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Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19

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ABSTRACT.
Purpose: **The SARS-CoV-2 RNA has been detected in tears and conjunctival samples from infected individuals. Conjunctivitis is also reported in a small number of cases. We evaluated ocular symptoms and ocular tropism of SARS-CoV-2 in a group of patients with COVID-19.**
Method: **Fifty-six patients infected with SARS-CoV-2 were recruited as subjects. Relevant medical histories were obtained from the electronic medical record system. Ocular history and ocular symptoms data were obtained by communicating directly with the subjects. The Ocular Surface Disease Index (OSDI) and Salisbury Eye Evaluation Questionnaire (SEEQ) were used to assess the anterior ocular surface condition before and after the onset of disease.**
Results: **Patients classified as severe COVID-19 cases were more likely to have hypertension compared to mild cases ($p = 0.035$). Of the 56 subjects, thirteen patients (23%) were infected in Wuhan, 32 patients (57%) were community-infected, 10 patients (18%) were unknown origin, 1 (2%) was a physician likely infected by a confirmed patient. Three patients wore face mask with precaution when contacting the confirmed patients. Fifteen (27%) had aggravated ocular symptoms, of which 6 (11%) had prodromal ocular symptoms before disease onset. The differences in mean scores of OSDI questionnaire and SEEQ between before and after onset of COVID-19 were all significant ($p < 0.05$ for both).**
Conclusions: **Ocular symptoms are relatively common in COVID-19 disease and may appear just before the onset of respiratory symptoms. Our data provided the anecdotal evidences of transmission of SARS-CoV-2 via ocular surface.**

Key words: coronavirus disease 2019 – severe acute respiratory syndrome coronavirus – dry eye – conjunctivitis

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Introduction

Coronavirus disease 2019 or COVID-19 (as proposed by the World Health Organization (WHO)) (Novel Coronavirus (2019-nCoV) Situation Report-22 at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports) was first reported in Wuhan, Hubei, China, in December, 2019. Within a matter of weeks, the coronavirus outbreak evolved to become a significant public health threat (Wang et al. 2020). Deep sequencing analysis of lower respiratory tract samples revealed a novel coronavirus and was officially named severe acute respiratory syndrome coronavirus (Wang et al. 2020) (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) (Zhu et al., 2020). Among patients with COVID-19, fever was the most common symptom, concomitant with dry cough, dyspnoea, fatigue and pneumonia. However, several non-respiratory clinical features were also reported, such as gastrointestinal symptoms (typically diarrhoea) (Gu et al. 2020) and, more rarely, ocular inflammation (conjunctivitis) (Guan et al. 2020; Lu et al. 2020). Patients with COVID-19 may show prodromal symptom of conjunctivitis in cases where eye goggles were not worn while in close proximity with COVID-19 positive patients, leading to suggestions that ocular exposure might be a potential route of SARS-CoV-2 infection

(Lu et al. 2020). During the SARS-associated coronavirus outbreak of 2003, one study found that the most predictive variable for transmission of the infection from infected patients to healthcare workers was whether or not the healthcare workers used protective eyewear (Raboud et al. 2010).

SARS-CoV-2 is a novel lineage B beta-coronavirus in the phylogenetic tree. The genome of SARS-CoV-2 is 29891 nucleotides in size, encoding 9860 amino acids, and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (Chan et al. 2020). The spike proteins of SARS-CoV-2 associated with the host receptor named angiotensin-converting enzyme 2 (ACE2) of sensitive cells and tissues can result in infection of target cells. Angiotensin-converting enzyme 2 (ACE2) is also the receptor for SARS-CoV, and both types of coronavirus can cause a severe acute respiratory disease and possess high human-to-human transmissibility (Benvenuto et al. 2020). The expression of ACE2 has been identified in multiple tissues in human body, including lung alveolar mucosa, oral mucosa, gastrointestinal duct, kidney and conjunctiva, indicating potential infection routes of SARS-CoV-2 via these tissues (Hamming et al. 2004; Xu et al. 2020).

