

Ocular findings in patients hospitalized for COVID-19

Yatırılarak tedavi edilen COVID-19 hastalarında göz bulguları

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ABSTRACT

Objective: The COVID-19 disease, which has affected the whole world, has seriously challenged the health system. In this period when the delivery of health services is in danger, understanding how the disease affects different parts of the human body has remained in the background. This study was conducted to identify patients with ocular complaints and findings from inpatient COVID-19 patients.

Methods: A cross-sectional, retrospective study was conducted in individuals aged 18 years and older who were followed up and treated for COVID-19 in a tertiary hospital between 25 March 2020 and 31 March 2021. Electronic health records of all patients were reviewed. In addition Procalcitonin, urea, and neutrophil levels were compared between patients with and without ocular symptoms.

Results: A total of 7060 patients with positive COVID-19 tests were included in our study. The mean patient age was 60.89±16.96 years. 52.8% (n=19) of the patients were female and 47.2% (n=17) were male. The ophthalmology consultation rate was 0.5% with a total of 36 patients. The most common symptom was visual changes in 47.2% (n=17) of the patients. The second most common ocular pathology was chemosis, followed

ÖZET

Amaç: Tüm dünyayı etkisi altına alan COVID-19 hastalığı, sağlık sistemini ciddi anlamda zora sokmuştur. Sağlık hizmetlerinin sunumunun tehlikede olduğu bu dönemde, hastalığın insan vücudunun farklı bölgelerini nasıl etkilediğinin anlaşılması geri planda kalmıştır. Bu çalışma, yatarak tedavi gören COVID-19 hastalarından oküler şikayetleri ve bulguları olan hastaları belirlemek amacıyla yapılmıştır.

Yöntem: 25 Mart 2020 ile 31 Mart 2021 tarihleri arasında üçüncü basamak bir hastanede COVID-19 nedeniyle takip ve tedavi edilen 18 yaş ve üzeri bireylerde kesitsel, geriye dönük bir çalışma yapılmıştır. Tüm hastaların elektronik sağlık kayıtları alınarak gözden geçirilmiştir. Ayrıca oküler semptomları olan ve olmayan hastalar arasında prokalsitonin, üre seviyesi ve nötrofil sayısı karşılaştırılmıştır.

Bulgular: Çalışmamıza COVID-19 testi pozitif olan toplam 7,060 hasta dahil edildi. Ortalama hasta yaşı 60,89±16,96 idi. Hastaların %52,8 (n=19)'i kadın, %47,2 (n=17)'si erkekti. Oftalmoloji konsültasyon oranı toplam 36 hasta ile %0.5 idi. Hastaların %47.2 (n=17)'sinde en sık görülen semptom görme değişiklikleri idi. En sık görülen ikinci oküler patoloji kemozdu, bunu konjonktival hiperemi ve göz

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by conjunctival hyperemia and eye irritation. 100% of the patients exposed to keratopathy had a history of intensive care ($p<0.001$). However, it was observed that the visual changes were not directly related to the intensive care unit. 88.2% of these patients did not have a history of intensive care ($p<0.001$). Significant elevations in the compared laboratory findings were observed in patients with ocular findings.

Conclusion: It was also emphasized that COVID-19 affects the eyes at a low rate, but ocular findings may remain in the background, especially in patients who have been hospitalized for a long time and at the first admission to the hospital. Although procalcitonin, urea and neutrophil counts were found to be higher in patients with ocular symptoms, it was not found that these patients affected the rate of admission to the intensive care unit.

Key Words: COVID-19, ocular findings, inpatient

irritasyonu izledi. Keratopatiye maruz kalan hastaların %100'ünde yoğun bakım öyküsü vardı ($p<0,001$). Ancak görme değişikliklerinin doğrudan yoğun bakım ünitesi ile ilgili olmadığı gözlemlendi. Bu hastaların %88,2'sinin yoğun bakım öyküsü yoktu ($p<0,001$). Oküler bulguları olan hastalarda karşılaştırılan laboratuvar bulgularında anlamlı yükselmeler gözlemlendi.

