

Conjunctivitis as a sign of persistent SARS-CoV-2 infection? An observational study and report of late symptoms

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Abstract

Purpose: To investigate if symptomatic conjunctivitis during the recovery phase of the disease could be associated to a persistent presence of SARS-CoV-2 in the upper respiratory tract. Secondary end points were to analyze the presence of SARS-CoV-2 in the conjunctiva of ocular symptomatic patients and to record the presence of ocular disturbances at this point of the disease.

Methods: An observational study including consecutive COVID19 patients treated at Humanitas Clinical and Research Hospital who were attending for nasopharyngeal swab to confirm the resolution of SARS-CoV-2 infection and end of isolation. We examined 129 consecutive patients from May to June 2020. The primary end point was to determine if symptomatic conjunctivitis at this point of the disease could be associated to a persistent presence of SARS-CoV-2 in the upper respiratory tract. Secondary end points were to analyze the presence of SARS-CoV-2 in the conjunctiva of ocular symptomatic patients and to record the presence of ocular disturbances at this point of the disease.

Results: One hundred twenty eight patients were included, 9.38% had conjunctivitis, none resulted positive to conjunctival PCR swab test, while two of them had positive nasopharyngeal result. Mean time elapsed since the first COVID-19 positive swab to the time of examination was 6 weeks (± 3). The only significant association was the presence of conjunctivitis with older age (65.3 ± 12.7 vs 56.7 ± 13.5 , $p = 0.046$). Nasopharyngeal swab resulted positive in 22 patients (17.19%). While 88 patients (68.2%) did not have any ocular complain during their COVID19 disease. The 40 patients (31.8%) reporting ocular disturbances complained about: redness (25.43%), tearing (19.53%), burning (18.35%), foreign body sensation (17.18%), itching (15.62%), and discharge (12.5%).

Conclusion: This study showed that late conjunctivitis cannot be considered as a marker of persistent infection when patients are sent to confirm the resolution of SARS-CoV-2 infection.

Keywords

Covid-19, conjunctivitis, SARS-COV-2, ophthalmology

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Introduction

Epidemiology

Coronaviruses (CoVs) represent a family of viruses associated with the common cold in humans (serotypes 229E, OC43, NL63, HUK1). The first was SARS-CoV-1, in 2002, responsible for a severe respiratory syndrome. In 2012, it was the turn of the MERS-CoV responsible for MER (Middle East respiratory syndrome). Finally, in

2019 SARS-CoV-2, was identified, initially spreading in Wuhan, China and then around the world, causing the

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WHO to declare a pandemic for the first time. Coronavirus disease 2019 (COVID-19) pandemic had a disruptive impact during the first wave and as of early November 2020, the WHO has confirmed over 46 million cases and 1.2 million deaths worldwide.¹ The pandemic currently poses an enormous stress on the health-care system making it difficult to establish an efficacious strategy to prevent viral spread.

Systemic presentation

SARS-CoV-2 is a highly contagious pathogen and is mainly transmitted through direct or indirect contact with infected people, through respiratory secretions (droplets) through coughing or sneezing; these droplets can, in fact, come into contact with the mucous membranes of people who are nearby and therefore be inhaled into the lungs. A wide range of clinical manifestations are observed in patients with SARS-CoV-2 ranging from mild, moderate, severe, and rapidly progressive and fulminant disease. The symptoms of SARS-CoV-2, therefore, are non-specific and the presentation of the disease can range from no symptoms (asymptomatic) to severe pneumonia and death. A study of 1420 patients with mild or moderate disease reported that the most common symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), gustatory dysfunction (54.2%), and sore throat (52.9%).² The International Severe Acute Respiratory and Emerging Infections Consortium based on 25,849 hospitalized cases of COVID-19 reported the five most common symptoms at admission were history of fever, shortness of breath, cough, fatigue, and confusion.³ An investigation of data from 4203 patients mostly from China identified hypertension (16%), cardiovascular disease (12%), and diabetes (10%).⁴ Currently there is no broadly accepted classification. Some authors distinguished clinical presentation as follows:⁵

Mild: mild clinical symptoms without pneumonia manifestation through image results

Moderate: fever and other respiratory symptoms with pneumonia manifestation through image results

Severe: meeting any one of the following: respiratory distress, hypoxia ($\text{SpO}_2 \leq 93\%$), abnormal blood gas analysis: ($\text{PaO}_2 < 60$ mmHg, $\text{PaCO}_2 > 50$ mmHg)

Critical: meeting any one of the following: respiratory failure which requires mechanical ventilation, shock, accompanied by other organ failure that needs ICU monitoring and treatment.

