Conjunctival Findings in Patients With Coronavirus Disease 2019

To the Editor We read with interest the article by Wu et al1 on ocular findings in coronavirus disease 2019 (COVID-19). We wish to understand more about the study in the following aspects.

First, the authors reported conjunctivitis in 12 of 38 patients with COVID-19 in a consecutive case series. Notably, the prevalence of conjunctival congestion was merely 0.8% (9 of 1109 patients) in another larger study from China.2 Could the authors clarify if they are implying that the conjunctivitis was associated with COVID-19 affecting the conjunctiva (ie, viral conjunctivitis) or nonspecific signs from conjunctival congestion or chemosis from COVID-19’s systemic manifestations,3 intensive care,4 or other benign causes (eg, dry eyes, conjunctival irritation)?

Second, 2 patients had positive conjunctival swab results, with each having different ocular manifestations. What do the authors hypothesize are the infective mechanisms? For example, could it be direct conjunctival invasion or infection via nasopharyngeal secretions?

Third, could the authors provide detailed clinical features of suspected cases? Do they have any clinical photographs? Also, how were the assessments performed, and what instruments were used to assess the conjunctivitis (eg, slit-lamp biomicroscopy, portable slitlamp, or handheld flashlight)? The authors reported 4 features: epiphora, chemosis, hyperemia, and secretions. However, each was used in isolation to diagnose conjunctivitis, which may not be specific. Could the authors indicate if there were supportive features, such as subjective complaints (itch and pain), the character of the discharge, and any papillary or follicular reaction of the palpebral conjunctiva?

Lastly, could the authors provide more about the course and outcome of the reported cases of conjunctivitis? What treatments were used? Were there any ophthalmic sequelae, such as corneal, episcleral, or scleral involvement? We thank the authors for considering these clarifications and providing some additional information.

Rupesh Agrawal, MMed, MD
Jianbin Ding
Xin Wei, MMed

Author Affiliations: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore (Agrawal, Wei); Singapore Eye Research Institute, Singapore (Agrawal); Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom (Agrawal); School of Material Science and Engineering, Nanyang Technological University, Singapore (Agrawal); Lee Kang Chian School of Medicine, Nanyang Technological University, Singapore (Agrawal, Ding).

Corresponding Author: Rupesh Agrawal, MMed, MD, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 11, Jalan Tan Tock Seng, Singapore 308433 (rupesh.agrawal@ttsh.com.sg).


Conflict of Interest Disclosures: None reported.


To the Editor We read with interest the article of Wu et al3 on the characteristics of ocular findings in patients with novel coronavirus disease (COVID-19). Wu et al3 reported that ocular manifestations consistent with conjunctivitis were found in 12 of 38 patients (31.6%) with COVID-19 and concluded that conjunctival involvement is associated with the severity of COVID-19, and the eye is not likely to play as a transmissi

© 2020 American Medical Association. All rights reserved.
Although conjunctiva is directly exposed to infectious droplets and fomites contaminating the ocular surface via splashing or hand-to-eye touching, viral conjunctivitis rarely occurs in patients with COVID-19.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) Viral conjunctivitis has been reported in 5 cases and SARS-CoV-2 RNA detected in 5 patients with COVID-19.\(^2\) These reports, however, do not determine the prevalence among individuals with COVID-19. The rarity of viral conjunctivitis in patients with COVID-19 may be interpreted by the less abundant expression of angiotensin-converting enzyme 2, the entry receptor of SARS-CoV-2, on conjunctival epithelial cells and poor binding capability of angiotensin-converting enzyme 2 protein on conjunctival epithelial cells to SARS-CoV-2 spike protein, as well as the protective effect of the antimicrobial agents in tears (eg, lactoferrin and secretory IgA) and tear rinsing, which continuously eliminate the viruses on ocular surface into nasolacrical duct.\(^1\) Hence, the conjunctiva is likely not a preferred portal of entry for SARS-CoV-2 to cause respiratory tract infection; SARS-CoV-2 exposed to the ocular surface may be continuously transported to nasal and nasopharyngeal mucosa by constant tear rinsing through the nasolacrical duct and then cause COVID-19.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\)

Zhe Liu, MD
Qing Xiao, MD
Chuan-bin Sun, MD, PhD

Author Affiliations: Department of Ophthalmology, Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Hangzhou, Zhejiang Province, China (Liu); Eye Center, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China (Xiao, Sun).

Corresponding Author: Chuan-bin Sun, MD, PhD, Eye Center, Second Affiliated Hospital of Zhejiang University School of Medicine, Jiefang Rd 88, Hangzhou 310009, Zhejiang Province, China (sunshine2012@zju.edu.cn).


Conflict of Interest Disclosures: None reported.


