

Evaluation of Ocular Manifestations of Hospitalized Patients with COVID-19 in Valiasr and Razi Hospital in Birjand

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Abstract

Background and Objective: Different studies have identified a wide range of ocular symptoms and manifestations in patients with the 2019 coronavirus (COVID-19). Considering the ambiguities in the field of ocular complications following the infection of COVID-19, the present study was conducted with the aim of estimating the prevalence rate of ocular manifestations including neuritis, uveitis, and vasculitis in patients with COVID-19.

Patients and Methods: In this cross-sectional descriptive study, 425 patients with a positive PCR test and hospitalized in the acute respiratory disease department of Valiasr and Razi Hospital in Birjand were included. Personal and medical information questionnaires were completed for each patient and patients who complained of eye and vision problems were examined by an ophthalmologist. Then, OCT of the optic nerve head was taken to investigate eye involvement such as neuritis, uveitis, and vasculitis in patients with eye symptoms. In the end, the prevalence of ocular manifestations was calculated and analyzed using SPSS statistical software

Results: The average age of the patients was 60.44 ± 15.22 and 56.1% were male. 64 patients (15.1%) had at least one eye-related symptom; While 361 people (84.9%) did not report any eye complications. The complications observed in the order of frequency included conjunctivitis (6.8%), blepharitis (4.7%), dry eyes (2.1%), mild vision loss (1.9%) and excessive tearing (1.2%). In OCT examination, the most common complication was uveitis (0.9%), vasculitis (0.5%) and neuritis (0.2%) were rarely observed. No significant relationship was found between age, gender, duration of hospital stay, BMI of patients and the occurrence of any of the eye complications.

Conclusion: In this study, 15.1% of hospitalized Covid-19 patients showed ocular signs and symptoms. The factor associated with severe systemic disease of COVID-19, i.e. the duration of hospitalization, was not associated with the development of eye abnormalities. Overall, the rate of ocular manifestations of COVID-19 should not be underestimated, so clinicians should routinely assess for ocular involvement in hospitalized COVID-19 patients.

Keywords: Covid-19; Ocular Manifestations; Neuritis; Uveitis; Vasculitis

Introduction

The novel coronavirus disease 2019 (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported and spread around a seafood mall in Wuhan, China. In the following weeks, the epidemic spread rapidly and the number of suspected and confirmed cases was steadily increasing, resulting in a much greater distribution of the respiratory syndrome of the coronavirus. This virus spread rapidly throughout China and many other countries such as Iran found [1,2]. In the meantime, several reports show some cases as potential drugs, although the clinical effectiveness of these drugs for Covid-19 has not yet been proven. The most promising drug seems to be Remdesivir [3]. Most clinical research on SARS-CoV-2 has focused on respiratory manifestations. However, a growing body of evidence has raised concerns about eye complications from SARS-CoV-2. Reported ocular manifestations of infection vary widely and include dry eye, foreign body sensation, itching, blurred vision, conjunctivitis, chemosis, and photophobia. Some studies have even reported conjunctivitis as an early symptom for the diagnosis of COVID-19 [4].

Ocular complications caused by the SARS-CoV-2 virus have been reported in both humans and animals. Ocular symptoms in COVID-19 patients include conjunctivitis, anterior uveitis, retinitis, and optic neuritis. However, eye infections caused by SARS-CoV-2 are more common than adenoviruses or influenza viruses. The prevalence of eye involvement in COVID-19 patients may be from 2% to 60% [5,6]. The 2019 coronavirus disease is an infectious disease caused by SARS-CoV-2 that mainly affects the respiratory system and can damage the walls of blood vessels in almost any area of the body. Changes that affect retinal vessels are a good indicator for systemic vascular changes. Recently, researchers found that both the retinal arteries and veins of patients with acute COVID-19 were significantly dilated compared to those not exposed to the virus [7]. ACE2 is the receptor of the COVID-19 virus on host cells. Research results show that ACE2 (angiotensin-converting enzyme 2) receptor exists in many other organs, such as eyes, nerves, and vessels, in addition to lung cells. Therefore, extrapulmonary involvement is not far from expected [8]. According to current evidence and clinical features of the patient, uveitis and optic neuritis (as uncommon manifestations) can be caused by the COVID-19 virus. Although ocular manifestations associated with COVID-19 are uncommon, conjunctivitis and vasculitic vein occlusion and neuritis (inflammation of the optic nerve) due to anti-myelin oligodendritis (MOG) antibody production have been reported in a few cases. Inflammation of the conjunctival tissue can be a sign of entering the acute respiratory syndrome of SARS-COV-2. The results of a meta-analysis estimated the prevalence of ocular manifestations in patients with COVID-19 at 23%, but the detection of SARS-COV-2 through conjunctival tissue is very low and about 1% [7-9].

