Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: a cross-sectional study

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ABSTRACT.

Purpose: **To investigate the ocular manifestations and clinical characteristics of COVID-19 patients caused by SARS-CoV-2 in Wuhan, China.**

Methods: **A total of 535 COVID-19 patients were recruited at Mobile Cabin Hospital and Tongji Hospital. Information on demographic characteristics, exposure history, ocular symptoms, eye drop medication, eye protections, chronic eye diseases, systemic concomitant symptoms, radiologic findings and SARS-CoV-2 detection in nasopharyngeal swabs by real-time PCR was collected from questionnaires and electronic medical records.**

Results: **Of 535 patients, 27 patients (5.0%) presented with conjunctival congestion and 4 patients had conjunctival congestion as the initial symptom. The average duration of conjunctival congestion was 5.9 ± 4.5 days (mean [SD]). The other ocular symptoms, including increased conjunctival secretion, ocular pain, photophobia, dry eye and tearing, were also found in patients with conjunctival congestion. Notably, hand–eye contact was independently correlated with conjunctival congestion in COVID-19 patients. We also found that some COVID-19 patients had chronic eye diseases, including conjunctivitis (33, 6.2%), xerophthalmia (24, 4.5%) and keratitis (14, 2.6%). Similar to the published studies, the most common clinical symptoms were fever, cough and fatigue. A total of 343 patients (64.1%) had positive SARS-CoV-2 detection in nasopharyngeal swabs.**

Conclusions: **Conjunctival congestion is one of the COVID-19-related ocular symptoms, which could occur as the initial symptoms. Frequent hand–eye contact may be the risk factor for conjunctival congestion in COVID-19 patients. Screening of patients with conjunctival congestion by ophthalmologists is advocated during the outbreak of COVID-19. It is essential to provide eye-care equipment and strengthen education on eye protection.**

Key words: conjunctival congestion – COVID-19 – hand-eye contact – ocular manifestations – SARS-CoV-2

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Introduction

The ongoing outbreak of the novel coronavirus disease (COVID-19) has been declared by WHO as a global public health emergency. COVID-19 was first reported in Wuhan, China, in December 2019, followed by an outbreak across Hubei Province, other parts of China and now all over the world, particularly in America, Spain, Italy and Germany (Huang et al. 2020). This serious infectious disease is caused by a novel enveloped RNA betacoronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lu et al. 2020a,b). A study in the *New England Journal of Medicine* by Zhong Nanshan and colleagues reported nine cases with conjunctival congestion among the 1,099 cases enrolled (Guan et al., 2020). Besides, a recent paper found that 31.6% COVID-19 patients had ocular manifestations consistent with conjunctivitis, including conjunctival hyperaemia, chemosis, epiphora or increased secretions (Wu et al. 2020). However, the complete profiling of COVID-19-related ocular symptoms, eye protections and other ocular characteristics is still insufficient. Several infected cases presented firstly with conjunctivitis before the onset of pneumonia, implying that the ocular route might be the potential transmission route of SARS-CoV-2 virus under certain conditions (Lu et al. 2020a,b; Xia et al., 2020). A recent study revealed that SARS-CoV-2 also uses the cell entry receptor, angiotensin-converting enzyme 2 (ACE2), similar to SARS-CoV (Wan et al., 2020; Zhou et al., 2020). Moreover, the expression and activity of ACE2 can be detected in the ocular surface, including the cornea and conjunctiva, which provides transocular entry potential for SARS-CoV-2 (Sun et al., 2004).

Several urgent questions need to be addressed, including (1) What are the detailed profiles of COVID-19-related ocular symptoms and diseases? (2) What are the clinical characteristics of COVID-19 patients with conjunctival congestion? and (3) Can COVID-19 spread through the ocular route or present as the primary infected site? To answer these questions, it is essential to perform ocular screening among patients with COVID-19. To our knowledge, comprehensive ophthalmological data on COVID-19 are still missing.

Hence, the present cross-sectional study was designed to describe the ophthalmic characteristics of COVID-19 patients in Wuhan, aiming to get a complete ocular screening of COVID-19, which may provide clinical clues for the diagnosis and treatment of the disease and a theoretical basis for appropriate protection guidelines in the population.

Materials and Methods

Study population

The study was conducted in accordance with the Declaration of Helsinki. It has been approved by the ethics committee of Tongji Hospital and the China Ethics Committee for Registering Clinical Trials (ChiCTR2000030489). Informed consent was obtained from the patients involved.

A total of 3149 patients were recruited from 1 February to 1 March 2020, at Mobile Cabin Hospital of Optical Valley and Tongji Hospital of Huazhong University of Science and Technology in Wuhan, China. The exclusion criteria were as follows: (1) current hospitalized patients; (2) severe COVID-19 patients; (3) patients without smartphone; (4) unable to contact by telephone; and (5) refused questionnaire. After evaluation with the exclusion criteria, a total of 535 patients were finally valid for the study (flow chart presented in Fig. 1). Diagnosis and classifications of COVID-19 were made according to the novel coronavirus infection pneumonia diagnosis and treatment guideline, 7th edition (National Health Commission of the people's republic of China).

Data collection

Demographic, epidemiological, clinical, laboratory and radiologic data were obtained from patients' electronic medical records and an electronic questionnaire completed by patients on a smartphone. Data about ocular manifestation, the use of eye drops and eye protection were obtained by ophthalmologists via telephone. If data were missing from the questionnaire or clarification was needed, we communicated directly with the patient by telephone after obtaining informed consent. Two researchers independently reviewed the data collection forms to double-check the data collected.