An intact tear film covering the anterior surface of the eye provides a formidable defensive barrier against potential pathogens such as bacteria and viruses from the external environment. Antimicrobial proteins and immunoglobulins in tears inhibit the spread of bacteria and viruses (Akpek & Gottsch 2003). The continuing flushing of tears from the anterior surface of the eye to the nasolacrimal system and the thick mucin layer overlying the epithelium reduce the opportunity for foreign particles to adhere to and potentially invade epithelial cells (Akpek & Gottsch 2003). Some respiratory pathogens, such as the adenovirus and H7 influenza virus, can cause sufficient disturbance to the cornea and conjunctival epithelial cells as to trigger an adaptive immune response, resulting in the inflammatory processes seen in conjunctivitis and keratoconjunctivitis (Creager et al. 2018). Other pathogens, such as the coronavirus and rhinovirus, do not appear to attract significant reaction from the immune defence system and consequently are rarely associated with inflammatory responses of the anterior ocular surface (Belser et al 2013). When a respiratory pathogen lands on the tear film, if it is not neutralized by the innate immune system, it is likely to end up in the nasopharyngeal space from where it could further infect respiratory tissues.

While it is well established that for most coronavirus infections, clinically significant conjunctivitis is rarely present, we were interested in sub-clinical involvement of the anterior ocular surface. The SARS-CoV-2 was found to infect the mucosa membrane epithelium and even lymphocytes, which are both abundant in ocular surface tissue (Hamming et al. 2004; Chen et al. 2020; Xu et al. 2020). We reasoned that a degraded anterior ocular surface, such as a dry eye or conjunctivitis, might be associated with the viral infection into ocular and nasopharyngeal tissues. In this study, we investigated subjective ocular symptoms in a group of patients with confirmed COVID-19 in order to gain further understanding of subtle ocular involvement in this disease.

Methods

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University and performed in accordance with the tenets of the Declaration of Helsinki. The First Affiliated Hospital of Zhejiang University is one of designated hospitals for the hospitalization of patients with COVID-19 in the city of Hangzhou, Zhejiang Province.

Subjects

Previously hospitalized patients (admission date from 19 January to 29 February 2020) in the isolation ward of the First Affiliated Hospital of Zhejiang University, diagnosed as COVID-19 positive based on their clinical symptoms and positive SARS-CoV-2 test results of their sputum swab specimens, were the target subject population. Convenient sampling was used. The estimated potential pool of patients was 64. For ethical and operational reasons, we chose to recruit only those patients who were discharged from the isolation ward of the hospital and had recovered well enough to return to their homes. Recruitment was conducted by one of us (NH) over the telephone. After explaining the purpose of the research and the research procedures and requirements, agreement to participate in this study was obtained verbally. As a standard practice of our hospital, all subjects had previously given written consent for the medical records to be used for approved research purposes. Participation involved answering questions about their ocular clinical history and questions from the Salisbury Eye Evaluation Questionnaire (SEEQ) and Ocular Surface Disease Index (OSDI; Allergan Inc., Irvine, CA) questionnaire (administered by NH). All potential subjects were contacted within 10 days after discharge from the isolation ward.

General and ocular history

General clinical presentation including severity of lung disease, medical history, exposure history, measures taken for personal protection, smoking history, comorbidities, allergies, thyroid diseases and rheumatic diseases were extracted from the hospital electronic medical record system. Ocular history (including myopia, optical aids used, hours of electronic products usage per day, ocular surface surgery, ocular trauma, previous ocular diseases and previous ophthalmic drugs used) before and after the onset of COVID-19 was taken by NH over the telephone for each subject. ‘Before the onset of COVID-19’ is taken to mean the period before the course of COVID-19 (in healthy condition). ‘After the onset of COVID-19’ is taken to mean the period in the course of COVID-19.

Ocular symptoms

Subjective recall

Each subject was asked to recall whether ocular symptoms were present before and after the onset of COVID-19.