In their 2021 article, Alexander C Rokohl, *et al.* made important points about ocular involvement in COVID-19: conjunctivitis and more. Ophthalmologists can encounter potential ocular symptoms or manifestations of COVID-19 in patients at any time, as well as become infected through close contact with the patient. Even without systemic infection, the surface of the eye can be in direct contact with airborne particles or fluids containing SARS-CoV-2 particles. Infection is also possible through hand-to-eye contact. A purely isolated ocular infection has not yet been demonstrated. Rather, it seems that ocular complications occur in the context of systemic infection. However, eye symptoms can also be the first symptom of COVID-19. The most common ocular complication of COVID-19 is mild follicular conjunctivitis. Hemorrhagic conjunctivitis, dry eye disease, episcleritis, or retinal involvement may also occur less frequently. There are currently no evidence-based treatment recommendations for ocular surface disease associated with COVID-19. Artificial tears may be helpful to relieve symptoms. There is no evidence for antiviral, antibiotic, or anti-inflammatory treatments, but these drugs may be used in individual cases. Potential intraocular complications include retinal artery occlusion and hemorrhage, as well as cotton wool spots from complement-mediated thrombotic angiopathy. Neuro-ocular complications such as Miller-Fisher syndrome or central blindness related to infarction also occur in very rare cases. Knowledge of possible transmission routes and personal protective equipment is as necessary for every ophthalmologist as basic knowledge of eye symptoms and complications [10]. Alnahdi, *et al.* in their 2023 report stated that the articles fully discussed cases and ocular manifestations of COVID-19 affecting adults, with less focus on the pediatric age group. The aim of this study was to describe the different ocular manifestations of children described in the articles. These manifestations may be

divided into separate events attributed to COVID-19 or occurring in the new multisystem inflammatory syndrome in children (MIS-C), a new entity associated with COVID-19 infection. Ocular manifestations affect almost all ages. They appeared in infants, children and adolescents. Episcleritis, conjunctivitis, optic neuritis, cranial nerve palsy, retinal vein occlusion, retinal vasculitis, retinal changes, orbital myositis, orbital cellulitis have been reported in articles with this emerging viral disease. Conjunctivitis was the most common ocular manifestation in MIS-C in almost half of the patients. Other ocular manifestations in MIS-C were anterior uveitis, corneal epitheliopathy, optic neuritis, idiopathic intracranial hypertension, and retinitis. The clinical outcome was favorable and the children regained their visual ability with minimal or no defects in most cases. Further follow-up may be necessary to better understand long-term effects and visual prognosis [11]. Several studies have reported the characteristics of the 2019 coronavirus disease, but there remains a gap in our understanding of the ocular manifestations of COVID-19. Therefore, according to the ambiguities in the field of eye complications following the infection of COVID-19, our study aims to “estimate the prevalence rate of eye manifestations in patients with COVID-19”. In similar studies conducted in Iran, patients with COVID-19 have been examined in terms of ocular manifestations such as retinopathy, conjunctival hyperemia, conjunctival edema, and cataracts. Complementary to extensive research aimed at evaluating the prevalence of ocular surface manifestations, our study seeks to investigate manifestations such as optic neuritis, uveitis, and vasculitis, which have been less discussed in other studies. Our findings complement the known symptoms of COVID-19 and will help the appropriate and timely intervention of physicians in the treatment of these patients. Knowledge of the prevalence and type of ocular manifestations of COVID-19 can help doctors better diagnose the infection earlier in the course of the disease.