For the reason of safety and disease control, the slit lamp examinations or other ophthalmic examinations cannot be realized. For the patients reporting conjunctival congestion or conjunctivitis, we further did the basic ophthalmologic examinations with flashlight or send them a representative picture of conjunctival congestion to confirm their symptoms.

Nucleic acid detection of SARS-CoV-2 in nasopharyngeal swabs

Nasopharyngeal swabs were collected from all patients by a trained healthcare worker using protective equipment. The swab samples were maintained in a viral-transport medium stored between 2°C and 8°C.

All samples were analysed by conventional qualitative reverse transcription polymerase chain reaction (RT-PCR). RNA was extracted from the clinical samples using a viral RNA kit. A 25 μl reaction containing 5 μl of RNA, 12.5 μl of 2 × reaction buffer provided with the one-step RT-PCR system with Platinum Taq Polymerase (Invitrogen, Darmstadt, Germany; containing 0.4 mM of each deoxyribont triphosphates (dNTP) and 3.2 mM magnesium sulphate), 1 μl of reverse transcriptase/Taq mixture from the kit, 0.4 μl of a 50 mM magnesium sulphate solution (Invitrogen), and 1 μg of nonacetylated bovine serum albumin. The SARS-CoV-2 specific primers are as follows: forward primer 5′-ACTTCTTTTT CTTGCTTTCGTG GT-3′; reverse primer 5′-GCAGCAG TACGCACACAATC-3′; and the probe 5′CY5-CTAGTTACACTAGCCATCC TTACTGC-3′BHQ1. (Huang et al. 2020) These primers were used to detect the

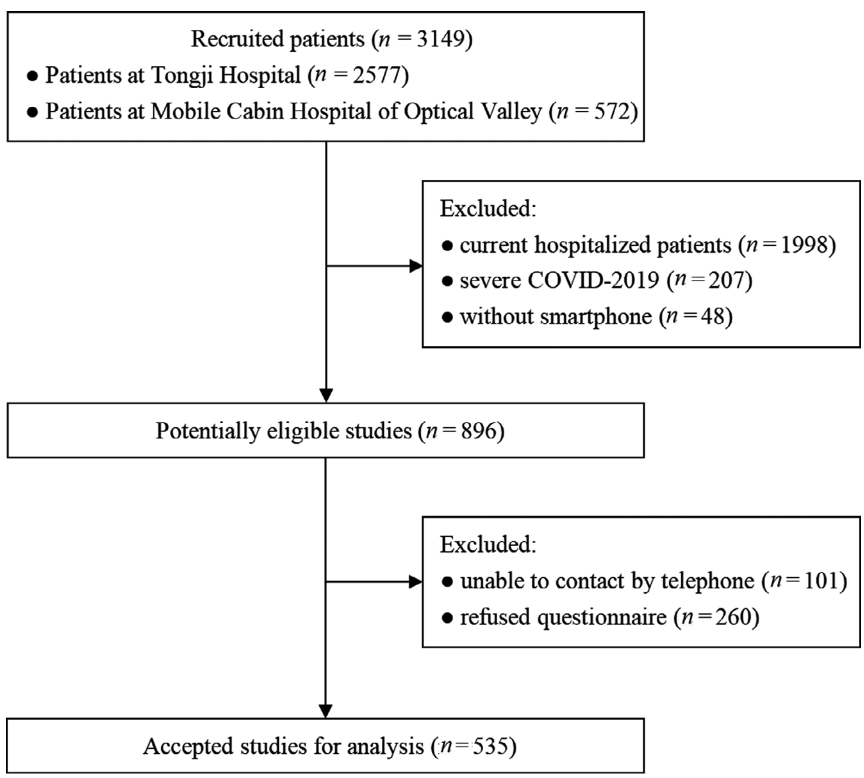

Fig. 1. Flow chart for the study profile. A total of 535 patients were finally valid for the study.

Table 1. Demographics and baseline characteristics of COVID-19 patients by conjunctival congestion.

Demographics and baseline characteristics	Without conjunctival congestion (N = 508)	With conjunctival congestion (N = 27)	p value
Median age (IQR) – years	44.0 (34.0–54.2)	44.0 (28.5–53.5)	0.529
Age group – no. (%)			
<15 year	0	0	0.211
15–44 year	259 (51.0%)	15 (55.6%)	
45–64 year	235 (46.3%)	10 (37.0%)	
≥65 year	14 (2.8%)	2 (7.4%)	
Female sex – no. (%)	255 (50.2%)	12 (44.4%)	0.56
Occupation			0.008*
Employee	207 (45.8%)	5 (20.0%)	
Self-employed	85 (18.8%)	5 (20.0%)	
Unemployed	79 (17.5%)	4 (16.0%)	
Retired	36 (8.0%)	3 (12.0%)	
Agricultural worker	22 (4.9%)	3 (12.0%)	
Student	9 (2.0%)	3 (12.0%)	
Medical staff	14 (3.1%)	2 (8.0%)	
Smoking history – no. (%)			0.464
Never smoked	456 (89.8%)	23 (85.2%)	
Former smoker	29 (5.7%)	2 (7.4%)	
Current smoker	23 (4.5%)	2 (7.4%)	
Exposure history within past 14 days – no. (%)			
Huanan Seafood Wholesale Market	5 (1.0%)	0	1.000
Contact with person with fever	149 (29.3%)	10 (37.0%)	0.393
Contact with COVID-19 patient in family or community	193 (38.0%)	10 (37.0%)	0.921
Chronic medical illness – no. (%)			
Hypertension	65 (12.8%)	5 (18.5%)	0.390
Diabetes mellitus	37 (7.3%)	1 (3.7%)	0.712
Hyperlipidaemia	6 (1.2%)	0	1.000
Cardiovascular and cerebrovascular diseases	18 (3.5%)	0	1.000
Respiratory system disease	36 (7.1%)	1 (3.7%)	1.000
Haematological system disease	3 (0.6%)	0	1.000
Chronic kidney disease	3 (0.6%)	0	1.000
Chronic liver disease	25 (4.9%)	0	1.000
Autoimmune disease	8 (1.6%)	2 (7.4%)	0.086

