Received: 22 July 2020 | Accepted: 6 August 2020

DOI: 10.1002/jmv.26412

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital

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Abstract

Purpose: The aim of this study was to investigate the ocular findings observed in patients with coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 and to present the relationship between ocular involvement, systemic findings, and laboratory results.

Material and Methods: This cross-sectional study was carried out between 1 May and 30 June 2020. The study included 359 patients diagnosed with COVID-19 and assessed by clinical evaluation, nasopharyngeal polymerase chain reaction, and lung computed tomography.

Results: One hundred ninety-seven (54.9%) of the patients were male and 162 (45.1%) were female. The mean age of the patients was 58.5 years (20-91). Two hundred ninety-four (81.9%) patients were treated in the inpatient clinic and 65 (18.1%) patients were treated in the intensive care unit. Various ocular diseases were observed in 16 (4.5%) of the patients. Although the rate of ocular disease was 12 out of 294 (4.1%) in patients followed up in the inpatient clinic, this rate was 4 out of 65 (6.2%) in intensive care patients. There was no systemic problem in one patient, in whom conjunctival hyperemia was the first and only reason for admission to the hospital. Four patients followed up in the inpatient clinic had conjunctivitis at the time of admission, and conjunctivitis occurred in three patients during hospitalization. Subconjunctival hemorrhage occurred in five patients and vitreous hemorrhage in one patient.

Conclusion: Ocular diseases are uncommon in COVID-19 patients but may occur during the first period of the disease or during follow-up. Ocular diseases may be the initial or only sign of COVID-19 infection.

KEYWORDS

conjunctivitis, COVID-19, ocular findings, SARS-CoV-2

1 | INTRODUCTION

A pneumonia outbreak was identified in Wuhan, China, in December 2019.[1] This highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was named COVID-19 by the World Health Organization (WHO). The disease has spread all over the world and has become an epidemic.[2] The first case in Turkey was detected on 11 March 2020. According to the official figures announced until 1 July, when this article was prepared, 201 098 people had become infected and 5150 people had died.

It is well known that many viral infections, such as adenovirus, enterovirus 70, and H1N1, may produce various ocular

symptoms in addition to systemic findings. The main target of the SARS-CoV-2 virus is the respiratory tract.[1] Direct contact formed through mucous membranes in coronavirus disease 2019 (COVID-19) cases is an important transmission route of the disease. However, the virus also targets many other systems and organs, where the effects and symptoms of the disease are still being described. Coronaviruses have been shown to cause severe ocular diseases in animals, including anterior uveitis, retinal vasculitis, and optic neuritis. However, ocular symptoms in humans are usually rare and mild.[3]

Ocular diseases are not common in COVID-19 cases. Conjunctival infection may occur from droplets or from infected structures coming into contact with the eye.[4] The most frequently reported ocular finding in COVID-19 patients to date is conjunctivitis. It has been reported that these diseases may occur as a first sign of the disease and sometimes during the progression of the disease.[5-7] In previous studies, different conjunctival infections related to COVID-19 have been identified and the presence of SARS-COV-2 in tear fluid has been demonstrated. Ocular structures may be a way of becoming infected and of infecting other people.[8]

Respiratory problems caused by the virus are well known in patients with COVID-19. However, the ophthalmological effects of the disease have not yet been clearly described. The aim of this study was to investigate the ocular symptoms and findings of patients diagnosed with COVID-19, confirmed by clinical findings and lung computed tomography (CT), and present the relationship between these findings and laboratory results.

2 | METHODS

This study was carried out between 1 May and 30 June 2020 in Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakir, Turkey, which was declared a pandemic hospital by the Republic of Turkey Ministry of Health. Ethics committee approval was received for the study from the Ministry of Health Science Board and the aforementioned hospital. Informed consent was obtained from the patients and the principles of the Helsinki Declaration was complied with in the study.

