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ORIGINAL PAPER

Infectious diseases

Evaluation of eye care and ocular findings in critically ill COVID-19 patients

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Abstract

Objective: The current study aimed to evaluate eyecare needs along with ocular findings in patients treated in intensive care units because of Covid-19 infection.

Materials and Methods: A total of 93 patients, 58 men and 35 women, who were under follow-up and treatment in intensive care because of COVID-19 infection from 1 January 2021 to 15 February 2021 were included in the study. Detailed eye examinations of the patients were performed with a portable handheld biomicroscope, direct and indirect ophthalmoscope. Cases requiring treatment for eye diseases were identified and treated.

Results: The mean patient age was 68.32 ± 9.97 years; 35 patients were followed up and treated with non-invasive mechanical ventilation and 58 patients with invasive mechanical ventilation support. Mild, moderate, and severe chemosis was observed in 19 patients (20.4%), 10 patients (10.8%) and 4 patients (4.3%), respectively. Conjunctivitis (8.6%) was observed in eight patients. Corneal abrasion was present in seven patients (7.5%). Keratitis secondary to exposure keratopathy was observed in one patient. Eye care and medical treatment were initiated for these patients. We noted eight patients (8.6%) with retinal haemorrhage; however, to the best of our knowledge, these patients may show acute retinal involvement secondary to systemic diseases or have previous retinal findings other than Covid-19 infection or treatments.

Conclusion: Findings of ocular involvement because of COVID-19 infection were detected in the present study. Retinal haemorrhages were detected in addition to the common findings in viral infections. Especially in patients supported with mechanical ventilation, the detection and treatment of conditions that require eye care for exposure keratopathy are very important for recovering from the disease and the quality of vision.

1 | INTRODUCTION

Covid-19, which has spread around the world leading to severe acute respiratory syndrome and was declared a pandemic by the World Health Organization (WHO), was detected in Turkey for the first time on 11 March 2020.[1]

Studies have shown that SARS-CoV-2 needs ACE-2 receptors infecting cells.[2] ACE-2 receptors are also found in the cornea and conjunctiva besides the lung alveoli.[3] This suggests that the ocular surface tissue may be the target tissue of the SARS-CoV-2 virus. Considering the similarities in coronavirus species, Covid-19 infection has been shown to cause ocular symptoms in patients.[4]

Although ocular findings such as conjunctivitis, chemosis, epiphora and conjunctival injection have been detected since the initial reports of Covid-19, it has also been reported that these findings may be the first sign of Covid-19 infection.[5] In various case reports, retinal haemorrhage and retinal vein occlusion have been shown as complications of the posterior segment associated with Covid. In a published report, patients without any systemic disease and decreased vision after the onset of Covid-19 infection and found to have unilateral or bilateral retinal vein occlusion were reported. The report suggested that there may be a vein occlusion associated with vasculitis and thromboembolism because of immune complex accumulation.[6,7] In another report published, Paracentral Acute Middle Maculopathy and Acute Macular Neuroretinopathy were reported in a case of Covid-19 because of the hyper-reflective lesions detected in OCT as a result of decreased vision.[8]

Since Covid-19 is a life-threatening infection, other organ interactions have not been fully determined, as many studies focus on the respiratory system to improve survival. Extra-pulmonary symptoms of SARS-Cov-2 should not be ignored, as they may be important causes of morbidity and a source of viral transmission. Therefore, the current study aimed to evaluate the ocular effects of Covid-19 infection and the treatments applied, especially in intensive care patients with severe disease, and to identify and treat patients who would require eye care.

What's known

- The coronavirus has been shown to cause serious eye diseases in animals but ocular symptoms in humans are rare and mild. Recent studies have defined endothelial damage as one of the most prominent causes of systemic vascular thromboembolic and inflammatory manifestations associated with Covid-19. SARS-CoV-2 may exhibit direct ocular diffusion through two blood-retinal barriers (BRBs) or associated with thrombotic sensitivity identified in Covid-19.

What's new

- Retinal haemorrhages and cotton wool spots were detected in addition to the common findings in viral infections. Eyecare in the intensive care unit and the application of treatments appropriate for ocular problems that may occur because of Covid-19 infection are vital for those who recover from Covid-19 infection to prevent vision loss and maintain quality of life.