Data are presented as median (IQR) or number (percentage). p values are calculated from Kruskal–Wallis test, chi-square test or Fisher's exact test.
* p value < 0.05.

presence of SARS-CoV-2 RNA. All oligonucleotides were synthesized and provided by Tib-Molbiol (Berlin, Germany). The RT-PCR condition was developed by the Clinical Laboratory of Tongji Hospital. Thermal cycling was performed at 55°C for 10 min for reverse transcription, followed by 95°C for 3 min and then 45 cycles of 95°C for 15 s and 58°C for 30 s.

Statistical analysis

Continuous variables were expressed as medians (interquartile range, IQR) and compared with the Kruskal–Wallis test. Categorical variables were summarized as counts (percentages) and compared by chi-square test or Fisher's exact test. Univariate and multivariate regression analysis were used to evaluate correlations between ocular protections and conjunctival congestion. No imputation was made for missing data. All the analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc. Boston, MA) and R (http://www.R-project.org).

Results

Demographics and baseline characteristics of COVID-19 patients by conjunctival congestion

A total of 535 COVID-19 patients (27 with conjunctival congestion) were enrolled in the study. The demographic data, exposure history and past medical history are summarized in Table 1.

The median age of patients with or without conjunctival congestion was 44 years. The majority (55.6% and 51.0%, respectively) were aged 15–44 years. There was a similar proportion of men and women (15/12 and 253/255, respectively) in the two groups. Nearly half (45.8%) of the patients without conjunctival congestion employed, and 14 (3.1%) infected cases were medical staff; 3 (12.0%) patients with conjunctival congestion were agricultural workers, and 2 (8.0%) patients were medical staff. Among all the subjects with or without conjunctival congestion, most had a contact history with a person with a fever (37.0% and 29.3%, respectively) or with a confirmed COVID-19 case in the family or community (37.0% and 38.0%, respectively). The top three ranked chronic illnesses were same in patients with or without conjunctival congestion, including hypertension (18.5% and 12.8%, respectively), diabetes mellitus (3.7% and 7.3%, respectively) and respiratory system disease (3.7% and 7.1%, respectively).

Clinical characteristics of COVID-19 patients by conjunctival congestion

The clinical characteristics, including the common symptoms of COVID-19, the radiologic findings of chest CT and the PCR results of SARS-CoV-2 detection, in nasopharyngeal swabs are summarized in Table 2.

The clinical symptoms of the patients in two groups were similar, but the percentages of involvement were various. The most common symptoms were fever (66.7% and 60.8% in patients with or without conjunctival congestion, respectively), cough (74.1% and 64.8%, respectively) and fatigue (51.9% and 38.6%, respectively). Besides, 40.7% of patients with conjunctival congestion and 42.5% of patients without conjunctival congestion had a temperature over 38.1° C. Of the patients with conjunctival congestion, 29.6% suffered from diarrhoea and 25.9% developed dyspnoea while hospitalized; of the patients without conjunctival congestion, these percentages were 31.5% and 22.2%, respectively. With regard to radiologic findings of the lung, most patients had bilateral involvement (69.2% and 76.5% in patients with or without

Table 2. Clinical characteristics of COVID-19 patients by conjunctival congestion.

Clinical characteristics	Without conjunctival congestion (N = 508)	With conjunctival congestion (N = 27)	p value
Symptoms – no. (%)			
Fever	309 (60.8%)	18 (66.7%)	0.544
Highest temperature			0.582
<37.3°C	199 (39.2%)	9 (33.3%)	
37.3–38°C	93 (18.3%)	7 (25.9%)	
38.1–39.0°C	170 (33.5%)	10 (37.0%)	
>39.0°C	46 (9.1%)	1 (3.7%)	
Cough	329 (64.8%)	20 (74.1%)	0.322
Sore throat	103 (20.3%)	6 (22.2%)	0.807
Fatigue	196 (38.6%)	14 (51.9%)	0.169
Poor appetite	139 (27.4%)	7 (25.9%)	0.870
Chest stuffiness	169 (33.3%)	9 (33.3%)	0.994
Shortness of breath	84 (16.5%)	4 (14.8%)	1.000
Dyspnoea	113 (22.2%)	7 (25.9%)	0.655
Nasal discharge	22 (4.3%)	3 (11.1%)	0.125
Nasal congestion	24 (4.7%)	3 (11.1%)	0.149
Headache	115 (22.6%)	6 (22.2%)	0.960
Myalgia or arthralgia	147 (28.9%)	8 (29.6%)	0.938
Diarrhoea	160 (31.5%)	8 (29.6%)	0.839
Abdominal pain	50 (9.8%)	3 (11.1%)	0.742
Radiologic findings – no./total no. (%)			
Chest CT			0.059
Single lung	90/463 (19.4%)	4/26 (15.4%)	
Bilateral lungs	354/463 (76.5%)	18/26 (69.2%)	
Normal	19/463 (4.1%)	4/26 (15.4%)	
Laboratory findings – no. (%)			0.807
SARS-CoV-2 in throat swab specimens by RT-PCR			
Positive	325 (64.0%)	18 (66.7%)	
Probable positive	27 (5.3%)	2 (7.4%)	
Negative	156 (30.7%)	7 (25.9%)	