Three hundred fifty-nine patients who were admitted to the hospital with a history of fever, cough, weakness, fatigue, or suspicious contact and were diagnosed with COVID-19 were evaluated. The diagnosis was determined by clinical symptoms, lung CT and nasopharyngeal swabs, with reverse-transcription polymerase chain reaction (RT-PCR), to confirm the presence of SARS-CoV-2. The ocular and systemic symptoms, neutrophil and lymphocyte counts, neutrophil/lymphocyte ratio, C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer levels were recorded. The ocular findings of patients who were treated in the inpatient clinic and intensive care unit (ICU) for severe COVID-19 disease (severe pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure) were evaluated. Systemic questioning and ocular evaluation were made during hospitalization and when patients were treated. All patients were examined by four experienced ophthalmologists using a binocular indirect ophthalmoscope.

2.1 | Statistical analysis

All the data were recorded using the SPSS 20 package for Windows (SPSS, Inc, Chicago, IL). The numerical variables were shown as mean ± standard deviation (min-max), and the categorical variables were shown by the number of cases (n) and percentage (%). The suitability of the data for normal distribution was evaluated with the Kolmogorov-Smirnov test. Mann-Whitney *U* test was used in binary comparisons of the data that did not fit the normal distribution. A $P < .05$ was considered as statistically significant.

3 | RESULTS

This study included 359 COVID-19 patients diagnosed by clinical evaluation, lung CT, and nasopharyngeal polymerase chain reaction (PCR). Of these patients, 197 (54.9%) were male and 162 (45.1%) were female. The mean age of the patients was 58.5 years (20-91). Two hundred ninety-four (81.9%) patients were treated in the inpatient clinic and 65 (18.1%) patients were treated in the ICU. Eleven (16.9%) of the 65 patients treated in the ICU received respiratory support with a mechanical ventilator.

In the systemic investigation, 64 (17.8%) of the patients were admitted to the hospital with fever, 55 (15.3%) with weakness, fatigue, and myalgia, 37 (10.3%) with a cough, and 22 (6.1%) with dyspnea; 49 (13.7%) patients had more than one symptom. One hundred thirty-two (36.8%) patients were admitted to hospital because of suspected contact with COVID-19 without any systemic symptoms. The demographic characteristics and laboratory parameters of the patients are shown in Table 1.

Various ocular diseases were observed in 16 (4.5%) of the patients. One (0.28%) patient did not have any systemic problems, conjunctival hyperemia being the only reason for presenting to the hospital.

TABLE 1 Demographic characteristics and laboratory parameters of the patients with COVID-19

Gender (M/F), n (%)	197 (54.9%)/162 (45.1%)
Age, y (min-max)	58.48 ± 15.89 (20-91)
Neutrophil, /mm^3 (min-max)	5963.8 ± 3808.2 (1162.3-27 830.4)
Lymphocyte, /mm^3 (min-max)	1451.5 ± 749.1 (210.7-4773.2)
Neutrophil/lymphocyte ratio (min-max)	5.95 ± 7.95 (0.74-62.33)
CRP, mg/L (min-max)	57.86 ± 51.09 (2.0-252.3)
LDH, U/L (min-max)	344.3 ± 141.1 (128-1041)
D-dimer, μg/L (min-max)	442.9 ± 513.5 (21-3535)

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LDH, lactate dehydrogenase.

The presence of one or more ocular symptoms such as conjunctival hyperemia, chemosis, epiphora, increased secretion, and photophobia were defined as conjunctivitis. Although conjunctivitis was found to be present in four (1.1%) patients who were treated in the inpatient clinic, the condition occurred in three (0.84%) patients while being treated in the hospital. Subconjunctival hemorrhage developed in five (1.4%) patients, three in the ICU, and two in the inpatient clinic. Vitreous hemorrhage developed in one patient who was diagnosed with diabetes mellitus 8 years ago. It was reported that the patient did not perform ophthalmology control for 4 months due to the COVID-19 outbreak. This patient was on anticoagulant drug therapy during the treatment period. The patient had a severe cough that started 3 days before the vitreous hemorrhage developed.