Research Method

This study was conducted on patients in the age group above 15 years with COVID-19 hospitalized in Valiasr and Razi Hospital in Birjand in 1401-1402. Inclusion criteria were age over 15 years, SARS-COV-2 positive nasopharyngeal PCR, admission to the acute respiratory disease center of the hospital. Not having gout absence of liver and kidney disease, no history of eye disease, no treatment with anticonvulsants. Informing the patient and his family about the process of conducting the study and signing the consent form. Exclusion criteria consist of not want to continue cooperation, or the patient dies, or the patient loses consciousness. After the project was approved by the Research Council of Birjand University of Medical Sciences and the code of ethics was obtained, the study began. In a descriptive-cross-sectional study, 425 people hospitalized in the acute respiratory disease department of Valiasr and Razi Birjand hospitals in the period of 1401-1402 with an age range of over 15 years if they have a positive nasopharyngeal PCR for SARS-COV-2 and have clinical symptoms of COVID-19 and considering the entry criteria, i.e. no history of eye disease, liver and kidney disease, gout and no treatment with anticonvulsant drugs, they were included in the study. After obtaining informed consent and signing the consent form, a personal and medical information questionnaire was completed for each person. If the patients were illiterate, the questions were asked by the doctor in the form of an interview. Then, according to the results of the questionnaire, if there are serious visual symptoms such as red eyes, sudden loss of vision, and blindness, the eye examinations of the people were started by an ophthalmologist, and OCT of the optic nerve head was taken from them (Figure 1). Optic neuritis leads to an increase in the thickness of the retinal nerve fiber layer (RNFL) due to inflammation in the retinal nerve fibers. After the resolution of the inflammation, atrophy of the optic nerve can be recognized as thinning of the RNFL. Uveitis is a type of eye inflammation that affects the middle layer of the eye wall tissue (uvea), and retinal vasculitis is characterized by inflammation of retinal vessels. The thickness of RNFL, uvea and blood vessels can be measured by 3D OCT device. With the OCT device, the ophthalmologist checked the parameters of the optic nerve head such as the thickness of the RNFL and the middle layer of the eye wall tissue and the structure of the blood vessels, and eye problems such as neuritis, uveitis and vasculitis were investigated in the subjects. Finally, the prevalence rate of each of the ocular complications of vasculitis, uveitis, neuritis, dry eye, blepharitis, conjunctivitis, excessive tearing and vision loss in patients with COVID-19 hospitalized in the acute respiratory disease department was calculated. Also, the relationship between eye symptoms and the factors of age, gender, length of hospitalization and BMI was evaluated. Data analysis method including the tool used was a checklist made by the researcher to check the demographic information and record the eye symptoms of the patients. The data was analyzed using SPSS.26 statistical software. Descriptive statistics were reported for the entire study group

and based on the status of having eye symptoms as well as the odds ratio (OR). Regression tests were used to evaluate the relationship between ocular symptoms, vasculitis, optic neuritis, and uveitis and the factors of age, gender, length of hospitalization, and BMI. p-value < 0.05 was considered statistically significant.

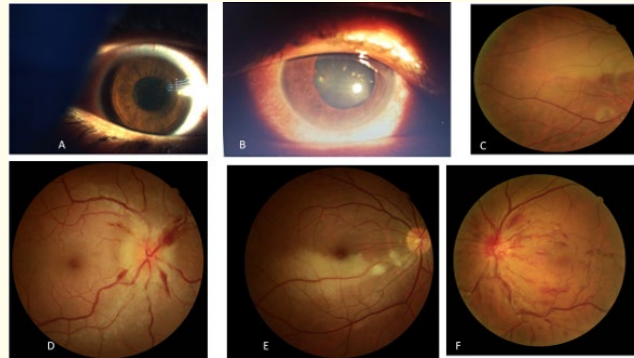


Figure 1: A and B: Uveitis cases. C-F: Retinal insult.

Findings

Frequency distribution of demographic and clinical information of a total of 425 patients with COVID-19 with an average age of 60.44 ± 15.22 were included in the study. The lowest age was related to an 18-year-old patient and the highest was related to a 95-year-old patient. The average BMI of the subjects was 21.66 ± 2.30. The minimum duration of hospitalization was 1 day and the maximum was 23 days, which was estimated to be 3.74 ± 6.55 days on average (Table 1). In terms of gender distribution, 186 (43.9%) participants were female and 238 (56.1%) were male (Table 2).

Variable	Minimum	Maximum	Mean ± STD
Age	18	95	60.44 ± 15.22
BMI	17	29	21.66 ± 2.30
Duration of admission	1	23	6.55 ± 3.74

Table 1: Demographic and clinical information of patients.