Sonuç: Bu çalışmada hastanede yatan COVID-19 hastalarının %0,5'inde göz ile ilgili şikayet ve bulgular tespit edilmiştir. COVID-19'un gözleri düşük oranda etkilediği ancak özellikle uzun süre hastanede yatan hastalarda ve hastaneye ilk başvuruda göz bulgularının arka planda kalabileceği de vurgulandı. Ayrıca, prokalsitonin, kan üre düzeyi ve nötrofil sayısı oküler semptomları olan hastalarda daha yüksek bulunurken bu hastaların yoğun bakım ünitesine yatış oranlarına etkisi saptanamadı.

Anahtar Kelimeler: COVID-19, göz bulguları, yatan hasta

INTRODUCTION

Over the past two decades, CoVs have caused three large-scale outbreaks: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. The place where the COVID-19 pandemic first started was the Chinese city of Wuhan (1). In Wuhan, several cases of severe pneumonia of unknown origin have been associated with the severe acute respiratory syndrome (SARS). The first person to report their similarities was ophthalmologist Dr. Li Wenliang. Dr. Wenliang contaminated with the virus after treating an infected glaucoma patient and subsequently he passed away (2). Studies have confirmed that the etiologic agent is a new Betacoronavirus associated with SARS-CoV (1,3). The first patients developed symptoms

on 1 December 2019, followed by rapid human-to-human transmission and intercontinental spread, and a pandemic was declared by WHO in March 2020 (4). The virus that causes coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, single-stranded RNA virus. It can be transmitted from a sick person through respiratory droplets at a high rate (3). Symptoms of the disease may appear within 2-14 days after exposure to the virus (5). The most common symptoms of COVID-19 are fever, headache, cough, weakness, shortness of breath, sore throat, inability to smell, conjunctivitis, and gastrointestinal complaints. Complications in severe cases include severe pneumonia, coagulopathy, encephalopathy, vasculopathy, cardiomyopathy, and renal failure. Recent reports reveal a strong association between

ocular symptoms and COVID-19 infection and also highlight the effects of COVID-19 infection on the eyes (6-8). The prevalence of ocular signs and symptoms reported in COVID-19 patients may vary. The overall rate of conjunctivitis in patients with COVID-19 was shown in a meta-analysis of three recent studies as 1%, 3%, and 0.7% in severe and non-severe patients, respectively (7). It has been claimed that eye involvement may be a sign of more severe COVID-19 infection (7,8). Understanding the signs, symptoms, and routes of transmission of COVID-19 infection is important for preventing transmission and diagnosing new cases. Therefore, in this study, it was questioned whether ocular findings are associated with the disease in COVID-19 patients hospitalized in a tertiary hospital.

MATERIAL and METHOD

This study was approved by the Health Sciences University Gülhane Scientific Research Ethics Committee (Date: 03.06.2021, Number: 2021/265). An electronic medical record review was made and all the health information was kept confidential.

All COVID-19 patients over the age of 18 who were hospitalized in Gülhane Training and Research Hospital between 25 March 2020 and 31 March 2021 were screened. For the study group, patients aged 18 years and older and PCR test positive for COVID-19 were determined. Age, gender, laboratory findings, the intensive care treatment processes, ocular symptoms, and ocular physical examination were extracted from the hospital information management system health record for each patient. The ophthalmic evaluation was performed by an ophthalmologist using consultation system. Upon the request of clinical consultation from the patients in the Covid clinic, the examination was performed by the ophthalmologist using the bedside ophthalmoscope. Examination findings were recorded to the hospital information management system. The collected data were entered in a Microsoft Excel sheet and statistical analyzes

were made in SPSS 22.0. Continuous variables were presented as age, median, and range (min-max). In addition, categorical variables were presented as frequency and percentage.