Although the rate of ocular disease was 12 out of 294 (4.1%) in all patients treated in the inpatient clinic, the rate was 4 out of 65 (6.2%) in intensive care patients. Conjunctival chemosis was not observed in any patient in the inpatient clinic. However, conjunctival chemosis developed in two (0.56%) patients in the ICU. One of these patients was treated with a mechanical ventilator for respiratory distress. The demographic, systemic, and ocular clinical features of the patients with the ocular disease are detailed in Table 2.

Laboratory values of patients with and without conjunctivitis symptoms were compared. Although the neutrophil/lymphocyte ratio was 6.01 ± 8.05 (median: 3.57) and CRP value was 57.62 ± 51.04 mg/L (median: 39) in patients without conjunctivitis (n = 349), this ratio was 4.47 ± 1.65 (median: 4.2) and 68.05 ± 42.34 mg/L (median: 64.45) in patients with conjunctivitis (n = 10), respectively. The difference between parameters was not statistically significant ($P = .451$ and $P = .275$, respectively).

4 | DISCUSSION

In this study, ocular diseases occurring in patients diagnosed with COVID-19 were evaluated in an outbreak hospital. It was observed that ocular diseases, although not common, may occur during the initial period of infection with COVID-19 or during follow-up. It was noted that subconjunctival hemorrhage may develop during treatment in these patients. Vitreous hemorrhage, which had never been reported before in conjunction with COVID-19, developed in one patient. It is conjectured that conjunctival hyperemia may be the initial and only sign of COVID-19 in some patients, although it is very rare.

On 10 January 2020, an ophthalmologist, the late Dr Li Wenliang, warned his country of a new viral syndrome, which he believed had been transmitted to him from a glaucoma patient. On 22 January, Guangfa Wang, a doctor with experience in pneumonia, developed conjunctivitis while visiting Wuhan to observe patients, and a SARS-CoV-2 test proved positive. Dr Wang noted the possible ocular symptoms of the disease and suggested that an alternative way of transmission of the virus may be by ocular infection.[9]

As with other viral infections, ocular symptoms of COVID-19 are often self-limiting and can be treated with symptomatic treatment. To date, there is no evidence that COVID-19 can cause vision loss. However, the severity of this and similar viral diseases is related not only to the infection but also to the host response. Also, it is still too early to observe the long-term clinical features of SARS-CoV-2.

In fact, a human coronavirus called severe acute respiratory syndrome coronavirus (SARS-CoV) was identified in 2004. The virus was first isolated from a 7-month-old child with symptoms of bronchiolitis and conjunctivitis.[10] The characteristics of the virus were later described in different studies; fortunately, this virus did not cause an outbreak worldwide. Studies have shown that there are genomic and structural similarities between the newly identified SARS-CoV-2 and SARS-CoV. In addition, the pathological and epidemiological features of these factors have been reported to show similarities.[11]

At present, it remains unclear how SARS-CoV exists in tears. Among possible explanations are that the conjunctiva may directly become infected with infected droplets, the lacrimal canal may transmit the infection through the respiratory system, or the infection may be transmitted by a hematogenous route to the lacrimal gland.[12] However, in a new study researchers reported that the hypothesis that the virus can pass from the nasopharynx to the ocular surface during COVID-19 infection is probably wrong. In this study, it was also reported that the attachment of the virus to ocular surface cells was not sufficient to initiate the COVID-19 infection.[13]

It is known that the SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE2) receptors located in the airway epithelium. In previous studies, the presence of these receptors in the retina and aqueous humor has been proven.[14] In a new study, researchers reported that there is no evidence of messenger RNA (mRNA) in the conjunctiva, while there is evidence of the expression of mRNA for ACE2 in the corneal epithelium.[15] In contrast, in two new studies, researchers reported specific ACE2 receptors for the SARS-CoV-2 entry in the conjunctiva epithelium.[16,17]