Variable	No	Percent (%)
Sex	Female	186 43.9
	Male	239 56.1

Table 2: Frequency distribution of gender of patients.

Frequency distribution of eye complications of patients

Out of a total of 425 people included in the study, 20 people (4.7%) had blepharitis (eyelid inflammation), 29 people (6.8%) had conjunctivitis, 9 people (2.1%) had dry eyes, and 5 people (1.2%) had excessive tearing. They were normal. Also, 8 people (1.9%) reported mild vision loss (Table 3). Ophthalmic examination according of OCT results showed that 1 person (0.2%) had optic neuritis, 4 people (0.9%) had uveitis, and 2 people (0.5%) had vasculitis (Table 4).

Ocular Complain		No	Percent (%)
Blepharitis	Yes	20	4.7
	No	405	93.3
Conjunctivitis	Yes	29	6.8
	No	396	93.2
Dry eye	Yes	9	2.1
	No	416	97.9
Excessive tearing	Yes	5	1.2
	No	420	98.8
Mild visual impairment	Yes	8	1.9
	No	417	98.1

Table 3: Ocular symptoms of patients with COVID-19 admitted to the acute respiratory ward.

Ocular Complain		No	Percent (%)
Optic neuritis	Yes	1	0.2
	No	424	99.8
Uveitis	Yes	4	0.9
	No	421	99.1
Retinal Vasculitis	Yes	2	0.5
	No	423	99.5

Table 4: OCT results of patients with COVID-19 hospitalized in the acute respiratory department.

Distribution of variables in two groups of patients with eye symptoms and patients without eye symptoms

Among the 425 patients in the study, 64 patients (15.1%) had at least one eye-related symptom (vasculitis, uveitis, neuritis, dry eye, blepharitis, conjunctivitis, excessive tearing, decreased vision). The rest of the people, i.e. 361 people (84.9%) did not report any eye complications. Based on this, people were divided into two groups: patients with eye symptoms and patients without eye symptoms. Then the distribution of gender variables and the average variables of age, length of hospitalization and BMI in these two groups were compared with each other. The results of the statistical analysis showed that the average BMI ($p = 0.044$) and the length of hospitalization ($p = 0.022$) in patients with eye symptoms were significantly higher than in patients without eye symptoms; But there is no significant difference in age and gender index in two groups of patients with eye symptoms and without eye symptoms (Table 5).

Variable		Patient with ocular symptom No 64 (15.1%)	Patient without ocular symptom (No 361) 84.9%	p-value
Sex	Female (%)	(46.9)30	(43.3%)156	0.599
	Male (%)	(53.1)34	(56.7%)204	
Age		61.04 ± 15.54	60.32 ± 15.20	0.730
BMI		22.20 ± 2.53	21.57 ± 2.25	0.044*
Duration of admission		7.54 ± 4.18	6.37 ± 3.64	0.022*

Table 5: Distribution of variables in two groups of patients with eye symptoms and patients without eye symptoms.

The chi-square test was used to analyze the qualitative variables of gender, and the T-test was used to analyze the quantitative variables of age, length of hospitalization, and BMI. In the above table, the percentage of each symptom in the population of patients with eye symptoms (having at least one visual symptom) is calculated and expressed. Since some people had more than one symptom, the total number of people is more than 64 people and the total percentage is more than 100%. Distribution of ocular signs and symptoms in people with vision problems by examining the distribution of eye signs and symptoms in especially people with vision problems, it was observed that the most common eye abnormality was conjunctivitis (29 people, 45.3%) followed by blepharitis (20 people, 31.3%). Complications of dry eyes (9 people, 14.1%), mild vision loss (8 people, 12.5%) and tears (5 people, 7.8%) were less common, respectively. Complications such as uveitis (4 patients, 6.3%), vasculitis (2 patients, 3.1%) and neuritis (1 patient, 1.6%) were very rare (Table 6).

Ocular complain	Person with ocular complain 64 NO
Conjunctivitis	29No (45.3%)
Blepharitis	20No (31.3%)
Dry eye	9No (14.1%)
Mild visual disturbance	8No (12.25%)
Excessive tearing	5No (7.8%)
Uveitis	4No (6.3%)
Vasculitis	2No (3.1%)
Optic neuritis	1No (1.6%)

Table 6: Distribution of eye symptoms and complications in people with vision problems.