Ocular symptoms questionnaires

To assess subjective ocular surface condition quantitatively, the Chinese versions of Ocular Surface Disease Index (OSDI; Allergan Inc., Irvine, CA) and Salisbury Eye Evaluation Questionnaire (SEEQ) were used (McAlinden et al. 2017). The questionnaire was administered over the telephone by NH. Each subject was asked to recall the status of their eyes before the onset of COVID-19 and answered the OSDI questionnaire and SEEQ accordingly. This was repeated for after the onset of COVID-19. The questionnaires were administered to subjects within 10 days of their discharge from hospital.

Statistical analysis

Categorical variables were described as frequency rates and percentages. Continuous normally distributed variable was described using mean and standard deviations (SDs), and other variable was described using median with range. The scores of OSDI questionnaire and SEEQ before and after the onset of COVID-19 were compared using a paired-sample *t*-test. For continuous variables, the Mann–Whitney *U* test was performed to analyse their differences. The chi-square test or Fisher's exact test was used for categorical variables. All statistical analyses were performed using SPSS (Statistical Package of the Social Sciences) version 19.0 software. The test value of $p < 0.05$ (two sides) was considered statistically significant.

Results

Altogether, 56 discharged patients diagnosed with COVID-19, out of a total potential cohort of 64 discharged patients, agreed to participate as subjects in this study. The baseline characteristics of the 56 subjects are shown in Table 1. According to the medical records, patients were classified into two disease states: 'mild' and 'severe'. This classification was determined by attending physicians in accordance with the diagnostic and treatment guideline for COVID-19 issued by Chinese National Health Committee (Version 4-6). For our subjects, 24 were classified as 'mild' and 32 were classified as 'severe'. There were more subjects in the severe group with hypertension than the mild group ($p = 0.035$, Fisher's exact test). Three subjects, including a medical doctor, claimed they wore a face mask when they came in close proximity with confirmed COVID-19 cases (Table 1).

The ocular characteristics of subjects are listed in Table 2. The ocular symptoms results are as follows:

SEEQ results

The mean scores of SEEQ questionnaire before the onset of COVID-19 was 0.21 (range 0–2, SD 0.46) and after the onset of COVID-19 was 0.46 (range 0–3, SD 0.74). It might be more intuitive to add mean score here as supplement. The differences between before and after onset of COVID-19 were significant ($p = 0.007$, paired *t*-test).

It is generally accepted that the SEEQ score is ≥1 for patients with dry eye (McAlinden et al. 2017). Eleven subjects (20%) scored higher than zero before the onset of COVID-19. Nineteen subjects (34%) showed ocular symptoms after the onset of COVID-19. The difference between mild and severe COVID-19 groups of SEEQ scores before onset of COVID-19 ($p = 1.00$, Mann–Whitney *U* test) and after onset of COVID-19 ($p = 0.351$) was not significant, respectively.

OSDI results

The median score of OSDI questionnaire before the onset of COVID-19 was 6.25 (range 0–47.92) and after the onset of COVID-19 was 6.81 (range 0–60.42). The difference between before and after onset of COVID-19 was also statistically significant ($p = 0.008$, paired *t*-test) (Table 2).

It is generally accepted that the OSDI ≥15 for patients with dry eye (McAlinden et al. 2017). Nine subjects (16%) scored higher than 15 before the onset of COVID-19. Fourteen subjects (25%) scored higher than 15 after the onset of COVID-19, nine subjects (16%) showed further deterioration of ocular symptoms after the onset of COVID-19. The difference between mild and severe COVID-19 groups of OSDI scores before onset of COVID-19 ($p = 0.801$, Mann–Whitney *U* test) and after onset of COVID-19 ($p = 0.827$) was not significant, respectively.