Virus detection by PCR analysis can be performed with a nasopharyngeal swab, as well as a conjunctival swab. However, conjunctival samples yielded a much lower rate of positive cases than nasopharyngeal swabs. In a new study, researchers reported that viral RNA was present in the plasma of COVID-19 patients in the presence of conjunctivitis, while the probability of a positive test for SARS-CoV-2 in the conjunctival swab was weak. This study noted that even if the RT-PCR test negative, the virus may appear on the ocular surface.[7] The negative results of the conjunctival swab may be related to low viral concentration and poor diagnostic methods. Negative conjunctival swab PCR results may need to be evaluated in the future, using more sensitive detection methods. Also, the timing of a conjunctival swab may mean that the high replication period of the virus is missed. It is necessary to take swabs in patients in the early period of their illness, but it should be remembered that the PCR test may be positive in the following days after a conjunctival swab has proven negative.

Many studies have observed that conjunctivitis may appear as the initial symptom of the disease in SARS-CoV-2 infection, but may also develop later as the disease progresses.[5,18] Scalinci and Battagliola[7]

TABLE 2 Detailed information about demographic, ocular clinical features, and laboratory parameters of COVID-19 patients with ocular disease

Case/gender/age, y	Systemic symptoms	Clinical type	Ocular symptoms	Chest CT	Neut./lymph. ratio	CRP	Nasopharyngeal swab PCR (SARS-Cov-2)
1/F/65	Dyspnea, cough	Critical	Chemosis, conjunctival hyperemia	Bilateral lungs	6.63	118.2	Positive
2/M/50	Weakness, fever	Moderate	Epiphora, secretion, photophobia	Unilateral lung	3.44	60.3	Positive
3/M/34	None	Moderate	Conjunctival hyperemia	Unilateral lung	4.65	16.4	Positive
4/M/59	Cough, weakness	Moderate	Subconjunctival hemorrhage	Bilateral lungs	1.58	14.4	Positive
5/M/47	Cough, fever, myalgia	Severe	Chemosis, hyperemia, secretion,	Bilateral lungs	3.21	85.9	Positive
6/F/62	Dyspnea, myalgia	Moderate	Hyperemia, secretion, photophobia	Bilateral lungs	4.34	136.7	Positive
7/M/44	Weakness, cough	Moderate	Epiphora, hyperemia, photophobia	Unilateral lung	2.23	37.9	Positive
8/F/48	Fever, cough	Moderate	Hyperemia, secretion	Bilateral lungs	3.17	44.2	Positive
9/M/56	Cough, fever	Critical	Hyperemia, epiphora, secretion	Bilateral lungs	5.44	68.6	Positive
10/M/44	Cough, fever	Severe	Subconjunctival hemorrhage	Bilateral lungs	2.87	44.7	Positive
11/F/68	Fever, dyspnea	Moderate	Vitreous hemorrhage	Bilateral lungs	8.34	74.8	Positive
12/M/28	Cough, fever	Moderate	Subconjunctival hemorrhage	Unilateral lung	4.05	65.4	Positive
13/M/39	Dyspnea, cough myalgia	Critical	Epiphora, hyperemia, photophobia	Bilateral lungs	7.54	101.4	Positive
14/M/51	Dyspnea, fever, cough	Severe	Subconjunctival hemorrhage	Bilateral lungs	5.46	56.8	Positive
15/F/42	Fever, cough	Moderate	Subconjunctival hemorrhage	Unilateral lung	3.14	7.45	Positive
16/F/72	Dyspnea, fever, weakness	Moderate	Hyperemia, secretion, epiphora	Bilateral lungs	4.05	10.9	Positive

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; neut./lymph., neutrophil/lymphocyte; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

reported five patients who tested positive in a nasopharyngeal swab PCR. None of these patients' systemic symptoms such as fever, weakness, or respiratory problems were observed during the disease period, although all cases showed conjunctivitis symptoms such as hyperemia, epiphora, or photophobia. Conjunctivitis may be unilateral or bilateral.[19,20] Chen et al[21] reported that conjunctival diseases may occur even 24 days after transmission.

