

**CONJUNCTIVITIS AS AN OCULAR MANIFESTATIONS OF COVID-19 – A
SYSTEMATIC REVIEW WITH META-ANALYSIS**

Kalina Trifonova, Kiril Slaveykov

*Medical Faculty, Trakia University, 2 Gen. Stoletov Str, Stara Zagora, 6000, Bulgaria,
kali_tr@yahoo.com, kirilslaveykov@gmail.com*

Abstract

Background: COVID-19 may pose challenges in clinical diagnosis because there is no pathognomonic symptom to detect the disease. It can affect almost every organ of the body. The visual system is no exception.

Aims: to determine the proportion of patients with conjunctivitis diagnosed with COVID-19 in general, conjunctivitis as the first/only sign, discuss the possibility of contamination from the conjunctiva and the relationship with the severity of the disease

Methods: a systematic literature review with meta-analysis. Pubmed, Google scholar were used as a database source.

Results: We included 14 cross-sectional studies of hospitalized patients with COVID-19. The meta-analysis showed that 9,2% of them had conjunctivitis and it was the first or even only sign in 1,6%. Many researches show a relationship between the severity of the disease and manifestation of ocular symptoms. Even though conjunctival swabs are rarely positive for COVID-19, it is still considered a possible way of transmission.

Conclusion: Ophthalmologists should be aware of the possible ocular manifestations of COVID-19 which will help us achieve a proper diagnosis, accurate and early treatment and prevent self-inoculation and further spreading of this life-threatening disease.

Key words: *eye complications, SARS-Cov-2, diagnosis, spreading*

Background: In December 2019, a novel coronavirus (CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China in the city of Wuhan. On March 11, 2020 the World Health Organization formally declared the COVID-19 outbreak a pandemic (7). COVID-19 may pose challenges in clinical diagnosis because there is no pathognomonic symptom to detect the disease. Several clinical symptoms have been frequently reported among COVID-19 patients including but not limited to cough, fever, fatigue, sore throat, nasal obstruction, shortness of breath, headache, sputum production, and hemoptysis (13). However, it can affect almost every organ of the body. The visual system is no exception. Since SARS-CoV-2 may lead to respiratory failure, most of the diagnostic and therapeutic efforts are focused on the consequences of the infection in the respiratory tract. It is important to be aware that other manifestations of the disease exist, especially because they are linked to alternative ways of transmission (2).

Conjunctivitis has been the most commonly reported ocular manifestation of SARS-Cov-2 and it can be the first and sometimes the only sign of the disease (24). Patients infected with SARS-CoV-2 can present with eye redness, ocular irritation, eye soreness, foreign body sensation, tearing, mucoid discharge, eyelid swelling, congestion and chemosis (27). Examination findings include those consistent with mild follicular conjunctivitis, including unilateral or bilateral bulbar conjunctival injection, follicular reaction of the palpebral conjunctiva, watery discharge, and mild eyelid edema. However, Navel et al. observed a case of severe hemorrhagic conjunctivitis and pseudomembrane formation in a patient with onset 19 days after the beginning of systemic symptoms (20). Hu observed hemorrhagic bilateral conjunctivitis with pseudomembrane formation and chemosis five days after the positive test (12). A case report published by Cheema et al. described the first case of keratoconjunctivitis as the presenting manifestation of COVID-19 (4).

Aims: to determine the proportion of patients with conjunctivitis diagnosed with COVID-19 in general, conjunctivitis as the first/only sign, discuss the possibility of contamination from the conjunctiva and the relationship with the severity of the disease.

Methods: We made a systematic literature review with meta-analysis using one-group meta-analysis in a random-effects model. The software we used is OpenMetaAnalyst, which is available from <http://www.cebm.brown.edu/openmeta/>. For database selection we used Pubmed, Google scholar and free search. Only large cross-sectional studies of hospitalized adult patients were included in the study. We excluded single case reports, studies from children’s hospitals, and outpatient studies. Subgroup analyses including only studies that had reported on a given outcome was undertaken.