Data are presented as median (IQR) or number (percentage). *P* values are calculated from Kruskal–Wallis test, chi-square test or Fisher's exact test.

conjunctival congestion, respectively). All patients underwent SARS-CoV-2 detection via nasopharyngeal swabs several times. Respectively, 66.7% and 64.0% of patients were confirmed with positive SARS-CoV-2 detection in nasopharyngeal swabs.

Ocular characteristics of COVID-19 patients by conjunctival congestion

The ocular characteristics, including ocular symptoms, recent use of eye drop medication, eye protections and previous eye diseases, are presented in Table 3.

In our study, the average duration of conjunctival congestion was 5.9 ± 4.5 days (mean [SD]). More accompanied ocular symptoms were found in patients with conjunctival congestion, including increased conjunctival secretion, ocular pain, photophobia, dry eye and tearing. In addition, a few patients suffered from dry eye in patients with or without conjunctival congestion (37.0% and 20.1%, respectively). According to the evaluation by ophthalmologists, patients with conjunctival congestion received eye drops of ofloxacin (18.5%), tobramycin (7.4%) and ganciclovir (7.4%). As for ocular protections, a total of 33.3% patients with conjunctival congestion and 28.0% patients without conjunctival congestion wore glasses or goggles. More than half of patients ever touched their eyes with their hands. Furthermore, patients with conjunctival congestion tended to touch their eyes frequently (22.2% vs. 7.9%, $P = 0.033$). During the hospitalization, most patients spent a lot of time on short-distance reading. 307 (60.6%) and 14 (51.9%) patients in two groups spent more than 4 hours per day on reading. A minority of patients had chronic eye diseases, including conjunctivitis, keratitis and xerophthalmia.

Correlations between ocular protections and conjunctival congestion in COVID-19 patients by multivariate regression analysis

Multivariate regression analysis between ocular protections and conjunctival congestion is performed in Table 4. Model I adjusted for age, gender and smoking history. Model II adjusted for the former factors, highest temperature and SARS-CoV-2 detection.

On univariate analysis, the frequency of hand–eye contact was associated with conjunctival congestion. After adjusting for other clinical factors in multivariate regression analysis, the frequency of hand–eye contact was still correlated with conjunctival congestion in model II. The regression coefficient was 4.01 (95% CI, 1.11–14.55, $p = 0.035$). No significant relation was fond between wearing glass or goggle, time of reading and conjunctival congestion.

Ocular profiles and clinical characteristics of patients with conjunctival congestion

The ocular symptoms, eye drop medications, eye protections, history of eye disease and clinical characteristics of all 27 patients with conjunctival congestion are summarized in Table 5. The duration of conjunctival congestion, onset date of clinical symptoms and days after clinical symptoms occurring conjunctival congestion are summarized in Fig. 2.

Eight patients had conjunctival congestion and increased conjunctival secretion (cases 4, 6, 8, 12, 13, 14, 19 and 26). Five patients had tearing (cases 2, 4, 6, 11 and 16). Five patients also had ocular pain (cases 1, 7, 10, 21 and 27), and five patients had foreign body sensation in the eyes (cases 4, 7, 17, 21 and 26). Nineteen patients ever touched their eyes with their hands, and 13 (cases 2, 3, 4, 6, 8, 9, 10, 11, 18, 22, 23, 24 and 26) of them did not wash their hands before touching their eyes. Of the patients with conjunctival congestion, most had bilateral lung involvement indicated by chest CT (18/26, 69.2%) and positive PCR results in SARS-CoV-2 detection (18, 66.7%).

The duration of conjunctival congestion ranged from 2 to 24 days. Conjunctival congestion appeared mostly after the first clinical symptoms

Table 3. Ocular characteristics of COVID-19 patients by conjunctival congestion.

