Ophthalmol Ther
https://doi.org/10.1007/s40123-020-00260-y

REVIEW

COVID-19 Disease and Ophthalmology: An Update

María A. Amesty · Jorge L. Alió del Barrio · Jorge L. Alió

Received: April 28, 2020

ABSTRACT

The worldwide outbreak of the severe and acute respiratory coronavirus disease (COVID-19) caused by the coronavirus strain SARS-CoV-2 is currently the focal point of discussion due to the suffering this syndrome is causing to humanity. However, the ophthalmological implications of this syndrome has not yet been well described. Both eyes and tears as portals of entry and sources of contagion have been the subject of debate by many authors. The purpose of this review is to summarize the evidence currently available on COVID-19 and its ocular implications and manifestations, in both animals and humans, with the aim to facilitate prevention and educate the ophthalmological community on this subject. A review of the literature revealed that the results of some studies suggest that ocular symptoms commonly appear in patients with severe COVID-19 pneumonia and that it is possible to isolate the virus from the conjunctival sac of these patients. Conjunctivitis is not a common manifestation of the disease, but contact with infected eyes could be one route of transmission. Consequently, ophthalmologists need to have correct prevention strategies in place. Some guidelines regarding the prevention and management of ophthalmology clinics are reviewed. However, well-designed trials should be conducted to rule out other ocular manifestations that may result from COVID-19 infection and to understand the transmission of the virus through the eyes.

Keywords: Conjunctivitis; Coronavirus; COVID-1; Ocular transmission; Ophthalmology; SARS-CoV-2

Digital Features To view digital features for this article go to: https://doi.org/10.6084/m9.figshare.12265232.

M. A. Amesty
Oculoplastic Department, Vissum (Grupo Miranza), Alicante, Spain

J. L. Alió del Barrio · J. L. Alió (✉)
Cornea, Cataract and Refractive Surgery Unit, Vissum (Grupo Miranza), Alicante, Spain
e-mail: jlalio@vissum.com

J. L. Alió del Barrio · J. L. Alió
Division of Ophthalmology, School of Medicine, Universidad Miguel Hernández, Alicante, Spain

Published online: 22 May 2020

Key Summary Points

The purpose of this review is to summarize the evidence currently available on COVID-19 and its ocular implications and manifestations, in both animals and humans, with the aim to facilitate prevention and educate the ophthalmological community on this subject.

Conjunctivitis is not a common manifestation of the disease, but contact with infected eyes could be one route of disease transmission.

Some guidelines regarding prevention and management of ophthalmology clinic are reviewed.

INTRODUCTION

Since December 2019, humanity has been having to deal with the emergence of a severe and acute respiratory coronavirus disease (COVID-19), caused by the strain of coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The respiratory problems caused by this pathogen is well known, but the ophthalmological implications of the syndrome have not yet been well described.

Coronavirus disease is not a new pathology. Three human coronaviruses have been known to exist since the mid-1960s: human coronavirus 229E (HCoV-229E), human coronavirus OC43 (HCoV-OC43) and severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) [1–9]. In 2004, human coronavirus NL63 (HCoV-NL63), a novel human coronavirus to date, was reported in a 7-month-old child suffering from bronchiolitis and conjunctivitis [10, 11]. The *Coronaviridae* family of viruses consist of enveloped viruses with a large plus-strand RNA genome (27–32 kb) that is capped and polyadenylated. Each serology type is characterized by a specific host range and genome sequence.

The most pathogenic of these four types of coronaviruses is SARS-CoV, which causes a life-threatening pneumonia [12–14]. This virus is likely to reside in animals and can affect humans through zoonotic transmission [15, 16]. Coronaviruses have been identified in mice, rats, chickens, turkeys, swine, dogs, horses, rabbits, cats and humans. They can cause a variety of health problems in humans, including gastroenteritis, respiratory tract problems [17, 18] and conjunctivitis [10, 11, 19–31].