We define the prodromal phase as the initial phase characterized by the onset of the first symptoms,⁶ the acute phase with the manifestation of some of the mentioned

symptoms, the convalescence phase with an improvement of symptoms, recovery phase as the first days without symptoms.

Ocular presentation

Conjunctival transmission is also currently considered possible.⁷ Since tear fluid from the ocular surface is transported to the inferior meatus of the nose, the ocular surface represents a significant bridge between the exterior and the respiratory system. SARS-CoV-2 infection can cause conjunctivitis, either as an early sign of the infection or during hospitalization for COVID-19. However, the prevalence of conjunctivitis in literature widely varies among published studies ranging from 2%⁴ up to 31%.⁸

Duration of infection

The reported median incubation period of COVID-19 is 5 days, and nearly all infected individuals who have symptoms will do so within 12 days of infection.⁹ Different scenarios are possible depending on the severity of cases, mild cases last around 14 days from the infection while severe cases can last 8 weeks or longer, estimated mean duration from onset of symptoms to death is 17 days.¹⁰ Although replication-competent virus was not isolated 3 weeks after symptom onset, recovered patients can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks.¹¹

Model of care

Currently, mild clinical presentation may not require hospitalization, and most patients manage their illness at home, while moderate to severe cases require hospitalization for management,¹² the general practitioner is in charge to guide the first steps of management. Isolation ends once clinical and microbiological healing are reached, this is defined as two negative rhino-pharyngeal swabs, executed at least 24 h apart, 7 days after resolution of symptoms.

Recent updates in COVID19 management have reduced quarantines and the need for testing after the disease, however there are many health policy makers worldwide aiming to reduce the number of PCR and incorporate people to work as soon as possible. Quarantines shorter than 14 days and late reintroduction in community of persistent positive patients generate a small possibility of spreading the virus.

We designed this observational study for a better understanding of the potential ophthalmological contribution in the established model of care of COVID-19.

Methods

We conducted an observational study including consecutive patients attending for nasopharyngeal swab to confirm the resolution of SARS-CoV-2 infection. The study adhered to the tenets of the Declaration of Helsinki, was approved by the institutional review board of Humanitas Clinical and Research Center and all patients signed informed consent prior to enrollment. The primary end point was to determine if symptomatic conjunctivitis at this point of the disease could be associated to a persistent presence of SARS-CoV-2 in the upper respiratory tract. Secondary end points were to analyze the presence of SARS-CoV-2 in the conjunctiva of ocular symptomatic patients and to record the presence of ocular disturbances at this point of the disease.

Conjunctivitis was defined as redness and discharge; it was evaluated by simple observation without the use of a slit-lamp and interview of the patients by ophthalmologist (JLVG and FIC). When performed, conjunctival swab was done in the most affected eye without any anesthetic drop. Other ocular disturbances were registered without a questionnaire to avoid inducing answers from patients. Severeness of the disease was based on the type of recovery, intensive care unit, ward, or just isolation.

We excluded all patients younger than 18 years old and those did not have fully filled electronic medical records or did not give signed consent to the study/conjunctival swab.

Conjunctival samples were analyzed by reverse transcription polymerase chain reaction.

Conjunctivitis and ocular symptoms association with age, sex, nasopharyngeal, and conjunctival swab, was explored with Chi-square test, with Fisher correction if necessary, or Mann Whitney test, as appropriated. A p less than 0.05 was considered significant.

Results

Enrollment of patients started on May 2020 and finished on June 2020, 129 individuals were enrolled, and only one

Table 1. Demographic characteristic of study population.