Univariate analysis of factors related to occurrence of eye symptoms In order to investigate factors related to the occurrence of eye symptoms, logistic regression analysis was performed. Based on the results of the analysis, the p-value for all variables is more than 0.05 and therefore not statistically significant. Therefore, it can be said that there is no significant relationship between age, gender, duration of hospitalization, BMI of patients and suffering from any of the eye complications such as optic neuritis, uveitis, vasculitis, dry eyes, blepharitis, conjunctivitis, excessive tearing and vision loss (Table 7).

Variable	Odds Ratio (95% confidential interval)	p-value
Age	1.01	0.295
Sex	0.80	0.440
BMI	1.13	0.059
Duration of admission	1.05	0.097

Table 7: Regression analysis of variables of age, gender, duration of hospitalization and BMI of patients with eye symptoms.

Discussion

According to our knowledge, the present study is the first study that examines the ocular manifestations and OCT findings of hospitalized patients with Covid-19 in Iran. In this descriptive-cross-sectional study, 425 people admitted to the acute respiratory disease department with an age range of over 15 years and having a positive SARS-COV-2 nasopharyngeal PCR and clinical symptoms of COVID-19 without a history of eye diseases were examined. In case of serious visual symptoms such as red eye, sudden decrease in vision and also blindness,

eye examinations of the subjects were performed indeed OCT of the optic nerve head was taken from them to determine the prevalence of each of the eye complications including vasculitis, uveitis, neuritis, dry eye, Blepharitis, conjunctivitis, excessive lacrimation and reduced vision should be estimated. Also, the relationship between eye symptoms and the factors of age, gender, length of hospitalization and BMI was evaluated. The average age of the patients was 60.44 ± 15.22 years, the average BMI was 21.66 ± 2.30 , and the average length of hospitalization was 6.55 ± 3.74 days. 43.9% of patients were female and 56.1% were male. Patients with ocular symptoms had a higher average BMI and longer hospitalization than patients without ocular symptoms; While no significant difference was found in the age and gender index in the two groups of patients. Of the 425 patients in the study, 64 patients (15.1%) had at least one eye-related symptom (vasculitis, uveitis, neuritis, dry eyes, blepharitis, conjunctivitis, excessive tearing, vision loss); While the majority of participants, including 361 people (84.9%), did not report any eye complications. In the meta-analysis study by Nasiri, *et al.* the prevalence of ocular manifestations in patients with covid worldwide was estimated to be 11.03% [4]. Aggarwal, *et al.*'s systematic analysis data also estimated the prevalence of ocular manifestations in COVID-19 patients to be 11.64% [12]. The results of the study by Sezgin Akçay BI and colleagues showed that the prevalence of chronic eye diseases and the use of eye medications in hospitalized patients with Covid-19 was significantly higher than that of outpatients [13]. Since in meta-analysis studies and systematic reviews, the prevalence of eye complications in patients has been reported in general, but the present study specifically examined hospitalized patients, it is likely that the higher prevalence in the present study is due to the hospitalization status of the patients the disease is more severe and the inclusion of the group. In the study of Feng Y, *et al.* which was conducted on hospitalized patients with covid, ocular signs and symptoms were observed in 9.5% of patients [14]. Also, in the study of Shaikh N., *et al.* the prevalence of ocular manifestations in hospitalized patients was estimated at 7.8%. The authors acknowledged that the incidence of ocular manifestations was lower in this study compared to other articles [15]. In Sarkar D., *et al.*'s study on 1,200 patients with positive RT-PCR of COVID-19 (group 1) and 1,200 negative RT-PCR patients (group 2), 144 people study, and one of its possible causes is the screening based on RT-PCR test. In the present study, the complications observed in the order of frequency included conjunctivitis (6.8%), blepharitis (4.7%), dry eye (2.1%), mild vision loss (1.9%) and excessive tearing (1.2%). In examining the distribution of eye complications in the group of people with vision problems, it was observed that the most common eye abnormality was conjunctivitis (45.3%) followed by blepharitis (31.3%). Complications of dry eyes, mild reduction of vision and tearing were reported in a smaller number (14.1%, 12.5% and 7.8%, respectively). Complications of uveitis, vasculitis and neuritis were very took place worldwide, were dry eyes or foreign body sensation (16%), redness (13.3%), tear shedding (12.8%), itching (12.6%), eye pain (9.6%). and secretion was (8.8%). In addition, conjunctivitis had the highest rate (88%) among eye complications reported in COVID-19 patients [4]. Similarly, in the systematic analysis of Aggarwal, *et al.* eye pain (31.2%), discharge (19.2%), redness (10.8%) and follicular conjunctivitis (7.7%) were the main symptoms [12]. In the study of Sarkar D., *et al.* ocular manifestations including burning sensation (6.7%), foreign body sensation and burning (7.0%), and conjunctival symptoms (2.7%) in RT-PCR positive patient group compared to RT-PCR negative group. It was statistically significant [16]. Although the prevalence values reported in different studies are largely aligned and close to each other, different background factors such as vaccination status, virus variant type during the study period, laboratory factors and immunity of patients before the disease and other still unknown parameters can influenced the causes of the difference in the prevalence and type of eye complications. Also in a study by Zhang, *et al.* since the eyes can reveal signs of various systemic diseases, a comprehensive understanding of ocular complications associated with COVID-19 can enhance the diagnosis and treatment of the systemic manifestations of COVID-19 and its aftereffects. Furthermore, the underlying mechanisms of pathogenesis of many of these sequelae remain poorly understood [17].

