

ORIGINAL ARTICLE

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Investigation of the relationship between eye involvement and systemic diseases in patients with COVID-19 **Abdulgani Kaymaz**,  **Rukiye Kilic Ucgul***Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Ophthalmology, Bolu, Turkey*

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**Abstract**

Investigation of whether there is a relationship between eye involvement and systemic diseases in patients diagnosed with Coronavirus Disease-2019 (COVID-19). One hundred and ten patients who admitted to our hospital and were diagnosed with COVID-19 by Polymerase Chain Reaction (PCR) and chest computed tomography (CT) were included in the study. The demographic characteristics and existing systemic diseases of the patients were questioned. Whether the patients had ocular involvement associated with COVID-19 was investigated. The patients with eye involvement were examined in terms of systemic diseases and the drugs they used. Sixty one of the patients were male and 49 were female. Eight (7.3%) of the 110 patients had ocular involvement. Six of these 8 patients had no comorbid diseases. Two patients with additional systemic disease had a common diagnosis of chronic kidney disease. The mean age of those with ocular involvement (44.88 ± 21.97 years) was lower than the average age of the total group (52.29 ± 22.93 years). The most common additional systemic disease in patients with COVID-19 was hypertension (26.4%). All patients had conjunctival hyperemia. Five of the patients had epiphora, 5 had secretion, 4 had burning-stinging and 2 had ocular pain. 3 of the patients were smokers. In 2 patients, the first finding of COVID-19 started with eye complaints. One of the patients with ocular involvement had a history of previous Fuchs uveitis. Although eye involvement in COVID-19 patients is not common, it may appear as the first finding. Detection of patients with eye involvement may be beneficial in terms of early diagnosis, treatment and prevent transmission. In addition, the relationship between comorbid diseases and eye involvement may be important in terms of prognosis.

Keywords: Comorbid diseases, conjunctival hyperemia, coronavirus disease-2019 (COVID-19), epiphora, eye involvement, fuchs uveitis**Introduction**

Coronavirus Disease-2019 (COVID-19) has been on the agenda of the whole world for more than 1 year. Although the main target of COVID-19 is the respiratory system, the virus also targets many other systems and organs. [1-3] People with underlying uncontrolled medical conditions have been found to have a higher risk of contracting COVID-19 (Such as diabetes mellitus (DM), hypertension (HT), cardiovascular diseases (CVD), chronic respiratory (CRD) and kidney disease (CKD), cancer patients receiving chemotherapy, smokers, organ transplant patients and chronically steroid users.). [4,5] It was also observed that the prognosis was worse and the mortality rate was higher in this patient group. [6-8] In addition, it has been determined that the virus can cause serious illness not only in the elderly but also in children. [2,9]

In COVID-19, direct contact with mucous membranes is an important transmission route for the disease. [10] It has been shown that COVID-19 can involve the anterior and posterior segments of the eye. [11-13] The most commonly reported ocular sign of COVID-19 is conjunctivitis. [14] Conjunctival infection can occur through droplets or contact of infected structures with the eyes. [15] It is known that ocular findings are rare and usually mild. [10] However, it should be borne in mind that the eye can be a way of both getting infected and transmitting the infection to other people. [16]

Although PCR from nasopharyngeal swabs has an important role in the diagnosis of COVID-19, false negativity rates of tests performed from conjunctival swabs are quite high. [17] Eye involvement in COVID-19 can sometimes occur as the first sign of the disease, and sometimes during the disease. Although there are many studies in the literature on the ocular findings of COVID-19, [14,15,18] the number of studies revealing the relationship between eye involvement and systemic diseases is quite limited. Determining the relationship between eye involvement and

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systemic diseases will provide important information about the prognosis and transmission of the disease. Therefore, such a study has been planned.

Materials and Methods

The study included 110 patients who were diagnosed with COVID-19 by PCR test and chest CT, hospitalized in the coronavirus (CoV) infection services of Bolu Abant İzzet Baysal University Training and Research Hospital. Ethics committee approval was obtained from the same university. Informed consent was obtained from the patients and the principles of the Declaration of Helsinki were followed.

The patients with COVID-19 included in the study were asked about their systemic diseases, medications they used, smoking cigarettes, existing eye conditions, wearing glasses, or contact lenses. The symptoms of those with eye complaints that may be associated with COVID-19 and the relationship of these symptoms with systemic diseases were investigated. The form prepared for the study was filled in by the physicians included in the study, with questions asked to patients and/or their relatives. Patients with confusion, shortness of breath, and speech difficulties, and patients who needed intensive care and had a poor general condition were not included in the study. The doctors participating in the study complied with all the necessary conditions at the maximum level to protect from CoV and prevent the spread of the disease outside the service.