	N (%)
Number of patients	128
Age	57.5 ± 13.6
Sex	
Male	71 (55.47%)
Positive naso-pharyngeal swab	22 (17.19%)
Clinical severity	
Home isolation	22 (17.19%)
Hospital ward	86 (67.19%)
Intensive care unit	19 (14.84%)
Mean time elapsed since the first COVID-19 positive swab to the time of examination	6 weeks ± 3 weeks

excluded for incomplete medical records. The details of the 128 patients are shown in Table 1.

Mean time elapsed since the first COVID-19 positive swab to the time of examination was 6 weeks (±3), similarly, mean elapsed time from the first COVID-19 positive swab to the first COVID-19 negative swab was 7 weeks (±3).

Only 12 patients (9.38%) had conjunctivitis when attending the nasopharyngeal swab to confirm the negativization of the infection, all of them had negative conjunctival swab for SARS-CoV2 RNA traces, while 2 of this patients had positive viral nasopharyngeal PCR ($p = 1$).

The only significant association of the conjunctivitis patients was the older age of this group ($p = 0.046$), all demographic details of the conjunctivitis subgroup are reported in Table 2.

Positive nasopharyngeal swab resulted in 22 patients (17.19%), there was no association between any other variable or ocular abnormality in this subgroup.

About 88 patients were completely ophthalmologically asymptomatic (68.75%); the detailed symptoms are reported in Figure 1, there was no significant association between any symptom and age, sex, inpatient ward or isolation and positive nasopharyngeal SARS-CoV2 swab.

Considering ocular symptomatic patients, onset of these complains was registered, we reported 40 patients (31.25%, 95% CI, 23.35–40.04) complaining of at least one ocular disturbance, in particular: redness (25.43%), tearing (19.53%), burning (18.35%), foreign body sensation (17.18%), itching (15.62%), and discharge (12.5%). There were no statistical differences when considering single symptoms and their beginning against all symptoms together, which were: ocular disturbances during the

Table 2. Details of the conjunctivitis subgroup.

	Affected by conjunctivitis, n (%)	Not affected by conjunctivitis, n (%)	p
Number of patients	12	116	
Age	65.3 ± 12.7	56.7 ± 13.5	0.046
Sex			
Male	7 (58.33%)	64 (55.17%)	1.000
Female	5 (41.67%)	52 (44.83%)	
Positive nasopharyngeal swab	2 (16.67%)	20/114 (17.54%)	1.000
Clinical severity			
Home isolation	2 (16.67%)	20 (17.39%)	
Hospital ward	4 (33.33%)	15 (13.04%)	
Intensive care unit	6 (50%)	80 (69.57%)	

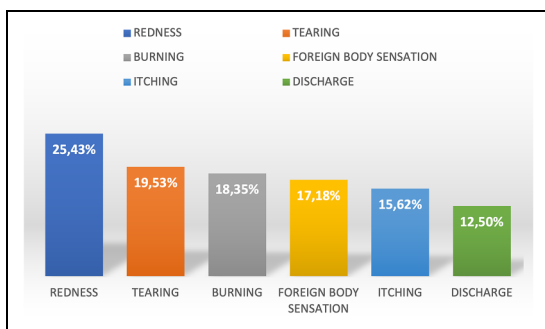


Figure 1. Different ocular symptoms reported in COVID-19 patients.

prodromal phase 12.5%, during the convalescence period 52.5%, and in the recovery phase 35%.

Discussion

While many studies have documented ocular surface symptoms during the acute phase, very few report ocular alterations as a late presentation of the disease.^{13,14} We summarized ocular complains of our patients in Figure 1, our COVID-19 patient cohort developed ocular symptoms mainly during a mid-late disease phase.

Conjunctivitis has been described as a first sign before pneumonia onset, suggesting ocular entry site for the virus in several cases.^{15,16} This made mandatory the adjunctive use of personal protective equipment covering eyes, such as goggles or face shields, since the beginning of the pandemic.¹⁷ Gravitational migration of the virus from conjunctival secretion and tears to the nasal mucosa has been reported, but also the inverted pathway has been suggested in patients that starting with other symptoms developed ocular disturbances further on supported with positive isolation of SARS-CoV2 RNA in conjunctival swabs. This upper migration could also be due to ocular autoinoculation secondary to eye rubbing with contaminated hands or respiratory droplets reaching the conjunctiva due to absence of face mask or to the upstream of condensation secondary to a not properly fitting upper edge of the facemask.¹⁸

Aggarwal et al.¹⁹ performed a systematic review and meta-analysis of literature regarding ocular surface manifestations in COVID-19 patients, concluding that 8.35–11.64% would present at least one symptom. Our study is not in range with the global result, we found 31.25% (95% CI, 23.35–40.04) of patients complaining of at least one ocular surface disturbance. Wu et al.²⁰ Hong et al.,²¹ and Tostmann et al.²² present prevalence of ocular symptoms more similar to our results, 31.6%, 26.79%, and 34.44%, respectively.

