polymerase Chain Reaction in detecting SARS-CoV-2. The research is a systematic review of the published scientific literature on findings of conjunctival swab of COVID-19 from PUBMED database and other additional sources (i.e: Google Scholar). The search method was done using "COVID-19 OR coronavirus OR SARS-COV2, AND conjunctivitis, AND ocular manifestations, AND conjunctival swab" as keywords. Inclusion criteria were any papers that related to the entered keywords and have conjunctival swab as a reported outcome. Letters, reviews, and editorials describing other studies reporting COVID-19 and conjunctival swab were excluded. Only four research papers were found and included in the literature review. From the four current research papers, positive SARS-CoV-2 results were yielded from 0-5.26% of conjunctival swab specimens. In conclusion, although the presence of the SARS-CoV-2 virus on the ocular surface remains unclear, the prevention of infection transmission through an ocular surface is mandatory by wearing goggles (or shield), mask (N-95 recommended) and gown.

© The Journal 2020. This article is distributed under a [Creative Commons Attribution-ShareAlike 4.0 International license](https://creativecommons.org/licenses/by-sa/4.0/).

1. Introduction

Coronavirus disease (COVID-19) is a communicable disease caused by the novel coronavirus and might cause mild to moderate respiratory symptoms and can be more serious in elderly and people with underlying diseases (chronic respiratory disease, cardiovascular disorder, diabetes mellitus, and cancer).¹ The pandemic COVID-19 began on December 31, 2019 with an outbreak of pneumonia-like illness in Wuhan, China.² COVID-19 has affected 210 countries and territories around the world. On April 13, 2020, the number of coronavirus cases reached 1,920,250 with 119,413 deaths. The largest number of cases have occurred in the USA

amounted to 584,862 cases with 23,555 deaths.³ On January 7, 2020, the disease was recognized as a novel coronavirus (nCoV) and on 11 February 2020, the WHO officially named it as Coronavirus Disease 2019 (COVID-19) and the original virus was previously named as SARS-CoV-2 (2019-nCoV severe acute respiratory syndrome-related coronavirus 2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses.⁴

A few reports have been evaluated for the manifestation of SARS-CoV-2 in tear fluid.⁵ Experience from health workers in Wuhan revealed that despite being fully dressed in N95 protective, viral infections still occurred with unilateral conjunctivitis as the first symptom, followed by the development of fever a few hours later.² An ophthalmologist (Dr. Li Wenliang) at Wuhan Central Hospital was infected by an asymptomatic glaucoma patient in early January

*Correspondence: indra.tri.m@mail.ugm.ac.id
Department of Ophthalmology, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmako, Sekip Utara, Yogyakarta, Indonesia

which caused his death a month later. Without eye protection, the virus allegedly can be transmitted by aerosol contact with conjunctiva and cause infection.⁶ Infection caused by 2019-nCoV has been characterized as a lower respiratory syndrome manifesting as pneumonia and/or acute respiratory distress. However, there are still many gaps in our knowledge concerning the global epidemiology of 2019-nCoV, particularly the route of transmission of COVID-19, especially through ocular surface, which has not yet been fully explained. The present study aimed to systematically review the employment of conjunctival swab Realtime Polymerase Chain Reaction (RT-PCR) in detecting SARS-Cov-2.

2. Method

2.1 Literature research

A systematic literature search was conducted during the period of April 2020 using PUBMED database and other additional sources (i.e: google scholar). Search strategies were performed to identify literature pertaining to the following search terms: *COVID-19* OR, *coronavirus* OR *SARS-COV2*, AND *conjunctivitis*,

AND *ocular manifestations*, AND *conjunctival swab*. No date nor language restrictions were applied.

2.2 Data extraction and synthesis

Papers were examined in terms of the instruments, patient selection, and COVID-19 diagnostic protocol used in the study. Inclusion criteria were any papers that related to the entered keywords and have conjunctival swab as a reported outcome. Letters, reviews, and editorials describing other studies reporting COVID-19 and conjunctival swab were excluded (Please see Figure 1). Only four articles were eligible for analysis after identified through the database searches.

