



# No secret hiding place? Absence of SARS-CoV-2 on the ocular surface of 1145 hospitalized patients in a pandemic area

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## Abstract

**Objectives** The aims of this study were to evaluate the isolated prevalence of real-time reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 on the ocular surface without systemic infection in hospitalized asymptomatic patients and to determine the risk for ophthalmologists and medical staff to be infected by prescreened asymptomatic patients in a tertiary eye care center.

**Methods** In this prospective, observational study, bilateral swaps of the conjunctiva in the lower fornices as well as nasopharyngeal swaps were collected in 1145 hospitalized asymptomatic patients of a tertiary eye care center. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis was performed for each swap to evaluate the prevalence of SARS-CoV-2. Demographic data and potential risk factors for an isolated infection of the ocular surface were noted.

**Results** Two thousand two hundred eighty-eight (99.9%) of all 2290 tested eyes had negative results in the RT-PCR analysis of the conjunctival swabs. One patient had bilateral false-positive results in the conjunctival swabs. None of the 1145 patients had any positive RT-PCR-confirmed result in the nasopharyngeal swabs.

**Conclusions** The risk for an isolated conjunctival viral activity in patients with a negative nasopharyngeal swab-based RT-PCR seems to be absent or extremely low, suggesting no need to perform additional conjunctival swabs in patients with negative nasopharyngeal swabs. Furthermore, the risk of a work-related SARS-CoV-2 infection due to direct contact with preselected asymptomatic patients in an eye care center is very low, especially when additional hygiene standards and safe distances are respected carefully. This might reassure medical staff and reduce the fear of SARS-CoV-2 infection.

## Key messages

- The risk of a work-related SARS-CoV-2 infection in a tertiary eye care center is very low if only prescreened asymptomatic patients are hospitalized and hygiene standards and safe distances are considered carefully.
- The risk for an isolated SARS-CoV-2 activity on the ocular surface in asymptomatic patients with a negative nasopharyngeal swab-based RT-PCR is absent or extremely low, and there is no need for additional conjunctival swabs in these patients.
- In pandemic times, corneal donation and transplantation can be processed using asymptomatic donors with a negative nasopharyngeal swab-based qRT-PCR and considering self-protection during explantation.

This article is part of a topical collection on *Perspectives on COVID-19*.

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## Introduction

The coronavirus disease 19 (COVID-19) pandemic, caused by the *severe acute respiratory syndrome*-related coronavirus (SARS-CoV-2), is a public health emergency of tremendous international relevance [1–6]. SARS-CoV-2 spreads via human-to-human and seems to be transmitted mainly through respiratory droplets and contact with infected persons, less commonly via smear infection [1, 2, 4, 5]. Furthermore, there seems to be a significant risk for ophthalmologists and medical staff to be infected with SARS-CoV-2 during the ophthalmological examination, treatment, or care due to the close proximity to infected (but often still asymptomatic) patients or colleagues [1, 2, 4, 7–9]. In addition, this potentially high risk seems to affect the mental health of ophthalmologists and the medical staff resulting in anxiety and depression symptoms [10].

Previous studies reported the presence of the entrance receptor of SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE 2), on the ocular surface and that a significant proportion of SARS-CoV-2-positive patients demonstrates unspecific conjunctivitis [1, 6, 11–13]. Furthermore, SARS-CoV-2 was detected in ocular tissues, in tears, and in conjunctival secretions of COVID-19 patients [3, 4, 6, 11, 14–16]. Therefore, a potential transmission and infection with SARS-CoV-2 by ocular secretions seem to be possible.

However, until now, it is not investigated, whether SARS-CoV-2 might exist isolated on the ocular surface without systemic infection. Furthermore, the risk of an infection with SARS-CoV-2 for ophthalmologists and the medical staff under pandemic conditions is also not determined, yet. Therefore, the purpose of this prospective, observational study was to evaluate the isolated prevalence of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 on the ocular surface and in nasopharynx in hospitalized asymptomatic patients and to determine the risk and risk factors for ophthalmologists to be infected by asymptomatic prescreened patients during work in a tertiary eye care center in Germany.