Ocular characteristics	Without conjunctival congestion (*N* = 508)	With conjunctival congestion (*N* = 27)	p value
Duration of conjunctival congestion – days	-	5.9 ± 4.5	
Ocular symptoms – no. (%)			
Conjunctival secretion	44 (8.7%)	8 (29.6%)	<0.001*
Ocular pain	18 (3.5%)	5 (18.5%)	<0.001*
Foreign body sensation	58 (11.4%)	5 (18.5%)	0.265
Photophobia	13 (2.6%)	3 (11.1%)	0.041*
Blurred vision	65 (12.8%)	3 (11.1%)	1.000
Dry eye	102 (20.1%)	10 (37.0%)	0.035*
Tearing	49 (9.6%)	6 (22.2%)	0.036*
Itching	49 (9.6%)	4 (14.8%)	0.329
Eye drops medication within past 14 days – no. (%)			
Ofloxacin	16 (3.1%)	5 (18.5%)	<0.001*
Tobramycin	2 (0.4%)	2 (7.4%)	0.014*
Ganciclovir	2 (0.4%)	2 (7.4%)	0.014*
Artificial tears	11 (2.2%)	1 (3.7%)	0.466
Wearing glass or goggle – no. (%)	142 (28.0%)	9 (33.3%)	0.545
Hand–eye contact – no. (%)			0.033*
Never	195 (38.4%)	8 (29.6%)	
Seldom	273 (53.7%)	13 (48.1%)	
Often	40 (7.9%)	6 (22.2%)	
Total time of short-distance reading in a day – no. (%)			0.934
<2 hr	110 (21.7%)	7 (25.9%)	
2–4 hr	91 (17.9%)	6 (22.2%)	
4–8 hr	163 (32.1%)	7 (25.9%)	
8–12 hr	103 (20.3%)	5 (18.5%)	
>12 hr	41 (8.1%)	2 (7.4%)	
Chronic eye diseases – no. (%)			
Conjunctivitis	30 (5.9%)	3 (11.1%)	0.228
Keratitis	13 (2.6%)	1 (3.7%)	0.520
Xerophthalmia	22 (4.3%)	2 (7.4%)	0.345
Cataract	9 (1.8%)	0	1.000
Glaucoma	4 (0.8%)	0	1.000
Macular disease	1 (0.2%)	0	1.000
Diabetic retinopathy	5 (1.0%)	0	1.000
Other retinal disease	3 (0.6%)	0	1.000
Optic nerve diseases	1 (0.2%)	0	1.000

Data are presented as median (IQR) or number (percentage). *P* values are calculated from Kruskal–Wallis test, chi-square test or Fisher's exact test.
* p value < 0.05.

of COVID-19. Four patients (cases 14, 17, 21 and 25) had conjunctival congestion as an initial symptom. Seven patients (cases 5, 7, 11, 16, 18, 22 and 23) developed conjunctival congestion within three days after the beginning of clinical symptoms.

Discussion

To date, the epidemiologic data on the incidence of conjunctivitis in COVID-19 patients range from 0.8% to 7.9% (Guan et al., 2020; Wu et al. 2020; Xia et al., 2020; Zhang et al., 2020) However, the precise incidence of ocular manifestations relative to COVID-19 is unclear. In our present study, we found that (1) of a total of 535 COVID-19 patients identified, 27 patients (5.0%) presented with conjunctival congestion; (2) the accompanied ocular symptoms were different between the two groups with or without conjunctival congestion, and dry eye (37.0%), conjunctival secretion (29.6%), tearing (22.2%), ocular pain (18.5%) ranked in the top four in patients with conjunctival congestion group; and 3) simultaneously, we also found the occurrence of conjunctival congestion in COVID-19 patients correlated with a higher frequency of hand–eye contact (22.2% vs. 7.9%).

Most recently, Wu et al. (2020) found that one-third of patients with COVID-19 had ocular abnormalities, consistent with conjunctivitis, including conjunctival hyperaemia or increased secretions. However, these epidemiological investigations did not fully observe other ocular manifestations besides conjunctival congestion. The present epidemiologic study summarized more manifestations present on the ocular surface mainly in the mild cases. We enrolled 535 patients and similarly found that COVID-19 patients exhibit ocular manifestations including conjunctival congestion (27), secretion (52), foreign body sensation (63), blurred vision (68), dry eye (112), itching (53), photophobia (16) and tearing (55). The demographics and baseline characteristics of COVID-19 patients with or without conjunctival congestion have no significant difference. The incidence of conjunctival congestion in our study is 5.0%, which is lower than Wu's report (3/38, 7.9%) (Wu et al. 2020) but higher than that in Zhong's large sample report (9/1099, 0.8%) (Guan et al., 2020) and Xia's study (1/30, 3.3%) (Xia et al., 2020). Wu found that conjunctival congestion occurred in patients with more severe COVID-19. Zhong and colleagues extracted data from 552 hospitals in 30 provinces, autonomous regions and municipalities in China, while 21 common-type and nine severe-type COVID-19 patients were observed by Xia in Zhejiang Province. However, the COVID-19 patients in our study mainly came from Tongji Hospital (271) or Mobile Cabin Hospital (264) in Wuhan, and they were mostly common-type. Therefore, the clinical type and region may be the causes of the various incidence of conjunctival congestion in COVID-19 patients.

Given that SARS-CoV-2 nucleic acid was not detected in patients' conjunctival swab sample, we did not diagnosis them with conjunctivitis directly. However, these 27 patients did not report any other chronic eye diseases nor any symptoms associated with intraocular diseases (such as iritis, choroiditis and retinal disease), which suggests that the possibility of endophthalmitis is very small, and conjunctivitis may be the primary cause of the conjunctival congestion. Moreover, conjunctival congestion and positive RT-PCR in pharyngeal swabs were found at the same time in four COVID-19 patients (cases 11, 20, 23 and 24) who reported no

Table 4. Correlations between ocular protections and conjunctival congestion in COVID-19 patients by multivariate regression analysis.