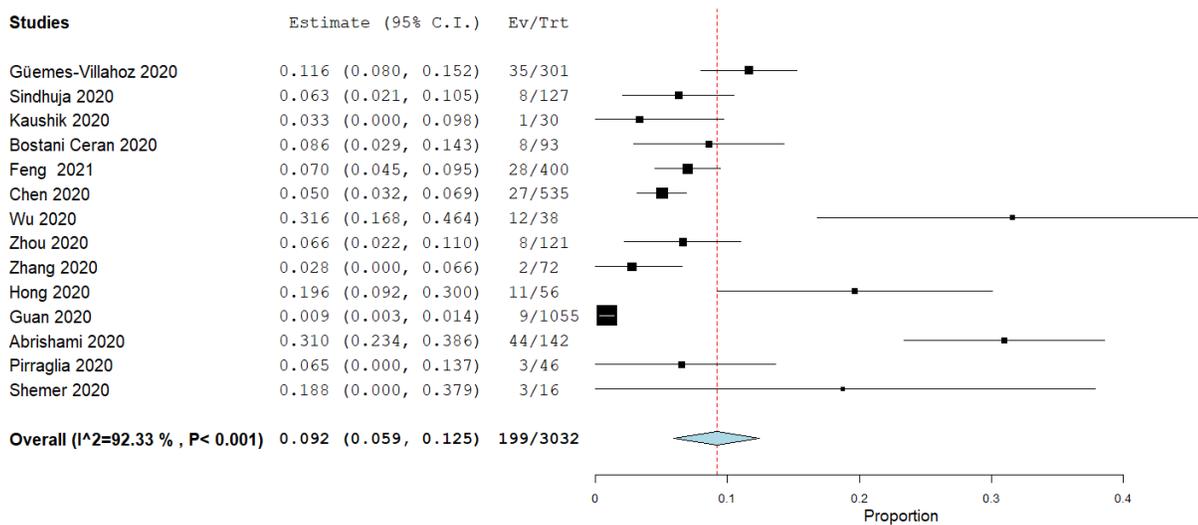
Results and discussion: Fourteen articles met the inclusion criteria and were assessed for the systematic review (table 1). It includes 3032 patients which were hospitalized for COVID-19 in eight different countries. From them 199 had symptoms of conjunctivitis. Overall, the pooled prevalence of conjunctivitis among COVID-19 patients was (fig. 1) 9,2% (95% confidence interval; 5,9-12,5). A random-effects model was utilized due to the heterogeneity ($I^2 = 92,33%$) between studies.

Table 1 Conjunctivitis as a COVID-19 complication in cross-sectional studies of hospitalized patients

Authors	Study base	Study subjects	Patients with conjunctivitis	Relationship with the severity of the disease	First/Only symptom	Positive Swabs
1. Güemes-Villahoz N, 2020 (10)	Spain	301	35 (11,6%)	No	---	---
2. Sindhuja K, 2020 (26)	India	127	8 (6,29%)	---	3(2,3%)	----
3. Kaushik J., 2020 (14)	India	30	1(3,35%)		---	2(6,7%)
4. Bostani Ceran B, 2020 (3)	Turkey	93	8(8,6%)	Yes	----	----
5. Feng Y, 2021 (8)	USA	400	28(7%)	No	----	---
6. Chen L, 2020 (5)	China	535	27(5%)	No	4(0,7%)	---
7. Wu P, 2020 (27)	China	38	12(31,6%)	Yes	1(2,6%)	2(5,2%)
8. Zhou Y, 2020 (32)	China	121	8(6,6%)	---	----	3(2,4%)
9. Zhang X, 2020(31)	China	72	2(2,78%)	---	1(1,39%)	1(1,39%)
10. Hong N, 2020 (11)	China	56	11(20%)	---	4(7,1%)	1(1,7%)
11. Guan W, 2020 (9)	China	1055	9(0,8%)	---	---	---

12. Abrishami M, 2020 (1)	Iran	142	44 (31%)	Yes	---	----
13. Pirraglia M, 2020 (22)	Italy	46	3(7%)	----	---	0(0%)
14. Shemer A, 2020 (25)	Israel	16	3(19%)	Yes	2(12%)	0(0%)

Fig. 1 Prevalence of conjunctivitis in patients with COVID-19



Ocular manifestations are mostly reported during the middle phase of the disease, and in patients with severe pneumonia (27). However, there are many single case reports of conjunctivitis being the first and even only sign of the disease (4, 6, 15, 21, 23, 29). We included in our meta-analysis six of the articles that mentioned this information. It showed that the pooled prevalence of patients with coronavirus that had conjunctivitis as the first or sole sign of SARS-CoV-2 infection was 1,6% (95% Confidence interval, 0,2-3) from a total of 844 patients. From those presented with conjunctivitis in 23% it was an initial sign of the disease.