SPSS version 22.0 was used for statistical analysis. Kolmogorov Smirnov and Shapiro Wilk Test were used as normality tests. Mann Whitney U test was used for two independent groups. $P < 0.05$ was considered significant. Missing value analyses were done for urea, creatinine, AST, ALT, CRP, D-dimer, glucose, and lymphocyte using a regression model. When the laboratory results were compared between ICU and clinic, age and gender match sample was chosen to avoid over-power.

RESULTS

Between 25 March 2020 and 31 March 2021, 7060 patients who were hospitalized in our hospital due to Covid-19 were examined. 186 patients under the age of 18 were excluded from the study. It was seen that ophthalmology consultation was requested 48 times from these patients. Since more than one consultation was requested from some of the patients and the records of 36 patients in total were reviewed.

The ophthalmology consultation rate was 0.5% with a total of 36 patients. The mean age of the patients was 60.89 ± 16.96 years. 52.8% (n=19) of the patients were female and 47.2% (n=17) were male. 75% of the patients had one consultation and the rest had more than one consultation. The most common symptom was visual changes in 47.2% (n=17) of the patients. This was followed by chemosis (27.8%), conjunctival injection (22.2%), periorbital edema (16.1%), eye irritation (13.9%), and conjunctivitis (8.3%) with decreasing frequency. Scleral hemorrhage, periorbital ecchymosis, conjunctival edema, Cranial Nerve 6 (CN6) Palsy diplopia, ocular pain and ptosis were observed even less frequently. Symptoms seen in COVID-19 patients are listed in Table 1. Exposure Keratopathy was found to be associated with the Intensive care unit process. 100% of the patients

exposed to keratopathy had a history of intensive care ($p<0.001$). Conjunctival injection was also found to be associated with intensive care. 87.5% of patients with conjunctival injection had a history of intensive care ($p=0.008$). It was observed that

the visual changes were not directly related to the intensive care unit. 88.2% of these patients did not have a history of intensive care ($p<0.001$). Ocular symptoms due to intensive care are listed in Table 2.

Table 1. Frequency of the ocular symptoms

	n	Frequency %
Vision Changes	17	47.2
Chemosis (Exposure keratopathy)	10	27.8
Conjunctival Injection	8	22.2
Periorbital Edema	5	16.1
Irritation	5	13.9
Discharge	4	11.1
Conjunctivitis	3	8.3
Glokom	3	8.3
Scleral Hemorrhage	2	5.6
Periorbital Echimosis	1	2.8
Conjunctival Edema	1	2.8
CN6 Palsy	1	2.8
Diplopia	1	2.8
Ocular Pain	1	2.8
Ptosis	1	2.8

Table 2. Frequency of the symptoms associated with intensive care

	Intensive Care		Total (n=36)	p*
	Yes (n=16)	No (n=20)		
Chemosis (Exposure keratopathy)				
Yes	10 (100)	0	10 (27,8)	<0,001
No	6 (23.1)	20 (76.9)	26 (72,2)	
Conjunctival Injection				
Yes	7 (87.5)	1 (12.5)	8 (22,2)	0,008
No	9 (32.1)	19 (67.9)	28 (77,8)	
Vision Changes				
Yes	2 (11.8)	15 (88,2)	17 (47,2)	<0,001
No	14 (73.3)	5 (26,3)	19 (52,8)	

*Fisher's Exact Test

The laboratory results of 6428 patients were accessible. Laboratory results were compared between patients with ocular symptoms and others. Urea, procalcitonin and neutrophil levels were found to be significantly higher in patients with ocular symptoms (Table 3). In addition, laboratory values were compared between intensive care and clinic patients. 5.3% of the patients were treated in the intensive care

unit (ICU) (n=343). Patients treated in the intensive care unit were significantly older than the others (70.76±14.50 and 58.58±17.79, respectively). There was a statistically significant difference between the groups in terms of urea, creatinine, AST, ALT, CRP, D-Dimer, glucose, lymphocyte, procalcitonin, ferritin, neutrophil, fibrinogen, FRTN2 (Table 4).