Statistical analysis of all data used in the study was done with SPSS version 25.0 for Windows. Parametric data were calculated as mean $\pm$ standard deviation, nonparametric data were calculated as percentages.

Results

The demographic characteristics and findings of existing systemic diseases of the 110 patients included in the study are summarized in Table 1. Sixty one of the patients were male (55.5%), 49 were female (44.5%) and their mean age was 52.29 ± 22.93 years (min-max: 7-90 y). While 38.2% of the patients did not have any comorbid diseases, 27.3% had 1, 16.4% had 2, 12.7% had 3, 4.5% had 4 and 0.9% had 5 additional systemic diseases.

The most common systemic disease accompanying COVID-19 was HT (26.4%). Other accompanying diseases were DM, CVD, CKD, CRD, central nervous system disease (CNSD), thyroid disease, and malignancy (respectively) (Table 1). The number of patients with CNSD (n=13) was equal to the number of patients with CRD (n=13). All 6 patients with thyroid disease had a diagnosis of hypothyroidism. Of the 4 patients in the other systemic diseases group, 2 had rheumatoid arthritis, 1 had ankylosing spondylitis, and 1 had chronic hepatitis B. One of the 2 patients with malignancy had colon cancer and the other had pancreatic cancer. Forty seven of all patients (42.7%) were not using any medication.

Eight (7.3%) of the 110 patients included in the study had ocular involvement associated with COVID-19. The characteristics of these patients are shown in Table 2. Of the patients with ocular involvement, 4 were male and 4 were female, and their mean age was 44.88 ± 21.97 years (min-max: 25-90 y). Eight of the patients

had conjunctival hyperemia, 5 had epiphora, 5 had secretion, 4 had burning-stinging and 2 had ocular pain. Remarkably in the study, only 2 (25%) of 8 patients with ocular involvement had comorbid disease and their mean age was lower than the mean age of the whole group. Two patients with ocular involvement and comorbid disease also had a diagnosis of CKD. One of the patients with ocular involvement had a history of Fuchs uveitis.

Table 1. Characteristics and comorbid diseases of patients diagnosed with COVID-19.

	Yes (n, %)	No (n, %)
Comorbid disease(s) (at least one)	68 (% 61.8)	42 (% 38.2)
Hypertension	29 (% 26.4)	81 (% 73.6)
Diabetes mellitus	25 (% 22.7)	85 (% 77.3)
Cardiovascular disease	21 (% 19.1)	89 (% 80.9)
Chronic kidney disease	15 (% 13.6)	95 (% 86.4)
Chronic respiratory disease	13 (% 11.8)	97 (% 88.2)
Central nervous system disease	13 (% 11.8)	97 (% 88.2)
Thyroid disease	6 (% 5.5)	104 (% 94.5)
Malignity	2 (% 1.8)	108 (% 98.2)
Other systemic diseases	4 (% 3.6)	106 (% 96.4)
Fever	45 (% 40.9)	65 (% 59.1)

Table 2. Characteristics of the patients with COVID-19 with eye involvement.

Gender/ age,y	Fever	Ocular symptoms	Systemic diseases	Jop	EG	Contact lens	Smoker
Case 1 F/38	No	Epiphora Burning-stinging Secretion Conjunctival hyperemia	No	Worker	No	No	No
Case 2 F/90	No	Burning-stinging Conjunctival hyperemia	DM HF CKD	Retired	No	No	No
Case 3 M/37	No	Secretion Epiphora Ocular pain Conjunctival hyperemia	No	Official	Yes	No	Yes
Case 4 M/30	Yes	Conjunctival hyperemia Ocular pain Secretion	No	Worker	No	No	Yes
Case 5 M/64	No	Burning-stinging Conjunctival hyperemia	CKD	Retired	Yes	No	Yes
Case 6 F/46	No	Conjunctival hyperemia Epiphora Secretion	No	Worker	No	No	No
Case 7 M/29	Yes	Secretion Epiphora Burning-stinging Conjunctival hyperemia	No	Official	No	No	No
Case 8 F/25	No	Conjunctival hyperemia Epiphora Secretion	No	Student	Yes	No	No

CKD: Chronic kidney disease, DM: diabetes mellitus, EG: eyeglasses, F: Female, HF: Heart failure, M: Male

Discussion

In this study we conducted to determine the relationship between ocular involvement and systemic disease, it was found that at least

one comorbid disease was present in 68 of 110 patients and ocular involvement was present in 8 patients. Only 2 of the patients with ocular involvement had comorbid diseases.