Subjective recall

Fifteen subjects (27%) reported ocular symptoms in the course of COVID-19, including sore eyes, itching, foreign body sensation, tearing, redness, dry eyes, eye secretions and floaters (Table 3). Among them, six subjects (11%) presented with ocular symptoms before onset of fever or respiratory symptoms. Of these six subjects, four (No. 19, 24, 36 and 40) reported the appearance of ocular symptoms one to seven days before the onset of fever or respiratory symptoms, while the remaining two subjects were uncertain about the temporal aspects of their reported ocular symptoms. Two subjects (~4%) (No. 35 (Fig. 1) and 48) developed conjunctivitis on the left eye after hospitalization. Conjunctival swab sample from the left eye of one patient (No. 48) showed positive virus RNA detection using real-time reverse transcription–polymerase chain reaction (RT-PCR) assays as described in another report from our hospital (Xia et al. 2020). No subject reported having blurred vision associated with the onset of COVID-19. One subject reported a floater in the right eye after hospital discharge (Table 3).

Discussion

Subject demographics

We contacted 64 discharged patients with COVID-19 and managed to recruit 56 subjects. Our subject sample represented those patients who were eventually cleared of the SARS-CoV-2 virus after three separate PCR tests. They represent the vast majority of patients. Those patients who succumb to COVID-19 or had to be hospitalized for a long time were not included. The average length of stay in the isolation ward of our subjects was 15 days.

Our subject pool did not favour any particular gender. Most subjects had a history of exposure to other confirmed COVID-19 cases (79%). The age of our subjects spanned from 24 to 68 years, suggesting that the SARS-CoV-2 virus infected both young and older people. Among the comorbidities, hypertension seemed to be a risk factor for the severe type of COVID-19 (Table 1, $p = 0.035$).

Ocular symptoms

We used well-established tools for dry eye assessment, the SEEQ and the OSDI questionnaires, to screen for ocular surface disturbance quantitatively. The SEEQ was used to assess the epidemiological features of dry eye and the OSDI questionnaire was used to rapidly assess the severity grade of eye irritation symptoms associated with dry eye (McAlinden et al. 2017). It is generally accepted that the SEEQ score is ≥1 and the OSDI score is ≥15 for

Table 1. Baseline characteristics of subjects With COVID-19.

		Disease severity		
	All subjects (*n* = 56)	Mild subjects (*n* = 24)	Severe subjects (*n* = 32)	p value
Age, mean (range, SD), y	48 (24–68,12.1)	47.5 (24–68, 12.55)	48.59 (29–67, 11.94)	0.77
Sex				
Female, *n* (%)	25 (44.6)	11 (19.6)	14 (25)	0.877
Male, *n* (%)	31 (55.4)	13 (23.2)	18 (32.2)	
Comorbidities				
AIDS, *n* (%)	1 (1.8)	1 (1.8)	0 (0)	0.429
Hypertension, *n* (%)	16 (28.6)	3 (5.4)	13 (23.2)	0.035*
Hepatitis B, *n* (%)	5 (8.9)	2 (3.6)	3 (5.3)	1
Diabetes, *n* (%)	5 (8.9)	3 (5.3)	2 (3.6)	0.642
Allergy history				
Yes, *n* (%)	10 (17.9)	4 (7.2)	6 (10.7)	1
No, *n* (%)	46 (82.1)	20 (35.7)	26 (46.4)	
Exposure History				
Wuhan, *n* (%)	13 (23.2)	4 (7.2)	9 (16)	0.358
Other, *n* (%)	43 (76.8)	20 (35.7)	23 (41.1)	
Familiar/cluster	32 (57.1)	17 (30.4)	15 (26.7)	
Doctor	1 (1.8)	0 (0)	1 (1.8)	
Unknown	10 (17.8)	3 (5.3)	7 (12.5)	
Precaution means				
Mask, *n* (%)	3 (5.4)	0 (0)	3 (5.4)	0.252
No, *n* (%)	53 (94.6)	24 (42.8)	29 (51.8)	
Smoker				
Yes, *n* (%)	8 (14.3)	4 (7.1)	4 (7.1)	0.713
No, *n* (%)	48 (85.7)	20 (35.7)	28 (50)	

AIDS = acquired immune deficiency syndrome, SD = standard deviations, y = year.
* p < 0.05 was considered statistically significant.