The authors of a recent study concluded that one-third of patients with COVID-19 had ocular abnormalities, a frequent manisfestation in patients with more severe disease and that although there is a low prevalence of SARS-CoV-2 in tears, it is possible to transmit the disease through ocular secretions [31]. Therefore, taking into consideration that there are more reports in the literature associating coronavirus and ophthalmic problems, the aim of this narrative review is to summarize, from an ophthalmological perspective, the pathogeny, the portal of entry and implantation of the virus at the conjunctiva, its ophthalmic implications, ocular complications, prevention in the ophthalmology context and possible treatment of the ocular disease. The relationship between COVID-19 and the ocular surface (conjunctiva, corneal epithelium and tear film) as a potencial portal of entry and as a transmission mechanism is currently under discussion due to the high transmission rate of the disease.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CLINICAL EVIDENCE ON COVID-19 AND EYE DISEASE

Etiology and Pathogenesis of COVID-19

In general, coronaviruses are able to cause a wide range of upper respiratory infections (common cold: alphacoronavirus HCoV-229E,

alphacoronavirus HCoV-NL63, betacoronavirus HCoV-OC43 and HCoV-HKU1), whereas other betacoronaviruses, such as SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), are responsible for more aggressive lower respiratory problems considered to be atypical pneumonias. The different infection sites are likely to be related to the presence of a viral surface spike composed of a dipeptidyl peptidase 4 glycoprotein that has a human receptor in the lower respiratory tract, known as angiotensin converting enzyme 2 (ACE2). Both SARS-CoV and MERS-CoV have this surface spike glycoprotein [32–34].

From the genetic point of view, SARS-CoV-2 is about 70% similar to SARS-CoV and, therefore, it is capable of using the same cell entry receptor (ACE2) to infect human cells [35, 36]. However, the SARS-CoV-2 glycoprotein spike binds to ACE2 human receptors at a 10- to 20-fold higher affinity than SARS-CoV [37].

Once SARS-CoV-2 enters the alveolar epithelial cells, its fast replication rate triggers a strong immune response causing cytokine storm syndrome (hypercytokinemia) and subsequence pulmonary tissue damage. In general, hypercytokinemias consist of a group of disorders that produce an elevation of the pro-inflammatory cytokines. These cytokines are an important cause of acute respiratory distress syndrome (ARDS) and multiple organ failure [38–40]. One analysis of the first 99 cases of SARS-CoV-2 revealed that a cytokine storm occurred in patients with severe COVID-19, of whom 17% had ARDS; among the latter patients, 11% deteriorated very rapidly and died of multiple organ failure [41]. In addition, the number of T cells (CD4 and CD8) are decreased in patients infected with SARS-CoV-2, suggesting a decreased immune function that subsequently allows a secondary infection that could worsen the respiratory failure [42].

Both viral diseases and immune problems can lead to ocular manifestations, such as conjunctivitis, uveitis, retinitis, among others. It is difficult to determine the pathogeny of the ophthalmic involvement. However, since the virus has been cultured from conjunctival secretions [43], COVID-19 ophthalmopathy is more likely to be related to the own virus infestation rather than the secondary immune reaction that the infection may cause.

Portal of Entry

It is known that SARS-CoV-2 can be transmitted through direct or indirect contact with mucous membranes in the eyes, mouth or nose [28, 44, 45] and that the respiratory tract should not be considered the only route of transmission. In fact, recent studies associate the enteric symptoms of COVID-19, such as diarrhea, nausea, vomiting [46, 47], with invaded ACE2-expressing enterocytes [48], with the oral–fecal route being another potential portal of entry.

Additional studies are required to test different portal of entries. Proposed theories include [30]:

1. Direct inoculation of the conjunctiva from infected droplets.
2. Migration of upper respiratory tract infection through the nasolacrimal duct.
3. Hematogenous infection of the lacrimal gland.

Evidence of Ocular Manifestations

Our analysis of some of the studies included in this narrative review (see Table 1) revealed that the most common ophthalmologic sign related to coronavirus infection was inflammation of the conjunctiva (conjunctivitis). Among the studies reviewed, six were performed in animals (feline, murine, canine and bird experimental models) [19–21, 24–26] and the other 11 in humans [10, 11, 22, 23, 27–31].

The first time that conjunctivitis was associated to a human coronavirus was in 2004, in a 7-month-old child [10, 11], then in 2005 [22, 23], due to the great interest in understanding the clinical manifestations of coronavirus during the first SARS-CoV crisis. However, it is not until this new 2019–2020 outbreak that conjunctivitis has once again been associated to a coronavirus outbreak and taken to be a sign of COVID-19.

