Review Article

CLINICAL CHANGES IN EYE DUE TO COVID - 19 PANDEMIC- A REVIEW

Abstract: *-COVID-19 is a coronavirus disease caused by the SARS-CoV-2 subtype. Coronaviruses have attracted global attention due to the emergence of severe respiratory syndrome infections such as SARS and MERS in 2003. They were triggered by the introduction of the coronavirus in humans.The ongoing COVID-19 pandemic is a reminder of the evolution of organisms. For SARS-CoV-2 and COVID-19, the two viruses have the same angiotensin converting enzyme 2 (ACE2).The human-to-human transfer of SARS-CoCoV-2 occurs through respiratory droplets and contact with the mucous membranes. Eye protection is often required to prevent the spread of SARS-CoBV-2.Human-to-person transmission of SARS-coV-2 occurs through respiratory droplets and contact with the body's mucous membranes. Eyewitnesses have raised concerns that the disease could be transmitted through the ocular surface.Several patients with COVID-19 exhibited ocular abnormalities.Several studies have shown that patients with COVID-19 exhibited ocular anomalies. Further studies suggest that this infection may have a relationship with SARSCoV-2 infection.SARS-CoV-2 is a respiratory illness that has caused thousands of fatalities globally. It has been named COVID-19Cases of pneumonia were reported in December 2019 in Wuhan, China. The infections were caused by the SARS virus.*

Keyword: *- Covid-19, Conjunctivitis, respiration, droplets.*

INTRODUCTION

The SARS-CoV-2 subtype of coronavirus is responsible for COVID-19. In 2019, it was first reported. Over 5,000,000 people have been affected and over 300,000 people have died because ofits worldwide.[1] The 2003 emergence of severe respiratory syndrome infections like SARS and MERS has brought global attention to coronaviruses. The ongoing COVID-19 pandemic is a reminder of the evolution of organisms. They were sparked by the introduction of the coronavirus to humans.[2] Angiotensin-converting enzyme 2 (ACE2) is shared by SARS-CoV-2 and COVID-19.[3] Human-to-human transmission of SARS-CoCoV-2 occurs through respiratory droplets and mucous membrane contact. To prevent the spread of SARS-CoBV-2[4], eye protection is frequently required. Respiratory droplets and contact with the body's mucous membranes carry SARS-coV-2 from one person to another. Several patients with COVID-19 exhibited ocular abnormalities, and several studies have demonstrated that patients with COVID-19 exhibited ocular anomalies. Eyewitnesses have raised concerns that the disease could be transmitted through the ocular surface.[5]SARS-CoV-2 is a respiratory illness that has resulted in thousands of deaths worldwide, and additional studies suggest that this infection may be related to SARS-CoV-2 infection.[6-8]SARS-CoV-2 is a respiratory illness that has caused more than 4 million cases and 280,000 deaths worldwide since it emerged in 2003.[11-15] The SARS-CoV-2 virus has caused a global epidemic. It has been referred to as COVID-19.[8-10]Since its discovery in 2001, it has infected over four million people and killed approximately 280,000 others.[16-20] In Wuhan, China, pneumonia cases were reported in December 2019. The SARS virus was to blame for the infections.The first known physician to report similarities between the symptoms of the illness and the virus was Dr. Li Wenliang.[21-24] A new RNA betacoronavirus was found to

be the main cause of the human disease. It was initially believed that the virus was introduced by bats. Human infections usually occur through coughing or sneezing.[25-28]

Coronaviruses can infect a wide range of mammals and birds. They can also cause respiratory failure in humans. Two humansCoVs, which were known to cause respiratory failure, were eradicated after SARS-CoV2.[29,30] Coronaviruses are mainly involved in the transmission of diseases among animals. Two humansCoVs have been known to cause respiratory failure.[31-33]One case report describes the positive PCR result of a tear sample for SARS-CoV, while other tests did not find evidence of viral load in the samples.[34-36] Non-structural proteins are responsible for the viral infection and the replication of pathogens. For instance, the surface spike glycoprotein enables the attachment of host cells to the virus.[35-40] Their primary target is the lung epithelial cells. Binding to the same cellular receptor can cause severe infections in the upper respiratory tract and lower respiratory tract.Currently, the reverse transcriptase-PCR (RT-PCR) is the most widely used diagnostic test for COVID-19.