In a report by the WHO-China Joint Mission, out of 55 924 COVID-19 cases, only 0.8% of patients showed conjunctival congestion.[22] However, in two different studies from China, which consisted of 99 and 140 patients, conjunctivitis was not observed as the initial symptom of the disease.[21,23] In another study, PCR did not find any positive results evaluating both tear and conjunctival swabs of 17 patients with confirmed SARS-CoV-2.[24] Seah et al[25] failed to demonstrate the presence of COVID-19 in the viral culture and PCR analysis of 64 tear samples collected simultaneously with nasopharyngeal swabs from 17 confirmed patients 3-20 days after the onset of the initial symptom. Xia et al[6] examined the tear and conjunctival samples of 30 patients who tested positive for SARS-CoV-2, PCR+ was detected in the conjunctival swab from one patient, but the virus could not be isolated in this patient. By contrast, Wu et al[5] detected PCR positive results in conjunctival samples in 5.2% of patients.

In three different studies from China, Xia et al[6] did not detect any association between the severity of the disease and the frequency of conjunctivitis, but Guan et al[4] and Wu et al[5] reported that the incidence of conjunctivitis was higher in patients with severe disease. A meta-analysis study conducted by Liu et al[26] reported that the presence of conjunctivitis may not be related to the severity of COVID-19. Although ocular diseases are frequently seen in patients with more severe COVID-19, the prevalence of SARS-CoV-2 is low in tears. Results from a study showed that the virus existed in eyes with conjunctivitis and that there was no virus present in the eyes without conjunctivitis.[6] However, Güemes-Villahoz et al[27] revealed the same rate of SARS-CoV-2 positive results among the group with and without conjunctivitis. They suggested that detecting SARS-CoV-2 in ocular fluids is not conditioned on the presence of conjunctivitis.

In the present study, the rate of ocular diseases in all patients was 4.5%. Conjunctivitis was the most common ocular disease in patients with COVID-19. The natural history of conjunctivitis in patients with COVID-19 seems to be self-limiting conjunctivitis that improves in a few days without specific treatment. All patients were treated symptomatically. Although one (0.28%) patient had no systemic problem, conjunctival hyperemia was the reason for presenting to the hospital. The rate of presenting to the hospital with conjunctival hyperemia was observed to be 0.7% (n = 4) in the study of Chen et al,[21] consisting of 535 patients. It should be noted that conjunctivitis may be the first complaint in admissions to the hospital of COVID-19 patients without any systemic findings. The potential mechanisms responsible for conjunctivitis are still not fully understood. The mechanism causing conjunctivitis may be a vasculitis or endothelial dysfunction. Also, conjunctivitis may be associated with host response to the general inflammation of the conjunctival vessels in patients with COVID-19.

It was observed in the present study that the ocular disease rate was higher in intensive care patients. Although conjunctival chemosis was not observed in any patient in the inpatient clinic, it occurred in two intensive care patients. One of them used a mechanical ventilator for respiratory distress. However, it should be noted that increased vena cava superior pressure due to the suppression of venous return with increased vena cava may cause changes in the ocular vascular structure in patients undergoing mechanical ventilation.[28] Stevens et al described orbital emphysema after orotracheal intubation in a 74-year-old COVID-19 patient. Researchers suggested that this could be a complication in COVID-19 patients.[29] However, such complications may occur with the effect of positive pressure in patients undergoing mechanical ventilation.

A subconjunctival hemorrhage is a common clinical eye condition characterized by the accumulation of blood in the space under the conjunctiva. The most common causes include trauma, hypertension, anti-aggregate or anticoagulant therapy, conditions that increase venous pressure (Valsalva maneuver, coughing, vomiting).[30] A new study Schwarz et al[31] reported that patients with COVID-19 treated in the intensive care unit may have a higher risk of subconjunctival hemorrhage. In another study, researchers noted that 8.3% of COVID-19 patients had subconjunctival hemorrhage.[27] In the present study, five patients developed subconjunctival hemorrhage during follow-up. This effect may be related to anticoagulant drug use, severe cough, or vomiting due to intolerance of medications used in treatment.