In a retrospective study, Vabret et al. investigated HCoV-NL63 infection in hospitalized

Table 1 Clinical evidence of coronavirus ophthalmic manifestions

First author [reference]	Year	Type of study	Main ocular problem	Other problems	Upper respiratory tract problems	Gastrointestinal signs
Hök K [19]	1993	Experimental	Conjunctivitis		Present	
Hök K [20]	1993	Experimental	Conjunctivitis		Present	Present
van der Hoek L [10]	2004	Clinical	Conjunctivitis		Present (bronchiolitis)	
Ahmad K [11]	2004	Clinical	Conjunctivitis		Present (bronchiolitis)	
Decaro N [24]	2004	Experimental	Conjunctivitis		Present (respiratory distress)	Present (enteritis)
Loon S-C [49]	2004	Clinical	Not specified		Present (SARS)	
Chan WM [51]	2004	Clinical	Not specified		Present (SARS)	
Fouchier RA [22]	2005	Clinical	Conjunctivitis		Present (pneumonia, SARS)	
Vabret A [23]	2005	Clinical	Conjunctivitis	Otitis, pharyngitis	Present (rhinitis, bronchiolitis)	Present
Terregino C [24]	2008	Experimental	Conjunctivitis		Present	
Ledbetter EC [25]	2009	Experimental	Conjunctivitis			
Stiles J [26]	2014	Experimental	Uveitis			
Chang LY [27]	2014	Clinical	Conjunctivitis			
Xia J [28]	2020	Clinical	Conjunctivitis			
Lai THT [29]	2020	Clinical	Not specified			
Seah I [30]	2020	Clinical	Conjunctivitis	Uveitis, retinitis, optic neuritis		
Wu P [31]	2020	Clinical	Conjunctivitis	Epiphora		
Chen L [43]	2020	Clinical	Conjunctivitis		Present (sore throat)	Present (diarrhea)
Zhang H [48]	2020		No evidence[a]			

Table 1 continued

First author [reference]	Year	Type of study	Main ocular problem	Other problems	Upper respiratory tract problems	Gastrointestinal signs
Cheema M [67]	2020	Case report	Keratoconjunctivitis		Present (rhinorrhea, cough, nasal congestion)	
Lan QQ [70]	2020	Clinical	No evidence[a]			
Hu K [71]	2020	Clinical review	Conjunctivitis		Present	
A-Yong [72]	2020	Clinical review	Conjunctivitis			

SARS Severe acute respiratory syndrome

[a] No evidence to support conjunctivitis related to coronavirus

children diagnosed with respiratory tract infection [23]. Of the 300 samples analyzed, 28 (9.3%) were positive for HCoV-NL63. The medical reports of 18 patients with HCoV-NL63–positive samples were retrospectively examined and the following symptoms noted: fever (61%, $n = 11$ patients), rhinitis (39%, $n = 7$), lower respiratory tract illness (bronchiolitis, pneumonia [39%, $n = 7$]), digestive problems (diarrhea and abdominal pain [33%, $n = 6$]), otitis (28%, $n = 5$), pharyngitis (22%, $n = 4$) and conjunctivitis (17%, $n = 3$) [23].

Xia et al. reported a prospective interventional case series involving 30 patients with confirmed novel coronavirus pneumonia [28]. Tear and conjunctival secretions were collected for reverse-transcription PCR (RT-PCR) assay. The authors demonstrated that SARS-CoV-2 were present in the tears and conjunctival secretions of coronavirus pneumonia patients with conjunctivitis; however, no virus was detected in the tears or conjunctival secretions of patients without conjunctivitis. These results could possibly indicate that tear and conjunctival secretions are not a common route of coronavirus transmission, given that the majority of COVID-19 patients do not manifest conjunctivitis. Nevertheless, this route of transmission could not be completely eliminated in such patients [28]. As ophthalmologists, we should be aware of this finding because any sign of conjunctivitis in the clinical setting should be considered to be a possible coronavirus conjunctivitis, especially when accompanied by other respiratory tract problems or fever.

A study carried out by Loon et al. in 2004 demonstrated the presence of SARS-CoV RNA in tears [49]. Tear samples collected from 36 suspected SARS-CoV patients were sent for RT-PCR analysis for the presence of SARS-CoV; SARS-CoV RNA was identified in three of these patients [49].

In contrast, there have been studies which have assessed both tears and conjunctival scrapes from 17 patients with confirmed SARS-CoV infection, with no positive results from the RT-PCR analysis [50, 51]. The authors propose three explanations of these results: (1) low sensitivity of RT-PCR on ocular surface secretions; (2) if there is viral shedding in ocular tissue, the window period may only last a short period of time; (2) the possibility that SARS-CoV does not exist in ocular tissues.

Regarding the severity of the COVID-19 disease, patients with ocular symptoms are 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 [31].