There are seven known human coronaviruses that can cause mild respiratory infections in humans. The most dangerous kinds of coronaviruses are SARS-CoV-2 and SARS-CoV-3. They can also cause life-threatening illnesses.[41-43]Human coronaviruses have been known to cause ocular diseases. The first known example of this was the HCoV-NL63 subtype, which was isolated from a child with respiratory illness.[44-48] In a case series, the authors did not find evidence of ocular complications in the patients with SARS-CoV infection. They also did not detect evidence of the virus' pathogenesis in these cases.[49-51] Since the outbreak started, a growing number of clinical reports of COVID-19 patients have been published. These reports include various symptoms, such as hyperemia, chemosis, and ocular congestion.[52-55] Subconjunctival hemorrhage, pseudomembranes, and impaired vision were also reported in

COVID-19. It is possible that SARS CoV-2 can infiltrate the ocular surface and cause conjunctivitis.[56-59] Subconjunctival hemorrhage, pseudomembranes, and impaired vision were also reported. Although the incidence of COVID-19 is low, evidence suggest that SARS-CoV-2 can infect the ocular surface.[60]

A 29-year-old nurse in an emergency department presented with persistent bilateral conjunctivitis and a watery discharge on the second day of her fever. A 30-year-old male patient was also diagnosed with COVID-19.[61-65]The acute onset of ocular symptoms with progressive hyperemia and watery discharge was associated with the SARS-CoV-2 infection. It was confirmed that the symptoms were viral conjunctivitis.The varying characteristics and definitions of conjunctivitis in different reports may have contributed to the different findings. Due to the potentially dangerous nature of the condition, some cases of conjunctivitis were performed using telemedicine or penlight examinations.[66-70]Conjunctivitis is a common eye disorder that can be caused by a variety of infectious or noninfectious causes.[71,72]

Conjunctivitis is often caused by non-infectious causes. In most cases, it is diagnosed as differentially if the affected patient has no ocular virus testing.[73] The chemosis and conjunctival congestion exhibited by COVID19 individuals are like the symptoms of conjunctivitis. They can be caused by various factors such as mechanical ventilation, electrolyte imbalance, and fluid overload.[74]Also, prolonged exposure to sunlight may affect the development of COVID-19. In addition, prolonged exposure to low levels of vitamin D may affect the development of COVID-19.[75]

It has been reported that the ACE2 protein is expressed in the retina and in aqueous humor. Also, coronaviruses can cause neuritis and retinopathy in animal models.[76]The authors did not test for SARSCoV-2 in the patients' bodies or the ocular surface. Instead, they focused on the

coronavirus's potential to infect intraocular tissues.[77]Most of the mild symptoms experienced during the SARS-CoV-2 pandemic were mild, and they did not cause sight-threatening complications.[79]It has been hypothesized that the coronavirus can cause proliferative diseases in animal models. Also, it has been observed that patients with COVID-19 exhibited no visual disturbance and no intraocular inflammation.[81]The authors did not test for the presence of SARS-CoV-2 in the body of COVID-19 patients. It is possible that the virus can also infect the intraocular tissues of COVID-19 patients.[82]

Most of the ocular manifestations in COVID-19 were mild, and they recovered in a relatively short time.[83]RTPCR-based testing for SARS-CoV2 is commonly performed in ocular specimens by amplifying the virus RNA using RT-qPCR in tears or fluids. This method can also be used for other applications.The detection of SARS-CoV2 in conjunctival or tear specimens can be done depending on the viral load and shedding profile of the samples.Viral loads in conjunctival specimens were lower than those in the other types of specimens after conjunctivitis onset. They showed that the decrease was undetectable for days 5 to 7 after onset.[83]

It has been hypothesized that SARS-CoV-2 can appear on the ocular surface during the onset of conjunctivitis. In a study, researchers detected the presence of SARSCoV-2 RNA in the ocular swabs of a patient with COVID-19.Then, they observed a five-day clinical effect after inoculating human tissue with the first positive specimen of SARS-CoV-2 cells. This effect was triggered by the inoculating cells.Although the effects of SARS-CoV-2 RNA and Vero E6 cells were not detected in tear samples from COVID-19 patients, the low viral loads were still found to be negative.Although it is possible that the results were obtained due to the contamination of testing items, further studies are needed to determine if SARS-CoV-2 can be transmitted through the eyes.In three cases, positive conjunctival swab samples were detected for COVID-19. Two of

the patients did not exhibit ocular symptoms.[80] Ocular swab samples were positive for 2 weeks in this patient, even though the former became negative. These observations indicate that the ocular surface could harbor SARS-CoV-2 without entering the cells.Although the ocular surface is a less likely route of infection for SARS-CoV-2 than the conjunctiva, it could still be infected through ophthalmic practice.The SARS-CoV-2 S protein is a key component of the coronavirus's infection pathway, which involves binding to host cells. It can also enhance the binding of the ACE2 protein.[84]