2 | MATERIALS AND METHODS

In the current study, we included 93 patients who were being followed up and treated in the intensive care unit from 1 January 2021 to 15 February 2021 because of the complications associated with Covid-19 infection, such as severe pneumonia, acute respiratory distress syndrome and multi-organ dysfunction. Both eyes of the patients were evaluated separately. Patient relatives were informed before the study and a signed consent form was obtained. The principles of the Declaration of Helsinki were complied with at all stages of the study. Ethical approval was obtained from the Clinical Research Ethics Committee (Decision number: 2021/21).

The diagnostic criterion for including patients in the study was a positive reverse transcription-PCR (RT-PCR) test of the nasopharyngeal swab sample for SARS-CoV-2. Three patients with a negative PCR test but typical Covid-19 appearance on chest CT scan and typical clinical symptoms, and patients of high clinical suspicion with high C reactive protein (CRP) and lymphopenia $<1100/mm^3$ in the blood sample were also included in the study.

Demographic findings such as age and gender of the patients were determined, and the presence of systemic diseases was evaluated. Treatments applied for Covid-19 infection and laboratory parameters, especially coagulation factors, were evaluated. Personal protective equipment was worn and precautions were taken before entering the patient rooms. The anterior segment findings such as cornea, conjunctiva, and eyelids were examined first with a portable handheld biomicroscope and direct ophthalmoscope for each patient. Subsequently, the eyes were dilated with 1% tropicamide, and retinal and optic nerve examinations were performed by the same ophthalmologist with an indirect ophthalmoscope and 28D lens. During the anterior segment examinations of the patients, conditions requiring eye care, especially in patients who were intubated and placed in the prone position, such as corneal epithelial defect, conjunctivitis and keratitis were determined. Intensive care personnel were also trained, and eye care and treatments were provided.

2.1 | Statistical analysis

The sample size of the study was determined by Power Test with the power of each variable considered at least 80% and type 1 error taken as 5%. We checked whether the continuous measurements in the study were normally distributed or not with the Kolmogorov-Smirnov test ($n > 50$) and Skewness-Kurtosis tests. Parametric tests were applied because the measurements were normally distributed. Descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum. "Independent *T*-test" was used to compare the measurements between the groups. "Pearson correlation coefficients" were calculated to determine the relationships between measurements. Chi-square test was used to determine the relationship between categorical variables. In the calculations, the statistical significance level (a) was taken as 5% and the SPSS (IBM SPSS for Windows, ver. 24) statistics package program was used for analysis.

3 | RESULTS

Mean patient age was 68.32 ± 9.97 years, 35 patients were followed up and treated with non-invasive mechanical ventilation and 58 patients with invasive mechanical ventilation support (Table 1). Patients were treated in the hospital for an average of 7 days from the onset of Covid-19 symptoms. As a result of the clinical worsening, the patients were followed and treated in the intensive care unit, and ophthalmological examination was also performed in the intensive care unit. Ophthalmological examinations were performed after an average of 12.43 (2-30) days of admission to intensive care (Table 2). It was observed in the files of the patients that no ocular symptoms were reported in any of the patients.

Patients who developed severe chemosis were those who were occasionally placed in the prone position for treatment. Severe keratitis because of lagophthalmos was detected in one patient, conjunctivitis with the purulent discharge was detected in one patient, and eye closure and drug treatment (moxifloxacin and artificial tear without preservative) were initiated. When these patients were examined for control purposes, improvement was observed in patients with corneal abrasion, but treatment responses could not be followed up in the patient with keratitis and purulent conjunctivitis considering that the patients were dead. In two of the cases with conjunctivitis, the PCR test was performed from conjunctival swabs to detect SARS-CoV-2, but a negative result was obtained.

Apart from retinal involvement because of systemic diseases, new intraretinal haemorrhages were observed in eight patients (8.6%). Bilateral haemorrhages were observed in one patient and splinter haemorrhages in the temporal side of the optic disc were observed in two patients. Cotton wool spots together with splinter haemorrhage in the temporal side of the optic disc were observed in one patient. In four patients, intraretinal haemorrhages were observed in the macula in the arch. One of the patients who had haemorrhage in the arch also had cerebral haemorrhage and bilateral papilloedema. There was no statistically significant difference in both comorbid systemic diseases and findings of laboratory parameters of these patients. The distribution and comparison of systemic disease and laboratory parameters of patients with retinal haemorrhage compared with other patients are shown in Table 3.