Another interesting detail regarding the ocular implication of this infection is that the human eye actually has its own intraocular renin–angiotensin system, and ACE2 receptors have been found in the aqueous humor [52]. As previously explained, the main receptor for SARS-CoV-2 is the ACE2 receptor, which indicates that aqueous humor could be a target in COVID-19 infection. More studies exploring the hypothesis of SARS-CoV-2 ocular manifestation through the ACE2 receptor need to be performed.

The study of ocular manifestations in animals could improve our current understanding of eye disease in humans. Therefore, in the following section, ocular manifestations associated with coronavirus infections in animals are discussed.

Association of Other Coronaviruses with Ocular Manifestations in Animals

Earlier studies have reported an association between coronaviruses and ocular problems in animal models. For example, feline infectious peritonitis (FIP) is caused by a feline coronavirus (FCoV). Vasculitis is a common feature in FIP, and ocular manifestations include pyogranulomatous anterior uveitis, coroiditis with retinal detachment and retina vasculitis, with perivascular cuffing by inflammatory cells [53–56]. These manifestations are more common in the non-effusive (dry) form than in the effusive (wet) form of the disease. Also, it can be present without other systemic signs of FIP [26]. The treatment of uveitis associated with FIP has been described: large fibrin clots in the anterior chamber were treated with intracameral injections of 25 μg tissue plasminogen activator. However, cats with mild uveitis responded only to topical therapy [26].

A murine coronavirus, the mouse hepatitis virus (MHV), has shown involvement of the posterior pole of the eye. The MHV neurotropic strains are of particular importance in animal model studies in the ophthalmology field. The two main strains are JHM (JHMV) and A59 (MHV-A59), both of which were isolated from a paralyzed mouse as a result of extensive demyelination and encephalomyelitis [57]. JHMV-infected mice were subsequently utilized for intravitreal inoculation to study the mechanisms of virus-induced retinal degeneration [58]. This model is known as the experimental CoV retinopathy (ECOR) model, and it is used to examine genetic and host immune responses that may contribute to retinal disease [30].

In the ECOR model, the infection has two phases, namely, inflammation in the early phase and retinal degeneration in the late phase. Following inoculation, the presence of the virus in the retina and retina pigment epithelium will result in the infiltration of immune cells and release of proinflammatory mediators. After the first week of infection, viral clearance is achieved. However, retinal and retinal pigment epithelial cell autoantibodies are subsequently produced, resulting in progressive loss of photoreceptors and ganglion cells as well as thinning of the neuroretina [59]. In this case, the autoimmune process is the cause of the majority of the retinal damage.

MHV-A59 models, on the other hand, have been used to create viral-induced optic neuritis. This line of research is based on the increasingly popular hypothesis that viral-induced inflammation is the likely etiology of multiple sclerosis. Shindler et al. inoculated MHV-A59 intracranially into mice, inducing meningitis, focal acute encephalitis and, most importantly, optic neuritis [60]. Inflammation of the optic nerve was detected as early as 3 days after inoculation, with the peak incidence at 5 days. Axonal loss was highlighted by the significant decrease in axonal staining compared to control optic nerves 30 days after inoculation [60].

It is important to note that in animal models, coronaviruses affect not only the anterior surface of the eye; thus, we should be careful as ophthalmologists and prevent any possible ocular transmission of the disease. It is important to learn more about the transmission mechanism to the eye and try to understand the pathogeny of the virus in the ocular tissues. We have clear knowledge of retinal and optic nerve problems related to coronavirus in animals, and

the implications thereof; consequently, we should be meticulous when examining patients who have tested positive for COVID-19. Nevertheless, to the best of our knowledge, there is no evidence of human coronaviruses causing intraocular ophthalmic problems, such as uveitis, retinitis and optic neuritis, as observed in animals.

Ophthalmological Prevention

According to a number of authors, ophthalmologists could have a higher risk of contracting SARS-CoV-2 infection due to face-to-face communication with patients, frequent exposure to tears and ocular discharge and the unavoidable use of equipment, such as slit lamp, tonometer, laser, etc. [29, 61]. Ssome guidelines have been recently published to minimize the risk of infection.

Before the patient's visit

The number of patients visiting the clinic should be strictly limited, and there should be a strict timetable of appointments to prevent any agglomeration of patients in the clinic waiting room [29, 61]. Online platforms, such as the hospital's official website, should be used. Telephone assistance could be useful in helping the patient distinguish between urgent and not-urgent ocular problems, recommending treatments for non-urgent diseases, reminding patients of the use of personal protection equipment (PPE) before coming to the clinic and answering questions on possible symptoms relative to COVID-19 [61]. A triage system is also important to identify patients with fever, respiratory symptoms and/or acute conjunctivitis or who have recently traveled to outbreak areas. Online ordering and delivery of prescribed medication, especially for chronic medication for chronic eye diseases, such as glaucoma, is also recommended [61].