Vitreous hemorrhage is one of the common complications of proliferative diabetic retinopathy. Vitreous hemorrhage can be caused by the pathogenic mechanisms of disruption of normal retinal vessels, bleeding from diseased retinal vessels, or abnormal new vessels.[32] In this study, it was observed that vitreous hemorrhage developed in a patient, who was followed up in the inpatient clinic who had proliferative diabetic retinopathy. Metabolic dysfunction, vasculopathy, or endothelial dysfunction triggered by COVID-19 disease may have caused this condition. But, it is not possible to know whether a vitreous hemorrhage is a condition that occurs in the normal course of proliferative diabetic retinopathy or is a condition triggered by COVID-19 disease. Further detailed studies are needed to illuminate this condition in the vascular system.

The immunological response to the virus in COVID-19 patients causes changes in their hematological and inflammatory mediators. Lymphocytopenia and increased neutrophil levels reflect a heightened inflammatory process and indicate a poor prognosis.[33] In addition, there is a positive correlation between the level of the acute inflammatory response mediator CRP and disease severity.[34] Zhou et al[35] reported that patients with ocular symptoms have higher neutrophil and CRP levels. In the study of Ceran and Ozates,[36] patients with advanced age, high fever, increased neutrophil/lymphocyte ratio, and high levels of acute-phase reactants were found to be at a higher risk of developing the ocular disease. However, Chen et al[21] found no relation between the presence of conjunctival congestion and advanced age. It has also been reported that the presence of fever is not a predisposing factor for conjunctival

involvement. In this study, patients with conjunctivitis symptoms had higher CRP values. However, the difference was not statistically significant. The low number of our patients may have caused this. Studies with more patients are needed to evaluate the relationship between ocular disorders and inflammation-related laboratory parameters in COVID-19 patients.

The available information suggests that there are some changes in the ocular and vascular system in patients with COVID-19. Whether there is conjunctivitis in all cases with a positive PCR in a conjunctival swab remains to be investigated. In addition, retinal vascular system evaluations could not be made in these patients because of the high risk of transmission and isolation requirements. In the future, evaluations using optical coherence tomography angiography may reveal the effects of this disease on the retinal vascular system. However, previously reported studies and clinical observations raise the suspicion that there may be a correlation between the severity of the disease and ocular abnormalities. In addition, such abnormalities may arise secondary to an aggressive inflammatory response to the disease.[33]

This study had some limitations. The first limitation was that conjunctival PCR could not be applied to patients. But it is not possible to have any certainty that there is a direct relationship between positive conjunctival PCR and conjunctivitis.[27] The second limitation was the absence of a control group that was not diagnosed with COVID-19. The incidence of conjunctivitis, which is high especially in the summer, maybe a misleading factor in determining the rate of conjunctival diseases.

In conclusion, the findings show that the incidence of SARS-CoV-2 infection on the ocular surface in COVID-19 patients is very low. Guo et al[37] stated that the ocular surface is not the main conduction pathways of the SARS-CoV-2 because the positive SARS-CoV-2 detection rate and viral load in the conjunctival sac are very low. However, the conjunctival mucosa is an entry and transmission point for COVID-19 infection, as with all other respiratory viruses. Therefore, special attention should be paid to protection measures in the form of goggles or face shields, even when looking at patients without typical COVID-19 symptoms. The presence of conjunctivitis may be one of the initial symptoms, albeit rare, of the disease. No serious complications of the ocular manifestations of COVID-19 have yet been reported. However, large case series and long-term follow-up have not yet been performed in these patients. Further research should be carried out to identify possible COVID-19 receptors located in ocular surface cells. The present study data should be compared with data from other populations.

AUTHOR CONTRIBUTIONS

Methodology, investigation (equal), and writing—review and editing (lead): HÖ. Data curation and formal analysis: FYÖ. Investigation (equal) and resources: MFA. Investigation (equal) and writing—review and editing: MÇ. Investigation (equal) and formal analysis: UD.

CONFLICTS OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Öncül H, Öncül FY, Alakus MF, Çağlayan M, Dag U. Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. *J Med Virol*. 2021;93:1126–1132. https://doi.org/10.1002/jmv.26412