All patients were seen in the period between May and June 2020, immediately after their disease, while coming

for the negativization swabs. We decided not to use a questionnaire to avoid underestimation due to conditioning question bias. Indeed we think a direct interview with an ophthalmologist is the more appropriate method to assess new ocular symptoms during COVID-19 disease. Unfortunately we did not comprehensively explore the patients, luckily this is not a great limit when diagnosing a conjunctivitis or reporting symptoms, but we could not describe ophthalmological signs of this new viral/reactive conjunctivitis. We observed conjunctivitis in 9.37%, which is similar to the reported literature,¹⁹ the only significant association ($p = 0.046$) to conjunctivitis was the older age of the patients $65.3 (\pm 12.7)$ versus $56.9 (\pm 14.6)$, more studies are needed to confirm this observation. Burning or itching was present in 25.78%, redness 23.43%, tearing 19.53%, foreign body sensation 17.18%, discharge 12.5%, there is not copious data available of detailed information regarding specific symptoms, only small case series to compare our results. We did not have any patient complaining of chemosis or eye swelling, as it is a more specific symptom, which can be easily seen in more critical patients under complex ventilation support or posturing issues. Severity of COVID-19, determined only as the type of recovery, without analyzing blood parameters or duration of the recovery, did not show any significant association with any specific symptom, prevalence or any other variable. None of the patients in intensive care units needed ophthalmological examination while unconscious or complained lately about a severe ocular disturbance. Unfortunately it is difficult to determine the real prevalence of ocular abnormalities in the most severe systemic manifestations, as priorities at that point are not mild ocular complains or ophthalmic signs. Future studies are needed as some reports have shown significant association between ocular symptoms and severe forms of COVID-19.^{23,24}

While in our series an opposite trend towards a higher prevalence of at least one symptom was seen as regarding severeness of COVID-19 (36.36% isolated patients, 31.4% ward patients, and 26.31% ICU patients). Aggarwal meta-analysis¹⁹ reports 6.91% prevalence in severe cases of ocular disturbances, Wu et al.²⁴ reported 50% of their conjunctivitis having critical COVID-19 and Wei-jie 2.3% conjunctival congestion.²³

Conjunctivitis patients who underwent conjunctival swab, resulted all negative. This is not very distant from published reports, a meta-analysis performed by Aggarwal et al.¹⁹ reports positivity only in 3.5% of 335 patients from various studies, with or without ocular symptoms, of RNA detected from ocular surface samples, not being fully detailed the stage of the disease at which it was tested.

We may also consider ocular symptoms as part of the flu-like spectrum comorbidity in COVID-19 patients or as an immune mediated reaction. Early or prodromal

conjunctivitis seems more related to an infective role of the virus,²⁵ while latter alterations can be more reactive/immune mediated.¹⁸ Delayed ocular symptoms, including conjunctivitis, are not associated to persistent infection of SARS-CoV2 in upper respiratory tract or conjunctiva.

The presence, survival, and replication of this new virus in ocular surface while causing ocular disease is still unknown, more studies are needed to clarify the viral load role in ocular surface disease.

Conclusion

By analyzing a wide cohort of patients, we demonstrated that there is no positive association between late ocular symptoms and persistence of SARS-CoV2 infection in the upper respiratory tract. Our results highlight that late ocular symptoms cannot be considered as a marker of persistent infection when patients are sent to confirm the resolution of SARS-CoV-2 infection.