Of the 93 patients followed, 19 (20%) patients survived, whereas other patients were lost because of complications because of Covid-19. Fourteen (15.05%) of the 19 patients were followed up and treated with non-invasive ventilation, five (5.3%) were treated with mechanical ventilation, and their treatment continued in the ward when the intensive care requirements decreased.

4 | DISCUSSION

Patients who are followed up and treated in the intensive care unit because of Covid-19 infection, in mechanical ventilation—including non-invasive ventilation—and at the prone position, are at risk for the development of ocular complications. The present study aimed to evaluate the eye care of patients recovering from Covid-19 infection to prevent vision loss as a result of ocular complications and to evaluate whether there is any ocular involvement during Covid-19 infection.

Although the main target of the SARS-CoV-2 virus is the respiratory tract, it is stated that it affects many other systems and that various symptoms are observed.[9] Furthermore, coronavirus has been shown to cause serious eye diseases such as retinal vasculitis, anterior uveitis, optic neuritis in animals, ocular symptoms in humans are rare and mild.[10]

The retina is considered as an extension of the central nervous system (CNS), therefore involvement may occur not only in the optic nerve (optic neuritis) but also in the retina (retinitis) in neuroinflammatory conditions and infections of the CNS.[11] The CNS is protected from viruses by its multilayer barriers and the immune system, but viruses can affect the brain in various conditions such as direct brain damage, hypoxic damage, upregulated ACE-2 receptors and immunodeficiency.[12] It is well-known that ACE-2 receptors are widely distributed among many tissues and cell types, as well as in the conjunctiva. Some reports have shown that CoV-2 could potentially spread through direct or indirect contact with the mucous membranes of the eyes.[5,13,14] Recent clinical and anatomopathological studies have defined endothelial damage as one of the most prominent causes of systemic vascular thromboembolic and inflammatory manifestations associated with Covid-19.[15-17] Therefore, vascular occlusion because of thrombotic sensitivity,

TABLE 1 Demographic data of patients

	Patients receiving NIMV support (37.6%)	Patients receiving IMV support (62.4%)	*P*-value
Female (37.6%)	12 (34.3%)	23 (65.7%)	0.605
Male (62.4%)	23 (39.7%)	35 (60.3%)	0.605
DM (26.1%)	5 (14.3%)	19 (33.3%)	0.043
HT (39.8%)	11 (31.4%)	26 (44.8%)	0.201
COPD (9.7%)	1 (2.9%)	8 (13.8%)	0.084
CAD (14%)	2 (5.7%)	11 (19.0%)	0.074
Hypothyroidism (2.2%)	0.0%	2 (3.4%)	0.267

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension.

TABLE 2 Ocular findings according to the ventilation status of the patients

	Patients receiving NIMV support (%)	Patients receiving IMV support (%)	*P*-value
Chemosis (mild)	2.9	31.0	0.001
Chemosis (moderate)	2.9	15.5	0.056
Chemosis (severe)	0.0	6.9	0.112
Corneal abrasion	2.9	10.3	0.185
Keratitis	0.0	3.4	0.267
Conjunctival hyperaemia	17.1	3.4	0.022
Eyelid oedema	0.0	5.2	0.171
Subconjunctival haemorrhage	0.0	5.2	0.171
Retinal haemorrhage	8.6	8.6	0.993

TABLE 3 Distribution and comparison results of systemic disease and laboratory parameters of patients with haemorrhage in the retina