SARS-CoV-2's S protein is cleaved to the serine 2 protease, which is activated by the transmembrane protease. It exhibits a different viral shedding pattern than that of SARS-CoV.The expression of ACE2 in the body can be used to identify potential infection routes caused by SARS-CoV-2. This protein is widely expressed in various organs, including the lungs, ileum, and colon.Through single-cell RNA-sequencing, they discovered that the ACE2 protein was expressed in the eye's various cell types. This finding supports the notion that the cell type that appears on the surface of the ocular is not differentiated.The expression levels of the two genes were lower in the eyes than in the lungs, which suggests that they could lower the risk of SARS-CoV-2 transmission.The expression level of human Ace2 and TMPRSS2 in the conjunctiva was significantly higher in comparison to that in the cornea. The results of this study support the notion that the cornea has the highest expression of these proteins for SARS-CoV-2 infections.[83]The distribution of ACE2 on the ocular surface has been suggested as a potential entry point for SARS-CoV-2 into the eye. In an ex vivo study, human conjunctival explant cultures wereextensively infected with SARS-CoV-2. The presence of ace2 on the surface led to the spread of the infection.[83]The distribution of ace2 on the ocular surface has been suggested as a possible route of SARS-CoV-2 infection. Hui and his colleagues investigated the presence of

SARS-CoV-2 in human explant cultures with higher infectious viral titers than those of SARS-CoV. Ocular surface is closely associated with the respiratory tract through the nasolacrimal system. It is composed of the tear film and the keratographia.The nasolacrimal system is a route that allows viruses to spread between the eyes and the upper respiratory tract.In two of four confirmed SARS cases, the specimens tested positive. None of the stool or swab samples from these patients were positive.[83] Viral loads were detected in the conjunctival swabs of macaques after they were inoculated using the intratracheal route. They also found no viral loads in the nasopharyngeal swabs of the animals.The authors proposed that SARS-CoV-2 could infect the surface cells of the nasopharyngeal tract and enter the respiratory tract through the secretion of the nasolacrimal system.The rapid emergence of COVID-19 has raised concerns about the transmission of the SARS-CoV-2 coronavirus. This infection can be transmitted through the contact with an eye or respiratory droplets.Due to the increasing number of cases of SARS-CoV-2 infections, the need for healthcare workers to protect their eyes is becoming more prevalent.Reports have been issued to inform ophthalmological clinics about the importance of protecting patients and healthcare providers from possible exposure to an infectious disease.[85]

Other symptoms of COVID-19 infection have also been screened. In patients with acute conjunctivitis infections, the symptoms can be seen in several different forms of illness.It is important that healthcare workers protect themselves from the harmful effects of ultraviolet radiation by wearing masks and performing good hand hygiene. Aside from these, healthcare workers also need to wear goggles and face shields.[85]

To minimize the risk of transmission of droplets, the use of slit lamps has been suspended. The use of non-touch tonometry machines has been restricted to prevent the aerosolization of drugs.

1. EYE COMPLICATIONS DURING COVID-19

1.1.CONJUNCTIVITIS

Since SARS-CoV-2 can cause respiratory failure, most of the treatment and diagnostic efforts are focused on the respiratory tract. However, other symptoms such as fever, muscle aches, and tears in the eyes can also be caused by the disease.[86-89] Conjunctival infection was reported to be a contributing factor to the COVID-19 outbreak. The viral RNA found in the patients' tears suggested that the infection was caused by the COVID-19 virus.[90-92] The presence of the ACE-2 receptor on the ocular surface could serve as a portal of entry for viral infection. This protein is a key component of the cell surface protease enzymes (TMPRSS2) that can allow access to host cells.[93-95] The presence of the ACE-2 receptor on the ocular surface could serve as a portal to enter an infected cell. This factor and the cell surface protease enzyme TMPRSS2 are known to bind with the virus and allow it to enter the host cell.[96-101]