Table 3. Laboratory tests in patients with ocular symptoms

	Yes		No		Z	p*
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)		
Urea	76,6 ± 52,4	59 (13 - 260)	53 ± 44,2	39 (5 - 424)	-3,509	<0,001
Procalcitonin	2,5 ± 8,1	0,2 (0 - 41,6)	1,5 ± 7,8	0,1 (0 - 98,3)	-3,396	0,001
Neutrophil	9,6 ± 8,3	7,9 (1,3 - 42,6)	6 ± 4,7	4,7 (0,1 - 113,6)	-3,245	0,001

*Mann Whitney U Test

Table 4. Descriptives of the patients treated in intensive care unit and clinic

	Intensive Care Unit (n=343)		Clinic (n=343)		Z	p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)		
Urea	112 ± 75,1	91 (9 - 405)	60,5 ± 40,7	51 (14 - 384)	-11,426	<0,001
Creatinine	2,1 ± 1,9	1,3 (0,4 - 11,8)	1,3 ± 1,2	1 (0,5 - 14,4)	-6,193	<0,001
AST	176,1 ± 687	42 (7 - 7588)	71,5 ± 273,7	34 (8 - 3451)	-3,813	<0,001
CRP	138,7 ± 104,1	122,4 (0,3 - 472,4)	209,6 ± 2385,9	55,2 (0,2 - 44240)	-7,795	<0,001
D-Dimer	6,9 ± 13,4	2 (0,2 - 80)	2,8 ± 8,7	0,7 (0,2 - 80)	-9,755	<0,001
Glucose	171,7 ± 104,4	143 (3 - 749)	149,5 ± 80,7	123 (41 - 732)	-3,750	<0,001
Lymphocyte	1 ± 1	0,8 (-3 - 8,9)	1 ± 0,7	0,9 (-2,6 - 3,9)	-2,595	0,009
Procalcitonin	7,4 ± 17,2	0,7 (0 - 95,2)	1,5 ± 6,8	0,1 (0 - 74,4)	-10,054	<0,001
Neutrophil	11 ± 7,6	9 (0,1 - 62,9)	6,8 ± 7,2	5,1 (0,8 - 113,6)	-9,860	<0,001
FRTN2	677,4 ± 517,2	525 (10,9 - 1500)	430,9 ± 428,3	251 (5,7 - 1500)	-5,870	<0,001

*Mann Whitney U test

DISCUSSION

Previous reports of Asian and European origin have been published on the eye findings of COVID-19 patients. Various rates of ocular findings have been reported in these reports. In a study conducted in India in which 127 COVID-19 patients with mild clinical presentation were examined, eye findings were reported in 9.45% of the patients (9). However, in our study, it was stated that visual changes were an evident symptom in 47.2% of the patients with eye findings. The etiology of vision changes could not be explained as the data were obtained retrospectively from limited electronic records, however probable mechanisms could be hypoxia, eye surface changes, or retinal pathology as in some previous studies reported. Again, other studies reported that very high CRP and lymphocyte levels were detected in patients with ocular manifestations also these patients had high fever levels and they were older (6,10). Intensive Care and D-dimer, ferritin, urea, other inflammatory markers such as procalcitonin and neutrophil were used as indicators for disease severity. Procalcitonin, urea, and neutrophil levels were compared with Mann Whitney U Test between patients with and without ocular symptoms (Table 3). Significant elevations in the compared laboratory findings were observed in patients with ocular findings. This situation was found to be compatible with some studies in the literature (11,12). In addition, the situations of the patients in the intensive care unit were evaluated. Although it was suggested as a result of the evaluation that patients with ocular symptoms were more likely to develop severe COVID-19 disease in the intensive care unit, we could not reach such a result in our study. However, more ocular findings were detected in the patients in the intensive care unit, but this was considered as a complication of long-term hospitalization. This may be due to the size of the patient sample (7060 patients), the difference in the COVID-19 clinical picture, compiling patient information and findings, or differences in the