2.3 Statistical analysis

Total of subjects, mean age, and sex proportion of each study were descriptively analyzed. A comparison of the percentage of positive results of nasopharyngeal swab versus conjunctival swab was analyzed using chi-square tests. The nasopharyngeal swab is the collection of specimens from nasal midturbinate

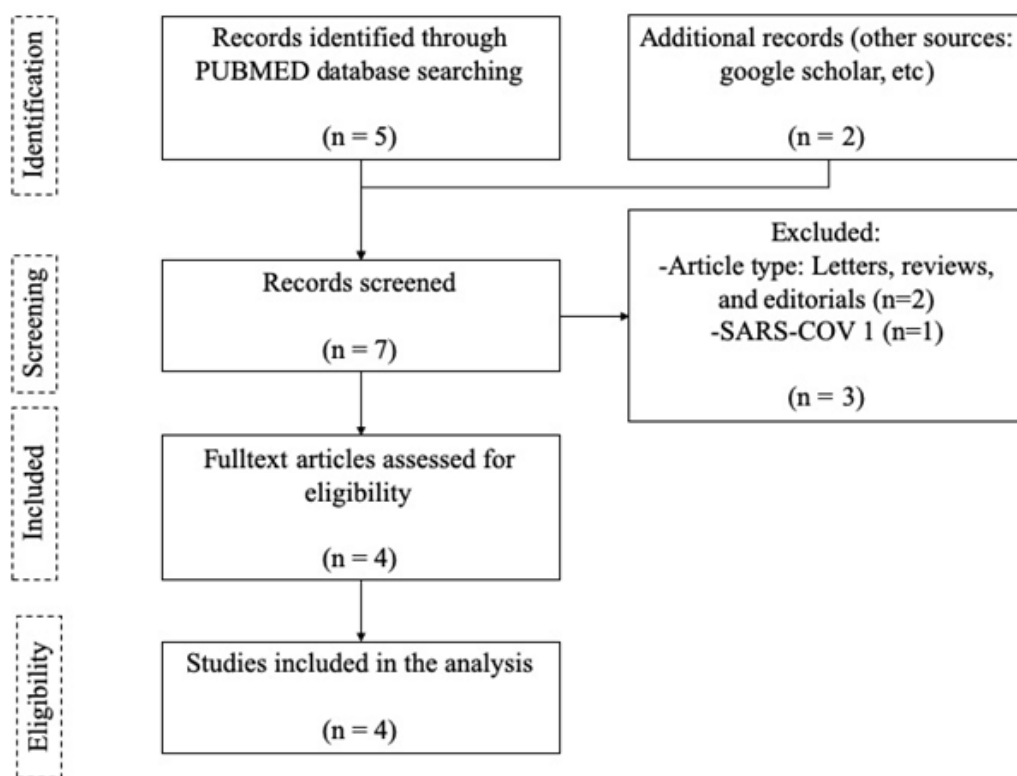


Figure 1. PRISMA chart of systematic review

Table 1. Characteristics of the current research findings

Study No.	Author and Title	Methods	Total subjects	Mean age	Sex proportion
1.	Xia et al. (2020) ⁴ : "Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection"	RT-PCR of conjunctival swab (to collect tears and conjunctival secretions)	30	54.50±14.17	Male: 70%
2.	Wu et al. (2020) ⁵ : "Characteristics of Ocular Findings of Patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China"	RT-PCR from conjunctival swabs	38	68	Male: 65.8%
3.	Zhou et al. (2020): "Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva"	RT-PCR from conjunctival swabs	67	35.7 ±10.6	Male: 37.31%
4.	Deng et al. (2020): "Ocular Detection of SARS-CoV-2 in 114 Cases of COVID-19 Pneumonia in Wuhan, China: An Observational Study"	RT-PCR from conjunctival swabs	114	61.4±16.7	Male: 54%

Note: RT-PCR, Real-time Polymerase Chain Reaction; COVID-19, coronavirus disease 2019.

Table 2. Effectiveness of nasopharyngeal and conjunctival swab in detecting SARS-CoV-2

Study No.	Author	Positive Nasopharyngeal swab (%)	Positive Conjunctival Swab (%)	P
1.	Xia et al. (2020)	26/30 (86.67)	1/30 (3.33)	<0.001
2.	Wu et al. (2020)	28/38 (73.68)	2/38 (5.26)	<0.001
3.	Zhou et al. (2020)	63/67 (94.03)	3/67 (4.47)	<0.001
4.	Deng et al. (2020)	90/114 (78.95)	0/114 (0)	<0.001

A case of COVID-19 was defined according to novel coronavirus pneumonia (NCP) criteria (clinical + PCR results).

and anterior nares specimen. Conjunctival swab technique is used to obtain conjunctival specimens (tears and conjunctival secretions from lower eyelid fornix) from patients.