Table 2. Ocular characteristics of subjects with COVID-19

		Ocular symptoms		
	All subjects (*n* = 56)	Yes (*n* = 15)	No (*n* = 41)	p value
Myopia				0.822
Yes, *n* (%)	20 (35.7)	5 (8.9)	15 (26.8)	
No, *n* (%)	36 (64.3)	10 (17.9)	26 (46.4)	
Previous ocular surgery				0.268
Yes, *n* (%)	1 (1.8)	1 (1.8)	0	
No, *n* (%)	55 (98.2)	14 (25)	41(73.2)	
Previous eye drops usage				NA
Yes, *n* (%)	0 (0)	0 (0)	0 (0)	
No, *n* (%)	56 (100)	15(26.8)	41(73.2)	
Previous contacted lens				NA
Yes, *n* (%)	0 (0)	0 (0)	0 (0)	
No, *n* (%)	56 (100)	15 (26.8)	41 (73.2)	
Electronic products time/day				0.854
>5 hr, *n* (%)	25 (44.6)	7 (12.5)	18 (32.1)	
<5 hr, *n* (%)	31 (55.4)	8 (14.3)	23 (40.1)	
Scores of SEEQ, median (range)				
Before onset of COVID-19	0 (0–2)			
After onset of COVID-19	0 (0–3)*			
Scores of OSDI questionnaire, median (range)				
Before onset of COVID-19	6.25 (0–47.92)			
After onset of COVID-19	6.82 (0–60.42)*			

OSDI = Ocular Surface Disease Index, SEEQ = Salisbury Eye Evaluation questionnaire, NA = not available.
* Comparison of scores of SEEQ and OSDI questionnaires before and after onset of COVID-19 using paired *t*-test shows statistical significance (p < 0.05).

people with dry eye (McAlinden et al. 2017). Before the onset of COVID-19, the scores of the OSDI questionnaire for most of our subjects were lower than the diagnostic threshold, indicating a healthy ocular surface.

Mild ocular symptoms associated with dry eye syndrome are commonly reported in Chinese populations. For adults, the prevalence of reported dry eye symptoms is about 21% (Jie et al. 2009). For our subject sample, based on the SEEQ and OSDI responses before onset of COVID-19, the prevalence of ocular symptoms was 20% (SEEQ) and 16% (OSDI). This suggests that our subject sample was not worse than the normal population in terms of ocular surface integrity prior to the onset of COVID-19.

After the onset of COVID-19, the mean scores of the SEEQ and OSDI questionnaires were significantly raised, suggesting a degraded ocular surface condition (Table 2). We speculate that the micro-environment of the ocular surface and the stability of tear film could be adversely affected by a number of factors, including (i) a generalized systemic immune system reaction to the respiratory infection by the SARS-CoV-2 virus, (ii) secondary infection by other opportunistic ocular pathogens and (iii) infection of ocular tissues by the SARS-CoV-2 virus. The possibility of virus inoculation to the conjunctival mucosal epithelium could not be excluded. The ACE2, which is the critical binding receptor of coronavirus invasion, has been identified in the human cornea and conjunctiva, although the expression level of ACE2 on the conjunctiva is less than that in lung, heart and Vero E6 cells (Sun et al. 2004a; Sun et al. 2004b; Sun et al. 2006), which can degrade the affinity of SARS-CoV-2 on ocular tissue compared to tissues in the nasopharyngeal and respiratory tract. Moreover, the ocular surface possesses an effective drainage and self-cleaning system. The ocular surface is not a calm environment. Viral particles landing on the tear film would be flushed away from the ocular surface relatively quickly and drained into the nasopharyngeal space, where it is calmer and more conducive for virus invasion. In addition, the outer lipid layer of tear film also enhances the resistance to the pathogen invasion (Johnson & Murphy 2004). This lipid layer is absent in the mucosal membrane of nasal and respiratory tract. This might explain the low rate of anterior surface inflammation observed. In our study, the results from the SEEQ and OSDI indicated a healthy ocular surface condition for

Table 3. Detailed Information of COVID-19 Subjects with Ocular Symptoms (*n* = 15)