	Patients with retinal haemorrhage	Patients without retinal haemorrhage	*P* value
Female/male	4 (50%)/4 (50%)	31 (36.5%)/54 (63.5%)	0.450
Age	64.38 ± 10.14	68.69 ± 9.93	0.243
DM	1 (12.5%)	23 (27.4%)	0.360
COPD	1 (12.5%)	8 (9.4%)	0.778
Mechanical ventilation/non-invasive ventilation	5 (62.5%)/3 (37.5%)	32 (37.6%)/53 (62.4%)	0.993
CRP (mg/dL)	8.90 ± 4.86 (2.14-16.64)	8.56 ± 7.29 (1.08-30.96)	0.900
Lymphocytes (×10/μL)	0.89 ± 0.58 (0.35-1.71)	0.64 ± 0.74 (0.15-1.74)	0.358
White blood cells (×10/μL)	16.45 ± 7.75 (8.83-32.98)	16.35 ± 8.70 (5.01-30.48)	0.975
D-dimer(μg/L)	3.09 ± 4.96 (0.44-15.10)	3.64 ± 6.42 (0.12-38.50)	0.816
Haemoglobin (11.4-15.5 g/dL)	10.23 ± 1.69 (7.20-12.80)	12.59 ± 12.40 (7.10-15.10)	0.592
Platelets (×10/μL)	265.25 ± 97.27 (175-360)	246.80 ± 128.32 (39-698)	0.693
INR	1.37 ± 0.45 (1.12-2.47)	1.31 ± 0.27 (0.99-2.59)	0.610
Fibrinogen (mg/dL)	432.89 ± 200.38 (146.40-739.70)	398.32 ± 127.31 (153.50-712.90)	0.488
PTT (sec)	36.94 ± 18.69 (16.80-71.50)	29.56 ± 16.90 (16.80-166.60)	0.245
Prothrombin time (PT)	13.88 ± 4.45 (11.40-24.80)	13.34 ± 2.65 (10.10-25.90)	0.610

Abbreviations: CRP, C-reactive protein; INR, international normalized ratio; PTT, activated partial thromboplastin time.

chorioretinitis or vasculitis directly caused by the virus may occur in the retina. Considering that SARS-CoV-2 may exhibit direct ocular diffusion through two blood-retinal barriers (BRBs) or associated with thrombotic sensitivity identified in Covid-19, as reported in the brain, eight of our patients who underwent retinal examination had intraretinal haemorrhages. Splintered haemorrhages in the temporal side of the optic disc were observed in one patient bilaterally and in two patients in the left eye. The Cotton wool spot was observed with a splinter haemorrhage in the temporal side of the optic disc in one patient. In four patients, intraretinal haemorrhages were observed in the macula in the arch. Marinho et al detected microhaemorrhages and cotton wool spots along the retinal arcade in four of 12 patients.[18] But since cotton wool spots can be identified in a wide range of diseases[19,20] and the comorbidities of patients that could lead to this condition were not specified, it was stated that it is impossible to definitively determine whether these were pathological cotton wool spot conditions.[21] In the present study, one patient with a cotton wool spot and retinal haemorrhage in the temporal side of the optic disc had diabetes mellitus, but there were no findings of diabetic retinopathy other than this haemorrhage. No statistically significant difference was observed between patients with haemorrhage in the retina and other patients in terms of both systemic diseases and laboratory parameters.

In three different studies conducted in China, Xia et al could not find any relationship between the severity of Covid-19 infection and the frequency of conjunctivitis,[22] whereas Guan et al[23] and Wu et al[14] showed that the incidence of conjunctivitis and other ocular symptoms were higher in patients with severe pneumonia. In the present study, conjunctivitis was seen with a rate of 8.6%. The mechanism of how conjunctivitis occurs is still not fully understood. It may be endothelial dysfunction, vasculitis or the host response of conjunctival vessels because of Covid-19 infection.[24]

More than 15% of patients affected by the Covid-19 pandemic are hospitalised and treated, a significant portion of which will require mechanical ventilation.[25] Decrease in orbicular muscle tone because of neuromuscular blocking agents applied in patients under MV support and turning patients to the prone position, which is one of the treatment stages, increase the risk of exposure keratopathy in intensive care patients.[26] Exposure keratopathy can be seen in patients who are connected to mechanical ventilation, especially in intensive care, and it can lead to progressive vision loss by causing microbial keratitis and ocular surface scarring.[27]

A guideline has been approved by The Royal College of Ophthalmologists (RCOphth) in collaboration with the Intensive Care Association to prevent keratopathy in intensive care patients. It contains precautions that can be taken together with closing the eyelids.[26] Kam et al also suggested an eye care protocol in an eye care study in critically ill patients, emphasising that clinicians should evaluate the closure of the eyelids in terms of lagophthalmos.[28] To prevent the progression to keratopathy, eyelid closure and medical treatment was performed in patients in our intensive care unit with corneal epithelial defects seen in the first examinations during the examination phase. The intensive care staff caring for the patients was trained about the risk factors for developing keratopathy and the necessary preventive measures. Subsequently, the presence of corneal epithelial defect and keratopathy, which was observed in the first examinations with a rate of 7.5%, was not observed in the subsequent examinations. Six patients requiring treatment and care because of conditions such as corneal epithelial defect, conjunctivitis and keratitis could not be followed up because of complications related to Covid-19. It was observed that the corneal epithelial defect in one patient resolved two days after eye care.