3. Result

Table 1 shows a summary of the current research findings related to conjunctival swab to find the appearance of SARS-CoV-2 on the ocular surface by RT-PCR. A study by Xia et al. (2020) aimed to evaluate the presence of SARS-CoV-2 in tears and conjunctival secretions. SARS-CoV-2 results were found only in pneumonia patients with conjunctivitis but not found in patients without conjunctivitis. Therefore, this indicated that ocular surface is not a common transmission route although the risk of transmission could not be eliminated.⁴ Wu et al. (2020) revealed only 5.26% yielded positive SARS-CoV-2 results from conjunctival swab although 12 of 38 patients (31.6%) had ocular manifestations consistent with conjunctivitis (conjunctival hyperemia, chemosis, and

increased secretions). These findings are consistent with previous studies on severe acute respiratory syndrome.⁵

Zhou et al. (2020) found that only 1 of 63 patients revealed a positive PCR result of conjunctival swab and moreover, patients with conjunctivitis yielded a negative result.⁸ This was in line with results from Deng et al. that revealed 0 positive conjunctival swabs RT PCR out of 114 patients SARS-CoV-2.⁹

4. Discussion

The present systematic review revealed very low results of SARS-CoV-2 nucleotide were found from conjunctival swab. However, patients who come to the ophthalmology clinic or the emergency room with conjunctivitis and have associated risk factors (traveling to high-risk areas or contact with people who have returned from those areas or those known to be infected) can transmit 2019-nCoV infection even before they experience other signs and symptoms of infection.⁷

A prospective interventional case series study revealed that SARS-CoV virus was not found in tear secretions of SARS patients in the Prince of Wales Hospital, Hongkong. The study result showed that 17 patients were confirmed positive after being tested with paired convalescent sera. Among these 17 patients, there were 5 samples from nasopharyngeal aspirate and stool specimens that tested positive using RT-PCR, but there were no tear swab and conjunctival scraping specimens which were positive. The authors concluded that the study of conjunctival swabs and conjunctival scraping was not valuable for diagnosing SARS-CoV.¹⁰ However, RT-PCR itself has a high specificity but low sensitivity that can make high false negative rates despite the presence of the virus. One study compares the viral load on nasopharyngeal swab compared to tears collected by Schirmer tear strips collection. It was found that patients with positive COVID-19 results on nasopharyngeal swab showed negative results from tear specimen.¹¹ Therefore, conjunctival swab has no superiority compared to nasopharyngeal swab.

Therefore, the exact route of transmission of SARS-CoV-2 remains unclear, although in this pandemic condition, it is suggested that high alertness is still mandatory regarding aerosol to mucosal virus transmission (through conjunctiva). It is important to apply preventive measures especially thorough hand washing, using personal protective equipment, eye protection (goggles) or face shield (face mask), not to touch the mucous membranes (eyes, nose, or mouth) and avoiding unnecessary direct contact.² The American Academy of Ophthalmology recommendations include the use of an N-95 mask and goggles.⁷

5. Conclusion

The present systematic review revealed very low results of SARS-CoV-2 nucleotide were found from conjunctival swabbing. This finding suggests that the virus might not be retained in or spread through the conjunctival tissue. However, the prevention of infection transmission is still mandatory, especially thorough hand washing, and not touching the eyes, nose, and mouth when in a risky location. Control of spreading to health workers can be done by using

personal protective equipment in the prevention and control of COVID-19 infections such as the use of an N-95 mask and goggles or shield and not touching the mucous membranes (eyes, nose or mouth) because spreading is associated with transmission through aerosol contact with the conjunctiva.

References

1. World Health Organization. Coronavirus. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1 [Accessed 02 April 2020]
2. Li JPO, Lam DSC, Chen Y, dan Ting DSW. Novel Coronavirus disease 2019 (COVID-19): The importance of recognising possible early ocular manifestation and using protective eyewear. *Br J Ophthalmol.* 2020; 104(3).
3. Worldometers. COVID-19 Coronavirus Pandemic. Available from: <https://www.worldometers.info/coronavirus/#countries> [Accessed 02 April 2020]
4. 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; 1–6.
5. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of ocular findings of patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 2020; 138(5): 575-8.
6. Lai THT, Tang EWH, Chau SKY, Fung KSC, Li KKW. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(5):1049-55.
7. Reviglio VE, Osaba M, Reviglio V, Chiaradia P, Kuo IC, O'Brien TP. COVID-19 and ophthalmology: a new chapter in an old story. *Med Hypothesis Discov Innov Ophthalmol.* 2020; 9(2): 71-73.
8. Zhou Y, Zeng Y, Tong Y, Chen C. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. *MedRxiv.* 2020 Jan 1. Available from: <https://www.medrxiv.org/content/10.1101/2020.02.11.20021956v1.full.pdf+html> [[Accessed 02 April 2020].
9. Deng, C., Yang, Y., Chen, H., Chen, W., Chen, Z.,

- Ma, K. and Wang, J., 2020. Ocular detection of SARS-CoV-2 in 114 Cases of COVID-19 pneumonia in Wuhan, China: an observational study. China. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3543587. [Accessed 02 April 2020].
10. Chan W. Tears and conjunctival scrapings for coronavirus in patients with SARS. *Brit J Ophthalmol.* 2004; 88(7): 968-9.
11. Seah I, and Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) affect the eyes?: a review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm.* 2020: 28(3).