During the patient's visit

The number of accessible entry points to the hospital/clinic should be reduced and checkpoints set up at the hospital entrance. The temperature of patients should be controlled and patients should be screening for COVID-19 symptoms and contact history with confirmed or suspected COVID-19 patients within the past 14 days. Patients should be provided with a mask if they do not bring one from home and social distancing in the registration and waiting area should be practiced. Patients with conjunctivitis or other similar infections should be seen in a separate clinic, and there should be a separate waiting area. Patients should be tested more than two times for SARS-CoV-2 RNA in the conjunctival sac and tears. Inside the clinical examination room, the number of people should be limited (1 doctor and 1 patient per room), with the exception of visually impaired patients, patients with communication/mobility difficulties or small children. The room should be well ventilated, and the instruments used should be disinfected immediately after each patient visit. Infection control training should be provided to all clinical staff. Installation of protective shields on slit lamps, frequent disinfection of equipment and provision of eye protection for staff should be implemented in all clinics. Universal masking, hand hygiene and the correct use of PPE should be promoted [29]. Direct ophthalmoscope examination is not recommended and could be replaced by slit light lenses, optical coherence tomography (OCT) or fundus photography [61].

Inpatient management and surgeries

Preoperative infection screening of the inpatients is recommended, especially before any surgical procedure. General anesthesia should be avoided, and local anesthesia is preferable to avoid contamination. Any emergency operation of a COVID-19–positive patient should be performed in a negative pressure operating room. If such a surgical area is not available, the patient should be referred to another qualified hospital equipped with such an operating room. Operations on healthy patients can be performed in a space with a positive pressure laminar flow, as is standard practice [61].

Staff management

Infection control training for all staff is necessary. The taking of temperature and the query-

and-questionnaire procedure before entering the hospital also applies to the staff. Strict hand hygiene is required, and gloves should be changed regularly; one pair of latex gloves should not be used for long periods of time [61].

According to current evidence, human coronavirus can remain infectious on inanimate surfaces for up to 9 days [62]. Therefore, reducing the viral load on surfaces by disinfection is very important. The World Health Organization recommends cleaning environmental surfaces with water and detergent and applying commonly used disinfectants, such as sodium hypochlorite [63]. Bleach is typically used at a dilution of 1:100 of 5% sodium hypochlorite, resulting in a final concentration of 0.05% [64]. It has also been suggested that a concentration of 0.1% is effective in 1 min. It therefore seems appropriate to recommend a dilution 1:50 of standard bleach in the coronavirus setting. In case of small surface desinfection, ethanol (62–71%) has shown an efficacy against coronavirus [62, 64]. Other biocidal agents, such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective [65]. Duan et al. found that irradiation with ultraviolet light for 60 min on several coronaviruses in culture medium resulted in undetectable levels of viral infectivity.

We speculate that some ocular spray disinfectants that contain hypochlorous acid, usually applied to treat blefaritis in order to reduce bacterial and viral load on the skin and eyelashes, could be used as a measurement of prevention for the facial area where many other chemical agents cannot be applied.

Treatment of Ocular Problems in Patients with COVID-19

Little evidence exists on the treatment of the viral conjunctivitis associated with COVID-19. Some antiviral systemic drugs have been used during this outbreak, such as umefenovir, lopinavir, ritonavir [43], but not specifically for the ocular problem. Chen et al. reported the possibility that ribavirin eye-drops could help the ocular symptom treatment [43]. Cheema et al. recently treated one patient who presented with pseudodendritic keratoconjunctivitis with oral valacyclovir 500 mg orally three times per day and moxifloxacin 1 drop once daily to the right eye, based on a presumed diagnosis of herpetic keratoconjunctivitis; this patient, however, turned out to have a positive SARS-CoV-2 conjunctival swab result [67].