## Patients and methods

The study was conducted at the Department of Ophthalmology, University of Cologne, Germany, in adherence to the tenets of the Declaration of Helsinki and its later amendments. Institutional Review Board approval was

obtained (20-1161). Inclusion criteria were hospitalizing for any reason at the Department of Ophthalmology of the University Hospital Cologne, Germany. All patients who were hospitalized in the University Eye Hospital Cologne between the 22nd of April and 11th of July were asked to participate. After explanation of the nature of the study, informed consent was obtained from all participants. None of the patients did report symptoms indicating COVID-19 including fever, cough, common cold, loss of smell or taste, headache, body aches, shortness of breath, sore throat, or fatigue. Demographic data of all participants including age, gender, and ethnicity were recorded. Furthermore, the reason for hospitalization, application frequency of topical eye medication per day, the use of antiviral or immunosuppressive topical medication, and contact lens use were queried as potential risk factors for SARS-CoV-2 infection of the ocular surface. In addition, the use of antiviral or immunosuppressive systemic medication, the use of systemic ACE inhibitors, and if the participants already had RT-PCR-confirmed COVID-19 were evaluated as potential risk factors for systemic or topical infection.

Afterward, body temperature was measured using a daily calibrated infrared ear thermometer (Genius 2™, Cardinal Health Germany 507 GmbH, Norderstedt, Germany). Body temperature was graded as normal ( $\leq 37.4$  °C) or elevated ( $\geq 37.5$  °C). Afterward, nasopharyngeal swaps and bilateral swaps of the conjunctiva in the lower fornices were collected. Nasopharyngeal and conjunctival swabs were placed each in a universal transport medium (UTM) (Copan Diagnostics, Murrieta, USA (USA)) and nucleic acids were extracted from UTM using a MagNA Pure 96 (Roche, Basel, Switzerland). SARS-CoV-2-RNA was detected by real-time RT-PCR confirming the presence of the viral E and RdRP genes (TIB molbiol, Berlin, Germany) or E and S genes (Altona Diagnostics GmbH, Hamburg, Germany), respectively, using a LightCycler 480 or LightCycler 480 II (Roche, Basel, Switzerland) [17]. SPSS version 26.0 for Mac (SPSS, Inc., Chicago, IL) was used for all statistical analyses.

## Results

Out of the 1145 hospitalized participants, 544 (47.5%) were males and 601 (52.5%) females with a mean age of  $59 \pm 22$  years (range, 0–95 years). One thousand one hundred fourteen (97.3%) were European, 5 (0.4%) African, 3 (0.3%) Asian, and 23 (2.0%) were from the Middle East. 11.4% ( $n = 131$ ) of the patients used ACE 2 inhibitors, 40 (3.5%) systemic immunosuppression medication, and 14 (1.2%)

systemic antiviral medication. None of the 1145 patients reported RT-PCR-confirmed COVID-19 before hospitalization.

Main reasons for hospitalization included corneal surgery (24.4%;  $n = 279$  patients); conduct of 24-h eye pressure measurements without surgery (23.2%;  $n = 266$ ); cataract surgery (16.3%;  $n = 187$ ); retinal or vitreous surgery (10.7%;  $n = 122$ ); strabismus surgery (8.3%;  $n = 95$ ); glaucoma surgery (6.9%;  $n = 79$ ); and eyelid (3.2%;  $n = 37$ ), tumor (3.0%;  $n = 34$ ), and lacrimal surgery (1.7%;  $n = 20$ ).

Contact lenses were used in 54 of 2290 (2.4%) eyes. Topical medications were used in 1330 (58.1%) eyes with a mean frequency of 3.7 per day. Topical immunosuppressive medication was used in 405 (17.7%) eyes and antiherpetic eye drops in 18 eyes (0.8%). During the evaluation time, the use of face masks was mandatory for all patients and hospital staff at all times.

None of the 1145 patients (100%) showed an elevated body temperature  $> 37.4$  °C or any symptoms of COVID-19. In addition, none of the 1145 patients (100%) had any positive RT-PCR-confirmed result in the nasopharyngeal swabs. Although most of the patients had a very high risk for self-inoculation of SARS-CoV-2 in the eyes by using several times a day topical eye medication, 2288 (99.9%) of all 2290 tested eyes had negative results in the RT-PCR analysis of the conjunctival swabs. One hospitalized patient had bilateral positive RT-PCR results in the conjunctival swabs, but this result was putatively wrongly positive because it could not be confirmed, neither in the second analysis of these positive swabs nor in further conjunctival swabs. Furthermore, this patient did not develop any symptoms of COVID-19 or conjunctivitis at a later point.