Four studies included in our systematic review showed a relationship between the severity of the disease and ocular manifestation of COVID-19 (3). Wu et al described in a series of 38 patients that those with conjunctivitis were more likely to have higher white blood cell and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms. A meta-analysis by Loffreto (17) shows that the rate of conjunctivitis is 3% and 0.7% in severe and nonsevere COVID-19 patients, respectively. It showed that patients with severe COVID-19 infection had, at admission to the hospital, increased incidence of conjunctivitis (odds ratio: 3.4; 95% confidence interval:1.1-10.2; P=.030). Abrishami et al found a higher frequency of conjunctival hyperemia and chemosis in patients admitted to the ICU compared to those in other wards. They believe that ophthalmologists should be a member of the therapeutic team for comprehensive

management of these patients (1). Bostanci Ceran et al found that older age, high fever, increased neutrophil/lymphocyte ratio, and high levels of acute phase reactants seemed to be risk factors for ocular involvement (3).

SARS-CoV-2 uses angiotensin converting enzyme-2 (ACE2) as its receptor on human cells, and binding to this facilitates infection (30). Expression of the gene for ACE2 has been shown in corneal and conjunctival epithelial cells, and preliminary evidence has been presented for the presence of the protein associated with these cells (16). The mechanisms of ocular transmission have not been fully elucidated, but studies have demonstrated the presence of viral RNA in the conjunctival sac and aerosolized secretions of contaminated patients; these droplets may come into contact with the eyes of uninfected bystanders, entering the respiratory system through the nose and gaining access to the lungs. Studies show that the virus can be effectively transmitted through the eyes, underscoring the importance of protective goggles for health care workers or potential transmitters of the virus, in addition to the need for additional education measures to encourage hand hygiene and discourage touching of the eyes (19). Chen et al showed that hand-eye contact is possibly a risk factor for conjunctival congestion in COVID-19 patients (5). Zhang et al report clinical cases in which ocular transmission was the possible mechanism (31).

On the other hand, contamination with the coronavirus from conjunctival secretions or tears can be controversial due to the low percentage of the virus proven from conjunctival swabs with PCR tests. We included information from 7 studies concerning collection of tear/conjunctival secretion samples from a total of 379 patients and calculated the pooled detection rate. The rate of detecting SARS-CoV-2 was very low - only 2% (95% Confidence interval; 0,6-3). According to Xia et al this possibly indicates a low prevalence of the virus in conjunctival secretions and tears (28). Alternatively, the virus could be present but with viral loads below the detection thresholds of existing PCR diagnosis techniques (6). A large number of ophthalmologists involved in the diagnosis and treatment of the disease on a daily basis accidentally acquired the disease, so that the transmission of SARS-COV-2 with tears and conjunctival secretions should not be ignored (18). However, it would be impractical to make the confirmative diagnosis of COVID-19 using samples from the eye.

Limitations: Many researchers probably did not pay attention to the ocular problems because they dealt with more serious issues. The studies are also bias because they include only hospitalized patients thus many patients with mild symptoms of coronavirus are not included.

Conclusion: Ophthalmologists should be aware of the possible ocular manifestations of COVID-19 which will help us achieve a proper diagnosis, accurate and early treatment and help with preventing self-inoculation and spreading this life-threatening disease. Further research needs to be done on larger groups of patients in order to have more accurate results considering the percentage of patients with ocular manifestations of COVID-19.

Literature:

1. Abrishami M, Tohidinezhad F, Daneshvar R, et al, Ocular Manifestations of Hospitalized Patients with COVID-19 in Northeast of Iran. *Ocul Immunol Inflamm*, 3;28(5):739-744, 2020
2. Bertoli F, Veritti D, Danese C, et al. Ocular Findings in COVID-19 Patients: A Review of Direct Manifestations and Indirect Effects on the Eye. *J Ophthalmol*. 2020
3. Bostanci Ceran B, Ozates S. Ocular manifestations of coronavirus disease 2019. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(9):1959-1963, 2020