The most common cause of infectious conjunctivitis is human adenovirus (HAdV), accounting for up to 75% of all conjunctivitis cases and affecting people of all ages and demographics. As a coronavirus, it can also cause systemic infections in the form of gastroenteritis and respiratory disease. HAdV causes lytic infection of the mucoepithelial cells of the conjunctiva and cornea, as well as latent infection of lymphoid and adenoid cells. Despite it being the most common ophthalmological viral infection, there is no U.S. Food and Drug Administration-approved antiviral for treating HAdV keratoconjunctivitis. Therefore, managing viral persistance and dissemination constitute a challenge. Some treatment modalities have been investigated, such as systemic and topical antivirals, in-office povidone-iodine irrigation, immunoglobulin-based therapy, anti-inflammatory therapy and immunotherapy. Other posible therapeutic options are sialic acid analogs, cold atmospheric plasma, *N*-chlorotaurine and benzalkonium chloride [68].

Although viral conjunctivitis can cause discomfort to patients, it is not a life-threatening condition. Therefore, all the treatment efforts in patients testing positive for SARS-CoV-2 are destined to be vital problems rather than serious threats to the eye itself. Treatment for viral conjunctivitis is mostly supportive, and the majority of cases are self-limited. Nonetheless, it is important that ophthalmologists to decrease the possible viral load on the conjunctiva and decrease the potential of transmission through tear and eye secretions. Some of the general ophthalmic recommendations for viral conjunctivitis could apply to COVID-19 patients in terms of reducing both the transmission rate and possible complications; these include hygienic measures (frequent hand washing, especially when eye drops need to be applied or contact lens are worn; avoiding touching or rubbing the eyes; changing pillowcases, sheets,

towels, regularly; not sharing personal items, etc.).

More studies should be conducted to establish a specific antiviral ocular treatment aimed at reducing the viral load, if present, on the conjunctiva of patients and reducing the transmission rate from the ophthalmological perspective. However, it is very difficult to determine a treatment when so many doubts still remain regarding the ophthalmic implications of SARS-CoV-2 infection [69, 70].

CONCLUSION

Our review of the literature reveal that some studies suggest that ocular symptoms commonly appear in patients with severe COVID pneumonia and that it is possible to detect viral RNA from the conjunctival sac of these patients. Apparently, conjunctivitis is not a frequent manifestation of the coronavirus disease in patients with non-severe COVID-19. Despite conjunctivitis generally being a self-limited and benign condition, it is an important route of viral transmission and, therefore, prevention is the most important aspect to remember as ophthalmologists to protect our patients and ourselves.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. María A. Amesty, Jorge L. Alió del Barrio and Jorge L. Alió have nothing to disclose. Jorge L. Alió is a member of the journal's Editorial Board.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Tyrrell DAJ, Bynoe ML. Cultivation of novel type of common-cold virus in organ cultures. Br Med J. 1965;1:1467–70. https://doi.org/10.1136/bmj.1.5448.1467.

2. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med. 1966;121:190–3. https://doi.org/10.3181/00379727-121-30734.

3. Almeida JD, Tyrrell DA. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J Gen Virol. 1967;1:175–8. https://doi.org/10.1099/0022-1317-1-2-175.

4. Thiel V, Herold J, Schelle B, Siddell SG. Infectious RNA transcribed in vitro from a cDNA copy of the human coronavirus genome cloned in vaccinia

virus. J Gen Virol. 2001;82:1273–81. https://doi.org/10.1099/0022-1317-82-6-1273.

5. McIntosh K, Dees JH, Becker WB, Kapikian AZ, Chanock RM. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl Acad Sci USA. 1967;57:933–40. https://doi.org/10.1073/pnas.57.4.933.

6. Hendley JO, Fishburne HB, Gwaltney JM. Coronavirus infections in working adults. Eight-year study with 229 E and OC 43. Am Rev Respir Dis. 1972;105:805–11.

7. Mounir S, Labonte P, Talbot PJ. Characterization of the nonstructural and spike proteins of the human respiratory coronavirus OC43: comparison with bovine enteric coronavirus. Adv Exp Med Biol. 1993;342:61–7. https://doi.org/10.1007/978-1-4615-2996-5_10.

8. Kunkel F, Herrler G. Structural and functional analysis of the surface protein of human coronavirus OC43. Virology. 1993;195:195–202. https://doi.org/10.1006/viro.1993.1360.

9. Bradburne AF, Bynoe ML, Tyrrell DA. Effects of a "new" human respiratory virus in volunteers. Br Med J. 1967;3:767–9. https://doi.org/10.1136/bmj.3.5568.767.

10. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med. 2004;10(4):368–73. https://doi.org/10.1038/nm1024.

11. Ahmad K. New human coronavirus isolated. Lancet Infect Dis. 2004;4(5):255.

12. Peiris JS, Chu CM, Chang VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361:1767–72. https://doi.org/10.1016/S0140-6736(03)13412-5.