In the OCT examination indeed of fundoscopic examination in present study, the complication associated to uveitis macular edema (0.9%) and vasculitis (0.5%) and optic neuritis (0.2%) were rarely observed. Khalid Sawalha, *et al.* presented a case report of a patient with COVID-19 without a history of previous illness with visual problems suggestive of optic neuritis. This patient had anti-MOG antibody and therefore it was concluded that probably COVID-19 can lead to neuritis by producing MOG antibody [9]. In addition to comparing patients with and without ocular symptoms, we also sought to determine whether specific factors may be associated with the development

of ocular signs and symptoms in COVID-19. The results of the present study indicated that there is no significant relationship between age, gender, duration of hospitalization, BMI of patients which suffering from any of the eye complications such as neuritis, uveitis, vasculitis, dry eyes, blepharitis, conjunctivitis and tearing.

The visual impairment, demographic characteristics such as age and gender do not increase the chance of ocular abnormalities among COVID-19 patients. In line with the present study, Shaikh N., *et al.* study there was no significant relationship between the incidence of ocular manifestations and gender or co-morbidities [15]. In addition, Feng., *et al.*'s study also reported no significant relationship between factors such as age and gender with the chance of eye abnormalities among COVID-19 patients [14].

As the findings of the present study show, only a small number of patients with COVID-19 show ocular symptoms. This finding is most likely due to the presence of inherent protective mechanisms of the eye against viral infections. The eye contains natural physiological and anatomical factors, such as the presence of cilia, that protect the eye from droplets carrying viral particles. However, methods for ophthalmic measures to reduce potential transmission have been suggested. Therefore, clinicians caring for patients with COVID-19 should be vigilant in monitoring ocular signs and symptoms, as patients recovering from COVID-19 may also have ocular symptoms related to SARS-CoV-2. On the other hand, emerging evidence suggests that extrapulmonary manifestations of COVID-19 are frequently seen and should not be ignored. Therefore, while an eye examination may have been performed but not documented, full electronic health record documentation for this disease should be emphasized in order to provide comprehensive patient care.

Conclusion

In general, the results of the present study show that the occurrence of eye complications in patients with covid-19 is not rare and the amount of eye symptoms and signs of covid-19 should not be ignored. Also, although in the present study, no significant relationship was found between the demographic and demographic factors of patients with the occurrence of eye complications, but the higher average BMI and length of hospitalization in patients with eye symptoms compared to patients without eye symptoms indicates the existence of some factors related to the development of symptoms and signs. It is ocular and therefore, in order to prevent severe complications, the examination and screening of patients should be done accurately. Offers As the pandemic is diminished but continues to impact the world, it is imperative for physicians and the general public alike to understand the manifestations of COVID-19. Considering the previous detection of viral RNA in conjunctival secretions, the transmission of SARS-CoV-2 through eye secretions cannot be ignored. Also, the predictive factors for the occurrence of ocular symptoms caused by COVID-19 should be identified in order to accurately inform the public about the manifestations of the disease. In the end, considering that our research was only a descriptive study, it is necessary to carry out a case-control study for a more detailed investigation of the impact of COVID-19 on eye health.

Conflict of Interest

The authors have no conflict of interest with the subject matter of the present study.

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