hospital information system. In addition, in our study, we examined whether some factors are associated with the development of ocular findings in COVID-19 (6,13). Studies are suggesting that eye findings may be the first manifestation of the disease (6-8). Since this study was retrospective and was based on hospital electronic records, new information could not be obtained about the beginning of eye symptoms in patients with COVID-19. Studies have shown the presence of SARS-CoV-2 receptors called ACE2 and TMPRSS2, which the virus uses to penetrate the eye even if it does not cause disease. So it's not surprising that there are eye symptoms of COVID-19 (9,14). In addition, there is substantial evidence that SARS-CoV-2 RNA can be determined from ocular tissue, including the conjunctiva, cornea, and vitreous (15). In our study, ocular symptoms were observed in only a small proportion of COVID-19 patients. This may be due to the entity of eye-protective mechanisms, as well as the presence of symptoms that are overlooked and remain in the background in the severely ill patient. (16). However, there may be a possibility of ocular transmission of SARS-CoV-2. It is useful to consider this possibility in ophthalmology practice to reduce transmission (10,17). Physicians treating patients with COVID-19 should be cautious in monitoring eye findings, as patients recovering from COVID-19 may improve ocular symptoms that may be associated with SARS-CoV-2. Physicians should not ignore this risk in their examinations and evaluations while dealing with hospitalized COVID-19 patients. Emerging evidence shows that the extrapulmonary manifestations of COVID-19 are frequently encountered and should not be forgotten. Doctors may choose to examine their COVID-19 patients at the bedside due to concerns about the risk of transmission. They may not be able to make a complete eye examination under the conditions of the outpatient clinic. For this reason, although the eye examination was performed, the patient examination information may not be fully recorded in the electronic health record (18), so our study has some limitations. Initially, the group

of patients in which the study was conducted was considered primarily for COVID-19, and as a result, ocular symptoms may remain in the background and rarely be significant enough to require ophthalmology consultation. Owing to viral contamination concerns and efforts to preserve healthcare professionals, only bedside examinations were possible. Minor ophthalmic events are likely to be overlooked or not reported due to the inability to perform ophthalmic examinations in detailed outpatient settings. Also, to preserve the totality of the data, the original definitions of documented and reported eye abnormalities have not been altered. In a retrospective study, it is rather difficult to propose a causal relationship between the ocular symptoms and COVID-19.

Some patients examined by an ophthalmologist were diagnosed with severe illness and exposure keratopathy with corneal ulcers as a result of prolonged hospitalization and intensive care unit stay. However, our investigation is clinically important and suggests that in addition to the primary eye symptoms caused by SARS-CoV-2, secondary eye symptoms may also consist in COVID-19 patients. Hence they may require extensive eye examinations by providers (19,20). Our study showed that a review of the hospital health record system alone may be insufficient to capture

all eye symptoms that develop during illness. Since the patients included in the study were hospitalized in a tertiary hospital, there were patients with long-term and severe clinical picture. This is why our patient population is different from those in secondary care or a private hospital. This potentially limits the ability to generalize. Finally, quite a few COVID-19 patients (n=36) with eye manifestations likely restricted our power to determine associations with clinically pertinent factors.

In conclusion, this study concluded that COVID-19 did not significantly affect the eyes. However, the factors associated with the development of ocular manifestations are still unclear. Since the main cause is COVID-19, it should be kept in mind that ophthalmic symptoms may be overlooked, especially in patients who have been hospitalized for a long time. All these suggest that the ocular findings of COVID-19 should be considered from the onset of the disease and should not be left behind. As the pandemic continues to affect the world, doctors and the public should understand the effects of COVID-19 on the eyes. For this purpose, especially prospective studies can be much more useful to understand the impact of the disease.

ETHICS COMMITTEE APPROVAL

* This study was approved by the Health Sciences University Gülhane Scientific Research Ethics Committee (Date: 03.06.2021 and No: 2021/265).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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