None of our symptomatic conjunctivitis patient had viral RNA detected in the conjunctival swab at this stage of COVID19 disease. Although direct examination allowed ophthalmologist to detect conjunctivitis, a limit of the study is that patients were not examined with the slit lamp. Further studies are needed to better understand the epidemiological management of the disease, of crucial importance due to the lack of resources in many countries.

Declaration of conflicting interests


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References

1. Cable J, Heymann DL, Uzicanin A, et al. Concise original report pandemic diseases preparedness and response in the age of COVID-19—a symposium report. 2020; 1–13.
2. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. 2020 Sep; 288: 335–344.
3. ISARIC; 2020. International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). COVID-19 Report: 19 May 2020 [Internet]. [cited 2020 Nov 8]. Available from: https://media.tghn.org/medialibrary/2020/05/ISARIC_Data_Platform_COVID-19_Report_19MAY20.pdf. Accessed 20 November 2020.
4. Zhang JY, Lee KS, Ang LW, et al. Risk factors of severe disease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis and meta-regression analysis. *Clin Infect Dis, Off Publ Infect Dis Soc Am*. 2020 May;
5. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med*. 2020; 201:1430–1434.
6. Kim ES, Chin BS, Kang CK, et al. Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: a preliminary report of the first 28 patients from the Korean cohort study on COVID-19. *J Korean Med Sci [Internet]*. 2020;35:e142–e142. Available from: <https://pubmed.ncbi.nlm.nih.gov/32242348>
7. Güemes-Villahoz N, Burgos-Blasco B, Vidal-Villegas B, et al. Novel insights into the transmission of SARS-CoV-2 through the ocular surface and its detection in tears and conjunctival secretions: a review. *Adv Ther*. 2020;37:4086–4095.
8. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei province, China. *JAMA Ophthalmol*. 2020;138:575–578.
9. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172:577–582.
10. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis*. 2020;20:669–677.
11. Li N, Wang X and Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. *J Med Virol [Internet]*. 2020;10./jmv.25952. Available from: <https://pubmed.ncbi.nlm.nih.gov/32347980>
12. Centers for Disease Control and Prevention (CDC). Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) [Internet]. [cited 2020 Nov 13]. Available from: [cdc.gov](https://www.cdc.gov)
13. Chen L, Liu M, Zhang Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. *Br J Ophthalmol*. 2020;104:748–751.
14. Guo D, Xia J, Wang Y, et al. Relapsing viral keratoconjunctivitis in COVID-19: a case report. *Virol J [Internet]*. 2020;17:97. Available from:
15. Casalino G, Monaco G, Di Sarro PP, et al. Coronavirus disease 2019 presenting with conjunctivitis as the first symptom. *Eye [Internet]*. 2020;34:1235–1236. Available from:
16. Ozturker ZK. Conjunctivitis as sole symptom of COVID-19: a case report and review of literature. *Eur J Ophthalmol [Internet]*. 2020 24;1120672120946287. Available from: <https://pubmed.ncbi.nlm.nih.gov/32703010>
17. Romano MR, Montericcio A, Montalbano C, et al. Facing COVID-19 in ophthalmology department. *Curr Eye Res*. 2020;
18. Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2

- infection. *J Med Virol [Internet]*. 2020;0–3. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32100876>
19. Aggarwal K, Agarwal A, Jaiswal N, et al. Ocular surface manifestations of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *PLoS One*. 2020;15: e0241661.
 20. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients With coronavirus disease 2019 (COVID-19) in hubei province, China. *JAMA Ophthalmol [Internet]*. 2020;2019:4–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32232433>
 21. Hong N, Yu W, Xia J, et al. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. *Acta Ophthalmol*. 2020;
 22. Tostmann A, Bradley J, Bousema T, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, march 2020. *Euro Surveill Bull Eur sur les Mal Transm = Eur Commun Dis Bull*. 2020;25.
 23. Guan W, Ni Z, Hu Y, , et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;1–13.
 24. Wu P, Duan F, Luo C, , et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in hubei province, China. *JAMA Ophthalmol*. 2020;138:575–578.
 25. Scalinci SZ and Trovato Battagliola E. Conjunctivitis can be the only presenting sign and symptom of COVID-19. *IDCases [Internet]*. 2020/04/24. 2020;20:e00774. Available from: <https://pubmed.ncbi.nlm.nih.gov/32373467>