To the Editor We congratulate Wu et al\(^3\) for their article on the ocular manifestations of coronavirus disease 2019 (COVID-19). The authors reported that 12 of 38 patients (31.6%) with COVID-19 had ocular signs and symptoms. They described epiphora, conjunctival congestion, increased secretions, and chemosis that occurred more frequently in patients with severe systemic manifestations. Although it is true that these signs may occur in viral conjunctivitis, they are also very common findings and may occur in other ocular conditions, such as blepharitis, uveitis, keratitis, or systemic conditions, such as fluid overload. How did the authors account for whether these other diagnoses were coincidental to COVID-19? In addition, could the authors explain how the ocular assessment was performed (eg, by an ophthalmologist vs another specialist, such as an internist)? Also, could the authors summarize at what point in the course of the disease the reverse transcriptase-polymerase chain reaction test was performed in each patient, which may affect the percentages of positive vs negative results obtained from the conjunctival swabs?

Florence Cabot, MD
Kara M. Cavuto, MD
Jean-Marie Parel, PhD

Author Affiliations: Ophthalmic Biophysics Center, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.

Corresponding Author: Jean-Marie Parel, PhD, Ophthalmic Biophysics Center, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 1638 NW 10th Ave, Miami, FL 33136 (jmparel@med.miami.edu).


Conflict of Interest Disclosures: Dr Parel reported a patent pending (62/812685). No other disclosures were reported.

To the Editor We read with interest the article by Wu et al\(^3\) evaluating the ocular manifestations in 38 patients with coronavirus disease 2019 (COVID-19). Contrary to another recent article reporting only 8 of 121 patients (6.6%) having ocular symptoms,\(^2\) Wu reported a higher proportion: 12 of 38 patients (31.6%) with conjunctival hyperemia, chemosis, epiphora, or increased secretions, which they described as “consistent with conjunctivitis.”\(^3\)\(^1\)\(^(p<0.05)\) We have reservations about their clinical descriptions of these ocular manifestations, independent of the COVID-19 laboratory findings from the conjunctival swabs.

In their article, two-thirds of these 12 patients were considered to have severe or critical cases. The constellation of manifestations described is compatible with signs of ocular surface disease (OSD), which are present in a variable proportion of patients in intensive care units.\(^3\) Chemosis, or conjunctival edema, also termed ventilator eye, can be present in 9% to 60% of patients in the intensive care unit.\(^4\) Positive pressure in mechanical ventilation and tight endotracheal tube taping increases jugular venous pressure, which decreases venous return from ocular vessels and results in the sequestration of fluid in the conjunctiva. A high positive end-expiratory pressure during mechanical ventilation encourages sodium and water retention, further provoking chemosis. A prone position can improve the ventilation-to-perfusion ratio. The gravitational force during the prone position can lead to venous pooling in the dependent area, potentially giving rise to facial and conjunctival edema. Sedation and muscle relaxant used in these patients also can impair the blink reflex and eyelid muscle tone, which can increase the risk of developing OSD.
Patients who are critically ill often have electrolyte disturbances and fluid overload. This loss of fluid equilibrium between the intravascular and extravascular compartments normally maintained by osmotic and hydrostatic forces can lead to chemosis. Chemosis itself can lead to lagophthalmos and tear film disruption. We believe that exposure keratopathy or OSD are common in this setting and may be more likely than infectious conjunctivitis to produce these manifestations. It would be of interest if the authors could provide data regarding patients receiving mechanical ventilation, in the prone position, or receiving prophylactic eye ointment or eyelid-taping treatment. Such data might help differentiate the real causative mechanisms of the ocular manifestations.

We agree with the authors that not carrying out a detailed ocular examination to exclude intraocular diseases is justified to minimize the spread of transmission. However, without a detailed examination to evaluate the defining features of conjunctivitis, such as conjunctival papillae or follicles, it may be premature to attribute these ophthalmic manifestations observed by the authors to conjunctivitis.

Kelvin H. Wan, MBChB, MRCS
Suber S. Huang, MD, MBA
Dennis S. C. Lam, MD

Author Affiliations: Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong (Wan); Retina Center of Ohio, Cleveland, Ohio (Huang); C-MER Dennis Lam & Partners Eye Center, C-MER International Eye Care Group, Hong Kong (Lam).

Corresponding Author: Dennis S. C. Lam, MD, C-MER Dennis Lam & Partners Eye Center, C-MER International Eye Care Group, 1-3 Pedder St, Central Building, Ste 1515, Central, Hong Kong (dennislam@hkcer.com).


Conflict of Interest Disclosures: None reported.


In Reply We thank the readers for their interest in our previous report on the ocular findings of patients with coronavirus disease 2019 (COVID-19). With great respect, we carefully have read those letters and we provide our responses.

Our study was a cross-sectional study in which each patient was at a different stage of COVID-19 when reverse transcription–polymerase chain reaction testing was performed. We only enrolled patients who were hospitalized within the week and had ocular symptoms or signs present after COVID-19. When collecting specimens, we recorded ocular histories with questionnaires and clinicians (nonophthalmologists) examined eyes with bedside flashlights. If possible, eye photographs were taken by cell phone in cases with ocular abnormalities. To minimize the spread of transmission, ophthalmologists were not allowed to enter the isolation ward, and no enrolled patients received any professional ocular therapy.