	Unadjusted	Model I	Model II
Wearing glass or goggle			
No	1.00	1.00	1.00
Yes	1.29 (0.57, 2.94) 0.546	1.31 (0.52, 3.28) 0.565	1.24 (0.49, 3.17) 0.648
Hand–eye contact			
Never	1.00	1.00	1.00
Seldom	1.16 (0.47, 2.85) 0.745	0.99 (0.37, 2.69) 0.989	0.92 (0.33, 2.59) 0.871
Often	3.66 (1.20, 11.11) 0.022*	3.88 (1.12, 13.39) 0.032*	4.01 (1.11, 14.55) 0.035*
Total time of short-distance reading			
<2 hr	1.00	1.00	1.00
2–4 hr	1.04 (0.34, 3.19) 0.951	1.29 (0.36, 4.65) 0.696	1.29 (0.35, 4.76) 0.698
4–8 hr	0.67 (0.23, 1.98) 0.473	0.62 (0.17, 2.19) 0.454	0.59 (0.16, 2.13) 0.417
8–12 hr	0.76 (0.23, 2.48) 0.653	0.54 (0.13, 2.30) 0.404	0.59 (0.14, 2.58) 0.483
>12 hr	0.77 (0.15, 3.84) 0.747	0.54 (0.08, 3.51) 0.519	0.46 (0.07, 3.17) 0.434

Data are presented as β (95% CI) p value.
* p value < 0.05. Model I adjust for age, gender, smoking history and occupation. Model II adjust for the former factors, highest temperature and SARS-CoV-2 detection.

chronic eye diseases. Our previous study found a rare case of nosocomial SARS-CoV-2 infection initiated with conjunctivitis in a nurse, and both the conjunctival and nasopharyngeal swabs tested for SARS-CoV-2 were positive.(Sun et al., 2020) However, the aim of this epidemiological study is to investigate the ocular manifestations of COVID-19 patients, and most of them were no longer exhibit conjunctival congestion when they performed investigation, which contribute to the conjunctival swab test data missing. Our study also found that the average duration of conjunctival congestion was 5.9 ± 4.5 days (mean [SD]), ranging from two to twenty-four days. Four patients diagnosed with COVID-19 patients had an initial symptom of conjunctival congestion, which reminds us that ocular manifestations occur early in the course of COVID-19. Therefore, healthcare workers should pay attention to patients' ocular symptoms and manifestations in the early stage of disease and should perform a conjunctival swab test for SARS-CoV-2 in patients with conjunctival congestion.

Table 5. Detailed information about the ocular profiles and clinical characteristics of patients with conjunctival congestion.

				Other ocular characteristics						Clinical characteristics		
Case	Gender	Age (years)	Ocular symptoms	Eye drops	Glass or goggle	Hand–eye contact	Wash hands before hand–eye contact	Reading	Chronic eye diseases	Temp (°C)	Chest CT	PCR
1	Male	18	CC, OP, P	No	Yes	Seldom	Yes	>12h	No	36.5	Single lung	+
2	Male	44	CC, DE, I, T	No	No	Seldom	No	8-12h	No	39.0	Single lung	–
3	Male	25	CC, BV, DE	No	No	Often	No	>12h	No	36.7	Normal	+
4	Female	30	CC, CS, FBS, P, BV, DE, T	No	No	Seldom	No	4-8h	No	37.7	Bilateral lungs	+/–
5	Female	47	CC	No	Yes	Seldom	Yes	4-8h	No	38.5	Bilateral lungs	–
6	Female	33	CC, CS, DE, T	Tobramycin	Yes	Seldom	No	4-8h	Conjunctivitis	37.5	Bilateral lungs	+
7	Male	18	CC, OP, FBS, DE	No	Yes	Seldom	Yes	8-12h	Conjunctivitis	36.6	Unclear	–
8	Male	18	CC, CS	No	Yes	Often	No	8-12h	No	36.8	Normal	+
9	Male	44	CC, DE	Ofloxacin	No	Seldom	No	4-8h	Xerophthalmia	36.5	Bilateral lungs	+
10	Female	27	CC, OP	Artificial tears	Yes	Often	No	4-8h	Xerophthalmia	37.8	Normal	+
11	Female	28	CC, T	Ganciclovir	Yes	Seldom	No	2-4h	No	38.2	Bilateral lungs	+
12	Female	64	CC, CS, BV, DE	No	No	Often	Yes	2-4h	No	37.5	Bilateral lungs	–
13	Male	56	CC, CS	No	No	Never	-	<2h	No	39.0	Bilateral lungs	+
14	Female	61	CC,DC, DE	No	No	Never	-	<2h	No	38.5	Single lung	–
15	Male	42	CC	No	No	Often	Yes	2-4h	No	38.6	Bilateral lungs	+
16	Female	40	CC, T	No	No	Never	-	2-4h	No	37.7	Bilateral lungs	–
17	Male	65	CC, FBS	No	No	Never	-	4-8h	No	39.0	Bilateral lungs	+
18	Male	45	CC	No	Yes	Seldom	No	<2h	No	39.4	Bilateral lungs	+
19	Male	62	CC, CS, DE	Ofloxacin	No	Seldom	Yes	<2h	No	36.8	Bilateral lungs	–
20	Female	58	CC	Ofloxacin Ganciclovir	No	Never	-	<2h	No	39.0	Single lung	+
21	Female	43	CC, OP, FBS	No	No	Never	-	<2h	No	37.0	Bilateral lungs	+/–
22	Male	65	CC, I	No	Yes	Seldom	No	8-12h	No	37.5	Bilateral lungs	+
23	Male	50	CC, I	Ofloxacin	No	Seldom	No	2-4h	No	39.0	Bilateral lungs	+
24	Female	51	CC, I	No	No	Seldom	No	2-4h	No	38.5	Bilateral lungs	+
25	Male	28	CC	No	No	Never	-	4-8h	No	37.5	Bilateral lungs	+
26	Male	29	CC, CS, FBS, DE, I	Ofloxacin Tobramycin	No	Often	No	8-12h	Conjunctivitis Keratitis	36.5	Normal	+
27	Female	51	CC, OP, P	No	No	Never	-	<2h	No	36.5	Bilateral lungs	+

CC, conjunctival congestion; CS, conjunctival secretion; OP, ocular pain; FBS, foreign body sensation; P, photophobia; BV, blurred vision; DE, dry eye; T, tearing; and I, itching.
+, positive; +/–, probable positive; and –, negative.