The incidence of chemosis in the conjunctiva in critically ill patients ranges from 9% to 80%.[29] Chemosis is classified as mild, moderate or severe according to the degree of conjunctival prolapse. Vascular permeability and lymph duct dysfunction in the conjunctiva lead to chemosis.[30] Mechanical ventilation increases jugular venous pressure and causes fluid to accumulate in ocular tissues. Long-term positive pressure ventilation and fluid electrolyte abnormalities in intensive care are factors that increase conjunctival chemosis.[31] Chemosis may cause keratopathy and related complications by causing irregular tear distribution on the ocular surface according to its severity.[32] Against the risk of developing keratopathy because of severe chemosis, especially in patients who are placed in the prone position, ocular evaluation should be performed before the patients are placed in the prone position, and eyelids should be taped by applying pomade to the eye.[33] Our patients were hospitalised for a long time because of Covid-19 infection, and mild chemosis was observed at a rate of 20.4%, moderate chemosis at a rate of 10.8%, and severe chemosis at a rate of 4.3%, especially in patients who were intubated. It was observed that lagophthalmos developed because of oedema in the eyelids in one patient, and it was observed that severe chemosis and exposure keratopathy developed. Eyelid closure and lubrication treatment were initiated for the patient, and considering that closing the eyelids would not be sufficient, tarsorrhaphy was planned in the patient but treatment and follow-up could not be performed because the patient died because of complications related to Covid-19 infection the next day.

Schwartz et al stated that subconjunctival bleeding may be more frequent in patients with Covid-19 infection treated in intensive care.[34] In another study, subconjunctival haemorrhage was observed at a rate of 8.3%.[35] In the present study, subconjunctival bleeding was observed in three (3.2%) patients. One of these cases was in the form of punctate bleeding foci with chemosis. It is thought that these bleedings may be because of severe cough, vomiting because of intolerance of the drugs used, or because of the effect of anticoagulant drugs given in treatment to eliminate the risk of hypercoagulability of Covid-19 infection.

In the present study, it was aimed to prevent ocular complications that may occur in all critical patients in the intensive care unit by providing eye care information such as daily examination of the eyes, lubrication in the presence of lagophthalmos and closing the eyelids by taping. Eye care in the intensive care unit and the application of treatments appropriate for ocular problems that may occur because of Covid-19 infection are vital for those who recover from Covid-19 infection to prevent vision loss and maintain quality of life.

The present study was conducted on patients who were being treated in intensive care. For this reason, as a limitation of our study, it was not possible to distinguish whether retinal haemorrhages were because of disease or drug use. We think that the application of systemic treatments to prevent the complications of Covid-19 infection before ophthalmological examination and hypoxia because of the disease makes it difficult to distinguish whether these findings are caused by Covid-19 infection or the treatment.

As a result, corneal abrasion because of lagophthalmos was observed in 10.3% of the patients who were followed up in the intensive care unit. Care should be taken in terms of exposure keratopathy, both because of not treating corneal abrasions, and also secondary to the development of severe chemosis and eyelid oedema in patients who are placed in the prone position. Daily eye examinations are required, especially in critical cases of Covid-19 under mechanical ventilation support.

We observed retinal haemorrhage at a rate of 8.6%. We observed that Covid-19 infection can directly cause endothelitis, thromboembolism or retinal haemorrhage and cotton wool spots because of the treatments used. There was no significant difference in terms of systemic disease and laboratory parameters in patients with haemorrhage in the retina compared with those without haemorrhage.

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DISCLOSURE

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

ZEG, AG, LAD, USK, KM and EG contributed to the design and conceptualisation of the study. ZEG, AG, LAD, USK contributed to in designing the search strategy and literature search. Data extraction was conducted by ZEG an AG. Data entry and statistical analysis were performed EG. Critical appraisal was done by ZEG, USK and KM. ZEG and KM contributed to drafting and writing the manuscript. All authors reviewed and contributed in editing the manuscript.

DATA AVAILABILITY STATEMENT

Research Data not shared.

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