Our data showed that among 38 patients, 12 had ocular abnormalities (eg, ocular symptoms and/or signs). Similar findings were reported by Hong et al in Zhejiang, China, and Chen et al in Wuhan, China. As the readers have questioned, we do not think those ocular findings were specific to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. In our study, 2 patients had positive findings on reverse transcription–polymerase chain reaction testing that were possibly associated with SARS-CoV-2 infection. Six (including these 2 patients) of 12 patients were treated with ventilators. We agree with Wan and colleagues’ comments that the constellation of manifestations were also possibly because of the use of ventilators, electrolyte disturbances, and fluid overload. In addition, secondary bacterial infection, long-term short-distance reading, and dry eye may also be the causes of ocular abnormalities. Thus, the diagnosis of viral conjunctivitis was not accurate because of the absence of viral nucleotides found.

Recently, studies have shown that angiotensin-converting enzyme 2, a receptor of SARS-CoV-2, is expressed in the cornea and conjunctiva, suggesting that ocular surface tissue is a potential target tissue infected by SARS-CoV-2. Similarly, some case reports, studies in cells and animals, and epidemiological investigations have shown that the eye is a transmission route of SARS-CoV-2 infection via invasion of the ocular surface tissue or transportation to the respiratory system through the nasolacrimal duct. Thus, we believe that the conjunctiva is a preferred portal of entry for SARS-CoV-2 to cause COVID-19. In addition, high levels of angiotensin-converting enzyme 2 in the retina and intraocular fluids have been reported, which may result in intraocular inflammation, although we have found no literature on this topic. We have stated that 12 patients had ocular surface manifestations, in contrast with the intraocular damage that may lead to blurry vision.

In conclusion, we found that 2 of the 38 patients yielded positive findings in their conjunctiva and the ocular symptoms and/or signs commonly appeared in patients with severe systemic disease. Combined with the up-to-date study results and our report, it appears that the eye plays as a transmission route of SARS-CoV-2 infection, which might, in turn, serve as a source of its spread, especially in those of patients with critical illness. We believe that eye protection is very necessary, especially for medical staff.

Ping Wu, MD
Kaili Wu, MD
Liang Liang, MD

Author Affiliations: Department of Ophthalmology, Yichang Central People’s Hospital, The First College of Medical Science, Three Gorges University, Yichang, China (P. Wu, Liang); Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-Sen University, Guangzhou, China (K. Wu).

© 2020 American Medical Association. All rights reserved.
Corresponding Author: Liang Liang, MD, Department of Ophthalmology, Yichang Central People’s Hospital, The First College of Clinical Medical Science, Three Gorges University, Yichang 443003, China (liangliang419519@163.com); and Kaili Wu, MD, Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-Sen University, Guangzhou 510060, China (wukaili@mail.sysu.edu.cn).


Conflict of Interest Disclosures: None reported.


CORRECTION

Error in Figure Legend: The Brief Report titled “Changes in Treatment-Naive Pigment Epithelial Detachments Associated With the Initial Anti–Vascular Endothelial Growth Factor Injection: A Post Hoc Analysis From the HARBOR Trial,” published online December 17, 2020, was corrected to fix the legend of Figure 2. An additional sentence at the end of the legend will read: “Vertical bars represent 95% CI.” This article was corrected online.


Error in Byline: The Research Letter “Intravitreal Anti–Vascular Endothelial Growth Factor Use in France During the Coronavirus Disease 2019 Pandemic,” published online December 17, 2020, had an error in the byline. The surname of first author Sophie Billiotide Gage was listed as de Gage. Her full surname is Billiotide Gage. The error has been corrected.


Error in Unit of Measure for Total Choroidal Area and Luminal Area: In the Original Investigation titled, “Characterization of Retinal Microvascular and Choroidal Structural Changes in Parkinson Disease,” which published online December 23, 2020, in JAMA Ophthalmology,1 the unit of measure for total choroidal area and luminal area should be units² instead of pixels². This article was corrected online.


Error in Data Presentation in Text: In the Original Investigation by Xie et al titled “Change in Postoperative Opioid Prescribing Patterns for Oculoplastic and Orbital Procedures Associated With State Opioid Legislation,” published online December 10, 2020, in JAMA Ophthalmology,1 the data for brow-lift and blepharoptosis repair were transposed in the second-to-last sentence of the second paragraph of the Results section. The sentence should read as follows: “In contrast, soft tissue procedures had a lower mean (SD) amount of opioids prescribed (brow-lift: 73.2 [37.8] MMEs; blepharoptosis repair: 64.7 [30.5] MMEs).” This article was corrected online.