13. Lai MM. SARS virus: the beginning of the unraveling of a new coronavirus. J Biomed Sci. 2003;10:664–75. https://doi.org/10.1007/BF02256318.

14. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967–76. https://doi.org/10.1056/NEJMoa030747.

15. Martina BE, Haagmans BL, Kuiken T, et al. Virology: SARS virus infection of cats and ferrets. Nature. 2003;425:915. https://doi.org/10.1038/425915a.

16. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science. 2003;302:276–8. https://doi.org/10.1126/science.1087139.

17. Holmes KV, Lai MMC. Coronaviridae. Fields Virol. 1996;2:1075–93.

18. Guy JS, Breslin JJ, Breuhaus B, Vivrette S, Smith LG. Characterization of a coronavirus isolated from a diarrheic foal. J Clin Microbiol. 2000;38:4523–6.

19. Hök K. Development of clinical signs and occurrence of feline corona virus antigen in naturally infected barrier reared cats and their offspring. Acta Vet Scand. 1993;34(4):345–56.

20. Hök K. Morbidity, mortality and coronavirus antigen in previously coronavirus free kittens placed in two catteries with feline infectious peritonitis. Acta Vet Scand. 1993;34:203–10.

21. Decaro N, Camero N, Greco G, et al. Canine distemper and related diseases: report of a severe outbreak in a kennel. New Microbiol. 2004;27(2):177–81.

22. Fouchier RA, Rimmelzwaan GF, Kuiken T, et al. Newer respiratory virus infections: human metapneumovirus, avian influenza virus, and human coronaviruses. Curr Opin Infect Dis. 2005;18(2):141–6.

23. Vabret A, Mourez T, Dina J, et al. Human coronavirus NL63, France. Emerg Infect Dis. 2005;11(8):1225–9. https://doi.org/10.3201/eid1108.050110.

24. Terregino C, Toffan A, Beato MS, et al. Pathogenicity of a QX strain of infectious bronchitis virus in specific pathogen free and commercial broiler chickens, and evaluation of protection induced by a vaccination programme based on the Ma5 and 4/91 serotypes. Avian Pathol. 2008;37(5):487–93. https://doi.org/10.1080/03079450802356938.

25. Ledbetter EC, Hombuckle WE, Dubovi EJ. Virologic survey of dogs with naturally acquired idiopathic conjunctivitis. J Am Vet Med Assoc. 2009;235(8):954–9. https://doi.org/10.2460/javma.235.8.954.

26. Stiles J. Ocular manifestations of feline viral diseases. Vet J. 2014;201(2):166–73. https://doi.org/10.1016/j.tvjl.2013.11.018.

27. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc. 2014;113(3):148–54. https://doi.org/10.1016/j.jfma.2013.12.008.

28. 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. 2020. https://doi.org/10.1002/jmv.25725.

29. Lai THT, Tang EWH, Chau SKY, et al. 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. https://doi.org/10.1007/s00417-020-04641-8.

30. Seah I, 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):391–5. https://doi.org/10.1080/09273948.2020.1738501.

31. 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. https://doi.org/10.1001/jamaophthalmol.2020.1291.

32. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA. 2020;323(8):707–8. https://doi.org/10.1001/jama.2020.0757.

33. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495:251–4.

34. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11:875–9.

35. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264–6.

36. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–27.

37. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260–3.

38. Villar J, Zhang H, Slutsky AS. Lung repair and regeneration in ARDS: role of PECAM1 and Wnt signaling. Chest. 2019;155:587–94.

39. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529–39.

40. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction síndrome. Am J Emerg Med. 2008;26:711–5.

41. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13.

42. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 11:827. https://doi.org/10.3389/fimmu.2020.00827

43. Chen L, Liu M, Zhan Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. Br J Ophthalmol. 2020. https://doi.org/10.1136/bjophthalmol-2020-316304.

44. Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet. 2020;395(10224):e39. https://doi.org/10.1016/S0140-6736(20)30313-5.

45. Carlos WG, Dela Cruz CS, Cao B, et al. Novel Wuhan (2019-nCoV) coronavirus. Am J Respir Crit Care Med. 2020;201:7–8.

46. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan China. JAMA. 2020. https://doi.org/10.1001/jama.2020.1585.

47. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382:929–36.

48. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. BioRxiv. 2020. https://doi.org/10.1101/2020.01.30.927806.