Studies have shown that the rate of ocular involvement in patients with CoV varies between 4.5-31.6%. [15,18,19]. Ocular involvement rate was found to be 7.3% in our study. Although this value is within the specified range in studies, it only expresses the rate of the inpatients. Similar to our study, Chen et al.[13] found ocular involvement in 8 patients in their study of 121 patients. In addition, they found positive conjunctival PCR of 2 patients without eye complaints and 1 patient with ocular involvement. As a matter of fact, it has been observed that even symptomatic patients with ocular involvement may have negative PCR test results. [14,15, 19]. Since eye findings are not sufficiently questioned or reported in the inpatient clinics, this rate can be detected lower than normal. In our study, the mean age of patients with ocular involvement was lower, but the limited number of patients makes it difficult to comment on the situation. In order to elucidate the unknown aspects of the disease, there is a need for large-scale studies that include outpatients, asymptomatic patients and intensive care patients.

While COVID-19 can cause simple anterior segment pathologies such as conjunctivitis and anterior uveitis, it can also lead to severe vision-threatening ocular symptoms such as retinitis and optic neuritis. [10-12,20] In our study, all 8 patients with ocular involvement had symptoms associated with the anterior segment. Detailed ophthalmologic examinations of the posterior segment could not be performed because the patients were hospitalized in the CoV clinics. Due to the difficulty in examining patients with COVID-19, establishing a special examination room for COVID-19 patients in ophthalmology clinics will enable more information about the eye involvement of the disease. Although eye involvement is not a common finding, it is important that it occurs as the first symptom of COVID-19 in two patients. Therefore, care should be taken to use preventative measures such as goggles or face shields, even when looking at patients with or without COVID-19 symptoms.

In the first studies on CoV, while lung involvement was at the forefront, it was later seen that the virus could involve and damage other organs. [1,3,21] The ability of the virus to infect many organs is particularly associated with angiotensin-converting enzyme (ACE)-2 receptors. [1] Because the CoV attaches to target cells through ACE-2 expressed by epithelial cells of the lungs, blood vessels, kidneys, and intestines. [3,22] Despite this, it is still not clear why the disease has different prognosis in different ages and groups. [23-25] It is known that patients with comorbid diseases are more affected by multisystem organ involvement. [26,27] In a meta-analysis of 34 studies, the most common comorbid diseases accompanying COVID-19 were found as HT, CVD, DM, and CKD, respectively. [26] In another study in which a meta-analysis of 24 studies was made, this ranking was found as HT, DM, CVD, and CRD, respectively. [4] In our study, 61.8% of the patients had at least one systemic disease and the most common comorbid disease was HT (26.4%). DM, CVD, CKD, CRD, and CNSD diseases followed HT, respectively. Our findings were similar to other studies.

Since there is no study investigating the relationship between

ocular involvement and systemic disease in the literature, 2 patients were identified in this study, one of whom was diagnosed with CKD, the other with CKD, DM, and HF. Although the number of patients with this relationship is small (only 2 patients), three questions come to mind. 1) I wonder if the rate of comorbid diseases is low in patients with eye involvement? 2) Do those with comorbid diseases have lower eye involvement rates? 3) Other receptors other than ACE-2 accompany this process? Of course, more research is needed to identify possible COVID-19 receptors on ocular surface cells and to determine the relationship of these receptors with other organs/tissues.

There were some limitations in our article. Only patients hospitalized in the CoV clinic were included in the study. Outpatients, intensive care patients, and undiagnosed asymptomatic patients were excluded from the study. In addition, since the patients were evaluated in the CoV clinics, the anterior and posterior segment findings of the patients could not be revealed in detail. Although not performing the conjunctival swab PCR test is another limitation of the article, Gue et al. reported that the viral load in the conjunctival sac may be insufficient for PCR positivity. [17] Despite all these limitations, it is important for the prognosis and transmission of the disease that patients with ocular involvement have a lower mean age, less comorbid disease association, and the first symptom of the disease can start with eye complaints.

Performing a detailed eye examination of all COVID-19 patients with and without eye involvement will further contribute to the literature on the ocular findings of the diseases. In addition, early diagnosis of patients with eye involvement will minimize transmission of the virus to both healthcare professionals and other people through eye fluids.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

This study was performed in adherence with the tenets of the Declaration of Helsinki and was approved by local ethical committee (no: 2020/315).

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