## Discussion

First of all, this study investigated the potential isolated prevalence of SARS-CoV-2 on the ocular surface and adds therefore significant new knowledge which is very important and should be considered by ophthalmologists in these pandemic times. In addition, the present study determines the risk for a work-related SARS-CoV-2 infection of ophthalmologists and medical staff by asymptomatic prescreened patients for the first time and has therefore several very important implications under the pandemic situation in Germany at the time analyzed:

- (i) The risk of a work-related infection due to direct contact with ocular fluids in an eye care setting with prescreened asymptomatic patients is very low. This might reassure ophthalmologists and medical staff and reduce the fear of a work-related SARS-CoV-2 infection.
- (ii) The risk for an isolated SARS-CoV-2 activity on the ocular surface in asymptomatic patients with a negative

nasopharyngeal swab-based RT-PCR seems to be absent or extremely low. Therefore, there seems to be no need to perform additional conjunctival swabs in prescreened asymptomatic patients with negative nasopharyngeal swabs.

- (iii) Reasons for the very low prevalence of positive results both in the nasopharyngeal and conjunctival swabs might be the sensitivity of these swabs or the relatively low prevalence rate of active cases in Cologne during the study period. On the other hand, only asymptomatic patients without any symptoms and without elevated body temperature were screened with nasopharyngeal and conjunctival swabs at the Department of Ophthalmology of the University Hospital Cologne. This preselection might reduce the likelihood of a positive result significantly. However, the results of this study should be confirmed in similar trials with higher prevalence rates of active cases during the study period.
- (iv) The results of our study imply also a virtually absent risk for contamination of ocular surface fluids and human corneal donor tissue if the donor was asymptomatic (and a conjunctival and/or nasopharyngeal swab-based qRT-PCR analysis was negative). These new findings are of very high relevance since there is considerable uncertainty under which conditions cornea donation should be conducted, on how to preselect corneal donors, and on how corneal tissue should be processed and tested in pandemic times.

In summary, based on the very low prevalence of SARS-CoV-2 infection in preselected asymptomatic hospitalized patients, the risk a work-related infection with SARS-CoV-2 in an tertiary eye care center seems to be low, especially when additional hygiene standards and safe distances are respected carefully [18, 19]. In pandemic times, corneal donation and transplantation can be processed using asymptomatic donors with a negative nasopharyngeal swab-based qRT-PCR and considering self-protection with protective equipment during corneal explantation.

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**Authors' contribution** ACR, CL, FK, CC, and LMH designed the study. ACR, LMH, PAW, RSG, FD, and GF performed the data analysis, interpreted data, and wrote the manuscript. HLK did the data collection. All authors approved the final version. The overall responsibility had LMH and CC.

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**Data availability** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Declarations

**Ethics approval and consent to participate** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained. Informed consent was obtained from all individual participants included in the study. No animal subjects were included in this study.