NO	Sex	Age, y	Ocular Symptoms	Scores of SEEQ		Scores of OSDI		Disease Severity	Myopia	Allergic history	Comorbidities	Precaution	Exposure history	Smoker
				Pre	Post	Pre	Post							
3*	male	35	Sore eye and increased eye secretions on the both eyes several days before fever	0	1	2.08	10.42	Mild	No	Yes	No	No	Cluster infection	No
4*	male	30	Dry eye on the both eyes several days before fever	0	1	8.33	35.42	Severe	Yes	No	No	No	Cluster infection	No
11	male	51	Eye itching on the both eyes	0	0	0	0	Severe	No	No	No	No	Wuhan	No
14	male	47	Dry eye on the both eyes occasionally	0	1	6.25	14.58	Severe	No	No	Hepatitis B	No	Cluster infection	No
16	male	57	Foreign body sensation on the both eyes	0	2	6.82	25	Mild	No	No	Diabetes	No	Wuhan	Yes
19*	female	50	Sore eye and dry eye on the both eyes 1 day before fever	0	2	6.82	11.36	Mild	Yes	No	No	No	Cluster infection	No
20	male	52	Foreign body sensation on the both eyes	0	0	11.36	15	Severe	Yes	No	Hypertension	No	Unknown	No
24*	Male	57	Sore eye and dry eye on the both eyes aggravated 1 day before fever	1	1	6.82	6.82	Mild	Yes	No	Diabetes/ Hypertension	No	Wuhan	No
29	male	51	Floaters on the right eye after hospitalized	0	0	16.67	16.67	Severe	No	No	Diabetes	No	Wuhan	Yes
30	female	59	Eye itching on the both eyes, difficult to open eyes when wake up	0	1	4.55	4.55	Mild	No	Yes	No	No	Cluster infection	No
35	female	46	Redness and foreign body sensation on the left eye after 1 week in hospital	0	2	2.27	6.82	Mild	No	No	Hypertension	No	Cluster infection	No
36*	male	55	Dry eye aggravated on the both eyes 5 days before onset of respiratory symptom	1	2	47.92	60.42	Severe	No	Yes	No	No	Cluster infection	No
40*	female	40	eye itching and eye secretion overabundance on the both eyes 7 days before fever	0	0	0	0	Severe	Yes	No	No	Mask	Cluster infection	No
45	male	66	Foreign body sensation on the both eyes	0	1	5	17.86	Severe	No	No	Hepatitis B/ Hypertension	No	Wuhan	No
48§	male	53	Redness and pain of eyes on the left eye 3 days after hospitalization	0	3	7.5	40	Severe	No	No	Hypertension	Mask	Unknown	No

OSDI = Ocular Surface Disease Index, SEEQ = Salisbury Eye Evaluation questionnaire.
* The ocular symptoms as the initial symptom.
§ RT-PCR showed positive result of left eye.

the most subjects before infection of SARS-CoV-2 (Table 2). However, the patient No. 48 with conjunctivitis and positive PCR result had pterygium surgery previously, highlighting the importance of an intact ocular surface for the resistance to virus invasion.

It is interesting that four subjects reported the appearance of ocular symptoms 1 to 7 days before onset of fever or respiratory symptoms (Table 3). This could suggest either a mild reaction to a local ocular infection or a generalized systematic reaction to an infection elsewhere of the SARS-CoV-2. The fact that no positive virus RNA results were found in tear and conjunctiva samples of these subjects points to the latter (Xia et al. 2020). Nevertheless, we cannot exclude the possibility that the viral load may be low and not reach the threshold

Fig. 1. The photograph of the both eyes of patient No. 35 showing more significant conjunctival congestion in the left eye than the right eye.

of detection by the RT-PCR. Further investigation is necessary to help explain this particular finding.