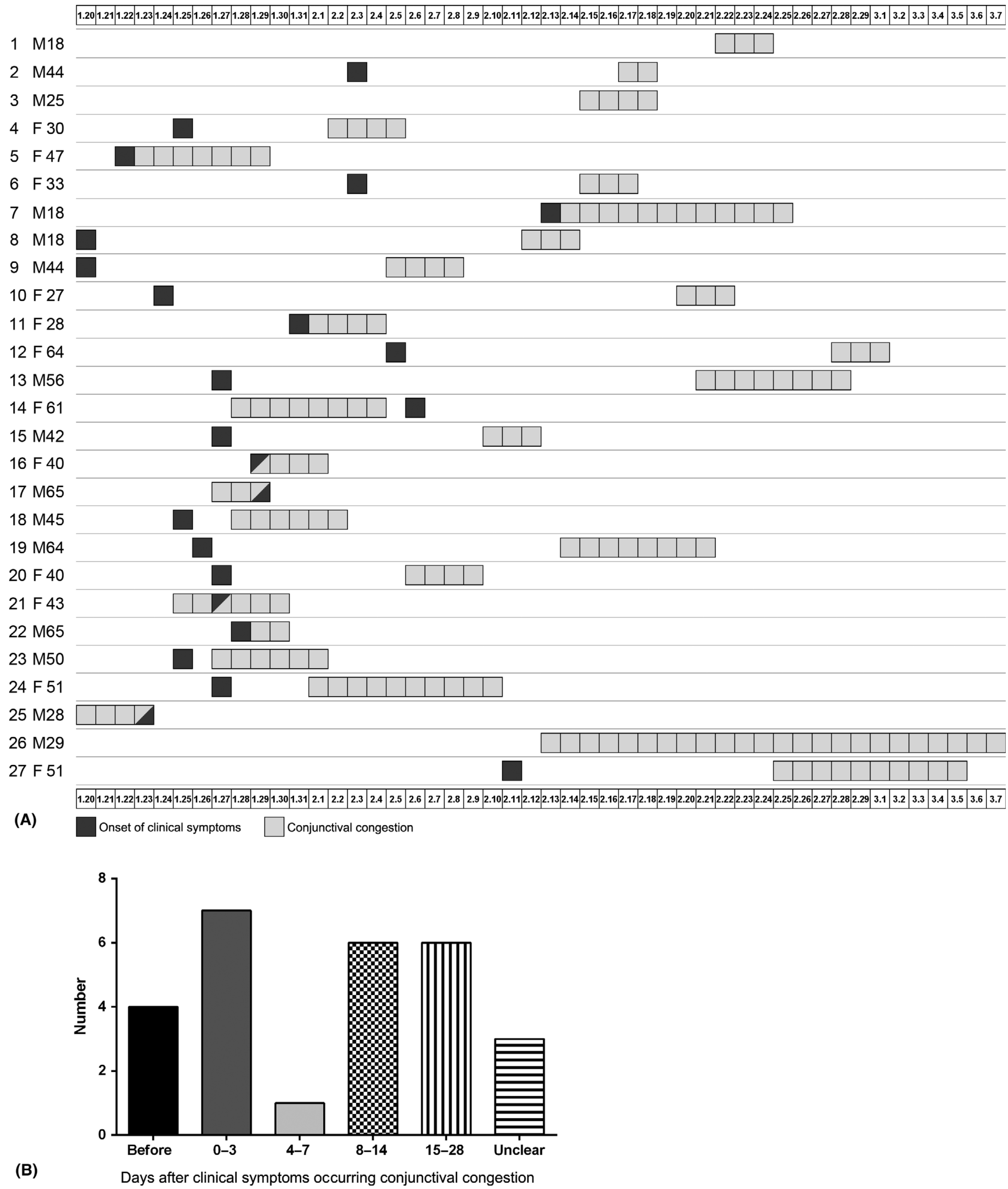

Fig. 2. Detailed information about the duration of conjunctival congestion, the onset date of clinical symptoms in 27 patients with conjunctival congestion. (A) The numbers in boxes are calendar dates from 20 January 2019 to 7 March 2020. Dark grey box – onset date of the first clinical symptoms; light grey box – conjunctival congestion. (B) Days after clinical symptoms occurring conjunctival congestion. Four (14.8%) patients had conjunctival congestion as an initial symptom.