**Conflict of interest** The authors declare no conflict of interest.

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## References

- Rokohl AC, Loreck N, Wawer Matos PA, Mor JM, Zwingelberg S, Grajewski RS, Cursiefen C, Heindl LM (2020) The role of ophthalmology in the COVID-19 pandemic. *Ophthalmologie* 117:642–647. <https://doi.org/10.1007/s00347-020-01148-9>
- Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirgmaier K, Zange S, Wolfel R, Hoelscher M (2020) Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 382:970–971. <https://doi.org/10.1056/NEJMc2001468>
- Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K (2020) Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol*. <https://doi.org/10.1001/jamaophthalmol.2020.1291>
- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. <https://doi.org/10.1001/jama.2020.12839>
- Luers JC, Rokohl AC, Loreck N, Wawer Matos PA, Augustin M, Dewald F, Klein F, Lehmann C, Heindl LM (2020) Olfactory and gustatory dysfunction in coronavirus disease 19 (COVID-19). *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciaa525>
- Lange C, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, Agostini H, Martin G, Reinhard T, Schlunck G (2020) What is the significance of the conjunctiva as a potential transmission route for SARS-CoV-2 infections? *Ophthalmologie*. <https://doi.org/10.1007/s00347-020-01255-7>
- Saban O, Levy J, Chowers I (2020) Risk of SARS-CoV-2 transmission to medical staff and patients from an exposure to a COVID-19-positive ophthalmologist. *Graefes Arch Clin Exp Ophthalmol* 258:2271–2274. <https://doi.org/10.1007/s00417-020-04790-w>
- Ruiz-Lozano RE, Garza-Garza LA, Cardenas-de la Garza JA, Hernandez-Camarena JC (2020) Slit-lamp evaluation during SARS-CoV-2 pandemic: safety first! *Graefes Arch Clin Exp Ophthalmol*. <https://doi.org/10.1007/s00417-020-04729-1>
- Bostanci Ceran B, Karakoc A, Taciroglu E (2020) Airborne pathogen projection during ophthalmic examination. *Graefes Arch Clin Exp Ophthalmol* 258:2275–2282. <https://doi.org/10.1007/s00417-020-04815-4>
- Shao Y, Zhang W (2020) Psychological and ocular surface state of ophthalmologists and ophthalmic nurses working with patients with coronavirus disease 2019. *JAMA Ophthalmol*. <https://doi.org/10.1001/jamaophthalmol.2020.2289>
- Grajewski RS, Rokohl AC, Becker M, Dewald F, Lehmann C, Fatkenheuer G, Cursiefen C, Klein F, Heindl LM (2020) A missing link between SARS-CoV-2 and the eye?: ACE2 expression on the ocular surface. *J Med Virol*. <https://doi.org/10.1002/jmv.26136>
- Rokohl AC, Loreck N, Wawer Matos PA, Zwingelberg S, Augustin M, Dewald F, Grajewski RS, Klein F, Lehmann C, Heindl LM (2020) More than loss of taste and smell: burning watering eyes in coronavirus disease 2019. *Clin Microbiol Infect*. <https://doi.org/10.1016/j.cmi.2020.08.018>
- Guemes-Villaloz N, Burgos-Blasco B, Garcia-Feijoo J, Saenz-Frances F, Arriola-Villalobos P, Martinez-de-la-Casa JM, Benitez-Del-Castillo JM, de la Muela MH (2020) Conjunctivitis in COVID-19 patients: frequency and clinical presentation. *Graefes Arch Clin Exp Ophthalmol* 258:2501–2507. <https://doi.org/10.1007/s00417-020-04916-0>
- Xia J, Tong J, Liu M, Shen Y, Guo D (2020) Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol*. <https://doi.org/10.1002/jmv.25725>
- Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, Talavera-Lopez C, Maatz H, Reichart D, Sampaziotis F, Worlock KB, Yoshida M, Barnes JL, Network HCALB (2020) SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med* 26:681–687. <https://doi.org/10.1038/s41591-020-0868-6>
- Casagrande M, Fitzek A, Puschel K, Aleshcheva G, Schultheiss HP, Berneking L, Spitzer MS, Schultheiss M (2020) Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocul Immunol Inflamm* 28:721–725. <https://doi.org/10.1080/09273948.2020.1770301>
- Augustin M, Schommers P, Suarez I, Koehler P, Gruell H, Klein F, Maurer C, Langerbeins P, Priesner V, Schmidt-Hellerau K, Malin JJ, Stecher M, Jung N, Wiesmuller G, Meissner A, Zweigner J, Langebartels G, Kolibay F, Suarez V, Burst V, Valentin P, Schedler D, Comely OA, Hallek M, Fatkenheuer G, Rybniker J, Lehmann C (2020) Rapid response infrastructure for pandemic preparedness in a tertiary care hospital: lessons learned from the COVID-19 outbreak in Cologne, Germany, February to March 2020. *Euro Surveill* 25. <https://doi.org/10.2807/1560-7917.ES.2020.25.21.2000531>
- Yang C (2020) Does hand hygiene reduce SARS-CoV-2 transmission? *Graefes Arch Clin Exp Ophthalmol* 258:1133–1134. <https://doi.org/10.1007/s00417-020-04652-5>
- Lai THT, Tang EWH, Chau SKY, Fung KSC, Li KKW (2020) Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. *Graefes Arch Clin Exp Ophthalmol* 258:1049–1055. <https://doi.org/10.1007/s00417-020-04641-8>

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