Coronaviruses are rarely associated with clinically significant conjunctival inflammation and conjunctivitis except for the HCoV-NL63 virus where conjunctivitis was reported to be found in 17% of confirmed cases (Vabret et al. 2005). From published reports, we know that conjunctivitis is an occasional finding in patients with COVID-19. In a study of 1099 patients laboratory-confirmed COVID-19, nine patients (0.8%) were documented with 'conjunctival congestion'(Guan et al. 2020). In our study, fifteen subjects (27%) reported new onset ocular irritation symptoms or aggravated pre-existing ocular surface irritation symptoms after infection of SARS-CoV-2. Two subjects (~4%) developed conjunctivitis, and SARS-CoV-2 was only identified by RT-PCR in the eye of one subject. At a practical level, it should be noted that patients with undiagnosed COVID-19 might present at eye care facilities with ocular symptoms, bringing about occupational exposure to staff and, in particular, the attending eye care professional.

The ocular surface as a portal to the respiratory system

Most of respiratory viruses have been documented to possess ocular tropism, causing ocular complications in infected individuals and establishing a respiratory infection following ocular exposure (Belser et al. 2013). Compared with the adenovirus and influenza virus, which can frequently cause keratoconjunctivitis or conjunctivitis, ocular diseases caused by coronavirus is relatively rare (Belser et al. 2013). However, conjunctivitis has been reported in the patients infected with SARS-CoV-2 (Guan et al. 2020; Xia et al. 2020). The novel coronavirus RNA was also detected in tears and conjunctival samples from infected individual (Xia et al. 2020).

We did not find statistically more ocular symptoms in our subjects who were later confirmed COVID-19 positive, compared with the prevalence data of dry eye based on large population. This observation should not be interpreted to mean the coronavirus does not use the ocular surface as a portal of entry to the respiratory system. Although not common, the SARS-CoV-2 has been identified in tear fluid (Xia et al. 2020), as had the SARS-CoV in 2003 (Loon et al. 2004). Our study provides additional anecdotal evidence to support the possibility of a SARS-CoV-2 respiratory infection via the ocular surface. As discussed earlier, six of our subjects reported ocular symptoms several days before the onset of fever or respiratory symptoms and altogether fifteen patients presented the aggravated ocular symptoms (Table 3). In addition, a further three subjects claimed to have worn face masks (without eye protection) during close contact with confirmed COVID-19 cases, but were nevertheless still infected. This is similar to the case report of Dr Wang Guangfa, a respiratory specialist from Beijing sent to investigate the epidemic situation in Wuhan in early January (Lu et al. 2020). He contacted COVID-19 and, upon reflection, shared his view that the infection was probably via the eye as he had taken all the usual precautions including wearing an N95 mask during site visits to fever clinics and wards but did not wear any eye protection. He reported developing conjunctivitis in his left eye, followed within hours by a fever and catarrh.

This study has several limitations. For practical reasons, it is not a typical 'pre and post' study using objective and clinical tools. Because of the infectious nature of COVID-19, quarantine protocols prevented access to patients during the active phase of the disease. After discharge from the hospital, we were not allowed to bring study subjects back to the hospital eye clinic for the sake of infection risks. Consequently, this study lacks the usual objective clinical assessment data of the anterior ocular surface such as tear volume and tear stability tests. As the study was entirely reliant on subjective responses, we were concerned about inter-examiner bias and consequently, only one of us (NH) conducted all the telephone interviews with our subjects. NH is an ophthalmologist experienced in treating ocular surface disease. NH also interviewed each subject within 10 days of discharge from hospital to minimize recall bias (Flynn et al. 2019). We managed to recruit over 85% of the potential pool of 64 subjects discharged from hospital which gives us confidence about the representativeness of our subject sample. Nevertheless, our potential pool of subjects consisted of patients admitted to the isolation ward of the hospital between 19 January and 29 February 2020 and it may not be representative of the wider population of patients with COVID-19.

In conclusion, in a cohort of 56 patients with COVID-19, we assessed ocular symptoms before and after the onset of COVID-19. We found that in about 1 in 4 subjects, ocular symptoms became more severe after the onset of COVID-19. In about 1 in 10 subjects, these ocular symptoms appear several days before the onset of fever or respiratory symptoms. The presence of ocular symptoms in COVID-19 requires further investigation into its significance and has occupational safety implications for eye care professionals.

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