4. Cheema M, Aghazadeh H, Nazarali S, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Can J Ophthalmol*. Epub ahead of print 2 April 2020
5. Chen L, Deng C, Chen X, et al. Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: a cross-sectional study. *Acta Ophthalmol*, 98(8):e951-e959, 2020
6. Daruich A, Martin D, Bremond-Gignac D. Ocular manifestation as first sign of Coronavirus Disease 2019 (COVID-19): Interest of telemedicine during the pandemic context. *J Fr Ophtalmol*. 2020;43(5):389-391, 2020
7. Douglas, K., Douglas, V., Moschos M., Ocular Manifestations of COVID-19 (SARS-CoV-2): A Critical Review of Current Literature. *In Vivo*, 34(3 suppl), 1619–1628, 2020
8. Feng Y, Park J, Zhou Y, Armenti ST, Musch DC, Mian SI. Ocular Manifestations of Hospitalized COVID-19 Patients in a Tertiary Care Academic Medical Center in the United States: A Cross-Sectional Study. *Clin Ophthalmol*, r 13;15:1551-1556, 2021
9. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Zhong, N., Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*, 382(18), 1708-1720, 2020
10. Güemes-Villahoz N, Burgos-Blasco B, García-Feijoó J, et al. Conjunctivitis in COVID-19 patients: frequency and clinical presentation. *Graefes Arch Clin Exp Ophthalmol*, 258(11):2501-2507, 2020
11. Hong N, Yu W, Xia J, Shen Y, Yap M, Han W. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19 [published online ahead of print, 2020 Apr 26], *Acta Ophthalmol*, 2020
12. Hu, K, Patel J., Swiston C et al, Ophthalmic manifestations of coronavirus (COVID-19)." *StatPearls* [Internet], 2021
13. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*, 69:1002–1009, 2020
14. Kaushik, J., Marwah, V., Singh, A., Chaitanya, Y. V. K., Gupta, R. M., Kumar, P., Estimation of conjunctival swab and nasopharyngeal swab specimens for viral nucleic acid detection in Coronavirus disease 2019 patients to compare the viral load, *Latin American Journal of Ophthalmology* 4, 2021
15. Khavandi S, Tabibzadeh E, Naderan M, Shoar S. Corona virus disease-19 (COVID-19) presenting as conjunctivitis: atypically high-risk during a pandemic. *Cont Lens Anterior Eye*; 43(3):211–212, 2020
16. Lin L, Yan S, Xin P et al. Expression of SARS coronavirus S protein functional receptor-angiotensin-converting enzyme 2 in human cornea and conjunctiva. *Chin Ophthalmic Res*; 22: 561–564, 2004
17. Loffredo L, Pacella F, Pacella E, Tiscione G, Oliva A, Violi F. Conjunctivitis and COVID-19: A meta-analysis. *J Med Virol*; 92(9):1413-1414, 2020
18. Lu C, Liu X, Jia Z., 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet*; 395:e39 10.1016/S0140-6736(20)30313-5, 2020

19. Matos A, Sarquis I, Santos A, Cabral L, COVID-19: risk of ocular transmission in health care professionals. *Rev Bras Med Trab*; 19(1):82-87, 2021
20. Navel V, Chiambaretta F, Dutheil F. Haemorrhagic conjunctivitis with pseudomembranous related to SARS-CoV-2. *Am J Ophthalmol Case Rep.*, 19:100735, 2020
21. Ozturker Z., Conjunctivitis as sole symptom of COVID-19: A case report and review of literature [published correction appears in *Eur J Ophthalmol.* 2020 Aug 27;1120672120956486]. *Eur J Ophthalmol*; 31(2):NP161-NP166, 2021
22. Pirraglia M, Ceccarelli G, Cerini A, Visioli G, d'Ettorre G, Mastroianni CM, et al. Retinal involvement and ocular findings in COVID-19 pneumonia patients. *Sci Rep*, 10:17419, 2020
23. Scalinci S., Battagliola E, Conjunctivitis can be the only presenting sign and symptom of COVID-19, *IDCases* 20: e00774, 2020
24. Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. *Indian J Ophthalmol*; 69(3):488-509, 2021
25. Shemer A, Einan-Lifshitz A, Itah A, Dubinsky-Pertzov B, Pras E, Hecht I. Ocular involvement in coronavirus disease 2019 (COVID-19): a clinical and molecular analysis. *Int Ophthalmol*; 14:1-8, 2020
26. Sindhuja K, Lomi N, Asif MI, Tandon R. Clinical profile and prevalence of conjunctivitis in mild COVID-19 patients in a tertiary care COVID-19 hospital: A retrospective cross-sectional study. *Indian J Ophthalmol*, 68(8):1546-1550, 2020
27. 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*;138(5):575-578, 2020
28. 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
29. Xuejie, L. I., Ming W, Jing D, et al, Novel coronavirus disease with conjunctivitis and conjunctivitis as first symptom: two cases report, *Chin J Exp Ophthalmol* 38: E002, 2020
30. Yan R, Zhang Y, Li Y et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*; 367: 1444–1448, 2020
31. Zhang X, Chen X, Chen L, et al. The evidence of SARS-CoV-2 infection on ocular surface. *Ocul Surf*;18(3):360-362, 2020
32. Zhou Y, Duan C, Zeng Y, et al, Ocular findings and proportion with conjunctival SARS-COV-2 in COVID-19 patients. *Ophthalmology*; 127: 982–983, 2020