49. Loon S-C, Teoh SCB, Oon LLE, et al. The severe acute respiratory syndrome coronavirus in tears. Brit J Ophthalmol. 2004;88(7):861–3. https://doi.org/10.1136/bjo.2003.035931.

50. Tong T, Lai TS. The severe acute respiratory syndrome coronavirus in tears. Br J Ophthalmol. 2005;89(3):392. https://doi.org/10.1136/bjo.2004.054130.

51. Chan WM, Yuen KS, Fan DS, Lam DS, Chan PK, Sung JJ. Tears and conjunctival scrapings for coronavirus in patients with SARS. Br J Ophthalmol. 2004;88(7):968–9. https://doi.org/10.1136/bjo.2003.039461.

52. Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system—focus on eye. Open Ophthalmol J. 2017;11(1):122–42. https://doi.org/10.2174/1874364101711010122.

53. Doherty MJ. Ocular manifestations of feline infectious peritonitis. J Am Vet Med Assoc. 1971;159:417–24.

54. Slauson DO, Finn JP. Meningoencephalitis and panophthalmitis in feline infectious peritonitis. J Am Vet Med Assoc. 1972;160:729–34.

55. Campbell LH, Reed C. Ocular signs associated with feline infectious peritonitis in two cats. Feline Pract. 1975;5:32–5.

56. August JR. Feline infectious peritonitis, an immune-mediated coronaviral vasculitis. Vet Clin N Am Small Anim Pract. 1984;14:971–84.

57. Bailey OT, Pappenheimer AM, Cheever FS, Daniels JB. A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin: II. Pathology. J Exp Med. 1949;90(3):195–21212. https://doi.org/10.1084/jem.90.3.195.

58. Robbins SG, Detrick B, Hooks JJ. Retinopathy following intravitreal injection of mice with MHV strain JHM. Adv Exp Med Biol. 1990;276:519–24.

59. Hooks JJ, Percopo C, Wang Y, Detrick B. Retina and retinal pigment epithelial cell autoantibodies are produced during murine coronavirus retinopathy. J Immunol. 1993;151:3381–9.

60. Shindler KS, Kenyon LC, Dutt M, Hingley ST, Das SJ. Experimental optic neuritis induced by a demyelinating strain of mouse hepatitis virus. J Virol. 2008;82(17):8882–6. https://doi.org/10.1128/JVI.00920-08.

61. Yong Y, Ruixue T, Xu S, et al. A comprehensive Chinese experience against SARS-CoV-2 in ophthalmology. Eye Vis. 2020;7:19. https://doi.org/10.1186/s40662-020-00187-2.

62. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246–51. https://doi.org/10.1016/j.jhin.2020.01.022.

63. World Health Organization. WHO 2020 infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. Interim guidance. https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125. WHO/2019-nCoV/IPC/2020.3. Accessed 25 Jan 2020.

64. World Health Organization. Annex G. Use of disinfectants: alcohol and bleach. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. Geneva: World Health Organization; 2014: 65–66.

65. Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246–51. https://doi.org/10.1016/j.jhin.2020.01.022.

66. Duan SM, Zhao XS, Wen RF, et al. Stability of SARS coronavirus in human specimens and environment and its sensitivity to heating and UV irradiation. Biomed Environ Sci. 2003;16(3):246–55.

67. 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. 2020. https://doi.org/10.1016/j.jcjo.2020.03.003.

68. Labib BA, Minhas BK, Chigbu DI. Managemente of adenorviral conjunctivitis: challenges and solutions. Clin Ophthalmol. 2020;17(14):837–52. https://doi.org/10.2147/OPTH.S207976.

69. Zhang MC, Xie HT. Whether conjunctival congestion in patients infected with 2019 novel coronavirus is definitely related the novel coronavirus? Zhonghua Yan Ke Za Zhi. 2020;56:E010. https://doi.org/10.3760/cma.j.cn112142-20200324-00218.

70. Lan QQ, Zeng SM, Liao X, Xu F, Qi H, Li M. Screening for novel coronavirus related conjunctivitis among the patients with corona virus disease-19. Zhonghua Yan Ke Za Zhi. 2020;56:E009. https://doi.org/10.3760/cma.j.cn112142-20200322-00213.

71. Hu K, Patel J, Patel BC. Ophthalmic manifestations of coronavirus (COVID-19). StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020.

72. A-Yong Y, Ruixue T, Xu S, et al. A comprehensive Chinese experience against SARS-CoV-2 in ophthalmology. Eye Vis (Lond). 2020;7:19. https://doi.org/10.1186/s40662-020-00187-2.