SARS-CoV-2 is thought to be transmitted from person to person mainly through respiratory droplets or close contact (Xu et al. 2020). The ocular surface is exposed to the outside environment, which may become a potential gateway for pathogens such as viruses to invade the human body.(-Belser et al. 2013; Stiles 2014)

Moreover, eye rubbing is another high risk factor for virus transmission, which has been confirmed in adenovirus-induced conjunctivitis.(Artieda et al. 2010) Simultaneously, we found that a total of 332 COVID-19 patients had a history of hand–eye contact, including 286 cases who reported seldom hand–eye contact and 46 who reported frequent hand–eye contact. Among the 27 cases with conjunctival congestion, 19 (70.4%) had a history of hand–eye contact, 6 (22.2%) with frequent contact. The results of multivariate regression analysis also showed that the high-frequency hand–eye contact correlated with conjunctival congestion, suggesting that hand–eye contact is possibly a risk factor for conjunctival congestion in COVID-19 patients.

The present study also found that the incidence of dry eye, blurred vision and foreign body sensation was the top three ocular symptoms in all patients (20.9%, 12.7% and 11.8%), which could be due to the fact that COVID-19 patients are more likely to have a lot of time to use electronic products. Our results showed that 321 of 535 COVID-19 patients spent more than four hours per day on short-distance reading and 43 of them even spent exceeded 12 hours per day on reading. Because of this, healthcare workers should propose patients reading scientifically and reducing short-distance reading time.

Consistent with previous studies, SARS-CoV-2-infected patients developed respiratory disorders with initial symptoms of fever, cough, chest stuffiness and fatigue, which quickly progress to pneumonia and even shortness of breath (Chen et al. 2020a,b; Huang et al. 2020; Zhu et al. 2020). However, extra-pulmonary manifestations were also observed in a number of patients at the onset of the illness, including headache, myalgia or arthralgia, and diarrhoea, and some even presented with asymptomatic infection (Chen et al. 2020a,b; Rothe et al. 2020). We also found that most of the enrolled COVID-19 patients had bilateral lung accumulation (372/489), and the SARS-CoV-2 RT-PCR test was positive at least once in 343 patients. However, no significant difference was observed between the COVID-19 patients with or without conjunctival congestion.

The present study has some limitations. First, the sample size was relatively small and the covered population excluded severe cases, since only patients with mild symptoms could complete our electronic questionnaire or telephone follow-up. Second, most of the ocular manifestations were self-reported retrospectively by the questionnaire owing to a physical examination by slit lam is not feasible, and conjunctival swab test for SARS-CoV-2 was not performed in early stage. However, a representative picture of conjunctival congestion was send to patients for reference, which made the conjunctival congestion data reasonable. To date, this is the most comprehensive survey with the largest sample related to the eyes. Fourth, no normal population was observed in our study; therefore, a normal control group should be included for comparison in future studies.

Conclusions

In conclusion, the significance of understanding the ocular manifestations of our present study lies in (1) helping to deepen the understanding of COVID-19-related eye diseases; identify ocular symptoms, manifestations and clinical outcomes; and enrich the symptom spectrum of COVID-19; (2) observing the difference between the COVID-19 patients with or without conjunctival congestion; and (3) providing a clue that hand–eye contact correlated with conjunctival congestion in COVID-19 patients. Our findings may provide useful information for the diagnosis and treatment of COVID-19. Simultaneously, it also provides clues for patients with ocular symptoms and manifestations in the early stage of disease should perform a conjunctival swab test for SARS-CoV-2 in patients with conjunctival congestion.

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References

Artieda J, Montes M, Vicente D, Martinez C, Pineiro L & Mendiola J(2010): Outbreak of follicular conjunctivitis caused by adenovirus in a geriatric centre. Enferm Infecc Microbiol Clin **28**: 690–693.

Belser JA, Rota PA & Tumpey TM (2013): Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev **77**: 144–156.

Chen H, Guo J, Wang C et al. (2020): Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet **395**: 809–815.

Chen N, Zhou M, Dong X et al. (2020): Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet **395**: 507–513.

Guan W, Ni Z, Hu Y et al. (2020): Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **382**:1708–1720.

Huang C, Wang Y, Li X et al. (2020): Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **395**: 497–506.

Lu C, Liu X & Jia Z (2020): 2019-nCoV transmission through the ocular surface must not be ignored. Lancet **395**: e39.

Lu R, Zhao X, Li J et al. (2020): Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet **395**: 565–574.

National Health Commission of the people's republic of China. (2020): Pneumonia diagnosis and treatment of novel coronavirus infection (Pilot version 7). Available at: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml (Accessed on 4 Mar 2020).

Rothe C, Schunk M, Sothmann P et al. (2020): Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med **382**: 970–971.

Stiles J (2014): Ocular manifestations of feline viral diseases. Vet J **201**: 166–173.

Sun Y, Pan X, Liu L & Ni CR (2004): Expression of SARS coronavirus S protein functional receptor ACE2 in human and rabbit cornea and conjunctiva. Rec Adv Ophthalmol. **24**: 332–336.

Wan Y, Shang J, Graham R, Baric RS, Li F & Gallagher T (2020): Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol **94**: e00127-20.

Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L & Wu K (2020): Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol https://doi.org/10.1001/jamaophthalmol.2020.1291.

Xia J, Tong J, Liu M, Shen Y & Guo D (2020): Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol **92**: 589–594.

Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W & Hao P (2020): Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci **63**: 457–460.

Zhang X, Chen X & Chen L (2020): The evidence of SARS-COV-2 infection on ocular surface. The Ocular Surface **18**: 360–362.

Zhou P, Yang XL & Wang XG (2020): A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature **579**: 270–273.

Zhu N, Zhang D & Wang W (2020): A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med **382**: 727–733.

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