A study has shown that the expression of TMPRSS2 in conjunctival and ptygpterium samples is not consistent. It has been hypothesized that the presence of this protein triggers the systemic infection.It is also believed that the severity of the response is not equal in all patients. This condition, which is known as a macrophage activated syndrome, can trigger both an immunological and inflammatory response.It is possible that SARS-CoV-2 exhibits a low conjunctival replication. However, it can still infect the conjunctiva through infected tears that travel through the nasolacrimal ducts. This infection could be initiated using an unidentified receptor.It is possible that the SARS-CoV-2 viruconjunctival the conjunctiva through infected tears, which can then be transmitted to the nasopharyngeal area. Infestation of the skin with the virus could also cause a low conjunctival replication.COVID-19 conjunctivitis is like other viral forms. It usually presents with various symptoms, including fever, dilated pupils, and inflamed

epiphora.At present, there are no reported cases of vision-threatening events. In a study, a patient with monoliteralkeratoconjunctivitis was described as the first symptom of COVID-19.[101]

Although the exact number of cases of COVID-19 conjunctivitis is still unknown, it is believed that around 31.6% of patients have the condition. In most cases, the viral load is higher than the threshold of test detection.[102] It is possible that patients who have already started antiviral therapy may have developed the infection through tears. Also, some of them may have developed ocular symptoms before the swab.[103] It is possible that the only disease-specific symptom of COVID-19 is conjunctivitis. In this case, the presence of SARS-CoV-2 RNA isolated on the normal conjunctiva of COVID-19 patients could indicate a viral spreading.[104]

The symptoms of COVID-19 have been self-limiting. They are caused by the virus' ability to infect the ocular surface cells. It is important to avoid getting infected with this disease and to maintain a safe and effective infection control program.[105-107]

1.2.KAWASAKI DISEASE

Kawasaki disease is a chronic and usually self-limiting vesicular disease that usually affects young children. It causes fever, oropharyngeal changes, and polymorphous rash.Although the exact cause of KD is still not known, it has been theorized that an infectious agent could trigger a cascade reaction. Several studies have reported an increase in the number of cases of severe capital depression (KD) in children. The prevalence of this condition was also found to be 80%.According to some authors, a severe form of KD has a 30-fold increased incidence of being diagnosed with COVID-19 serology. Other studies also suggest that there are unusual clusters of cases in the US and UK.[108]The first case of COVID-19 infection in a 6-month-old girl was observed in a setting of fever and minimal breathing symptoms. The KD is especially relevant to ophthalmologists due to its possible ocular involvement. Most of the time, it shows signs of

iridocyclitis or punctate keratitis.[110]As the SARS-CoV-2 epidemic spreads globally, it is expected to create new cases of Kawasaki-like disease in the US. This condition could cause diabetic retinopathy and other eye diseases.[111]

1.3.DIABETIC RETINOPATHY.

Due to the global outbreak of coronavirus, many countries have adopted isolation policies. These policies may cause patients to adopt a sedentary lifestyle, which can impair their insulin sensitivity and worsen their lipid metabolism.The increasing prevalence of diabetes mellitus may have unforeseen effects on public health. This could result in an increase in the number of visits to an ophthalmologist for eye complications due to diabetes.The policies that restrict patients' physical activity and sedentary behavior can have detrimental effects on their health.The pandemic may have unforeseen effects on public health, such as an increase in the number of people with diabetes and other eye complications.This could have consequences for public health, such as the worsening of diabetes or the onset of new cases of diabetes. It is also possible that the coronavirus pandemic could lead to an increase in severe cases of diabetes retinopathy.[112]

1.4.RETINAL FINDINGS.

A recent report analyzed optical coherence tomography findings in 12 patients infected with SARS-CoV-2 and revealed hyperreflective lesions in the inner plexiform layers of the eye.[113-116] Results of an OCT angiography and a ganglion cell complex analysis were normal. Four patients presented with subtle cotton-wool spots or microhemorrhages on the retinal arcade.[117] Concerns have been raised about the interpretation of hyperreflective areas in patients with COVID-19 microcircular damage. It has been hypothesized that these areas may represent normal retinal vessels.[118] The complement system activation is a known cause of ocular vascular damage. This

condition is characterized by unusual cases of hemolytic uremic syndrome.[119] It is also known that high serum levels of C3, which is known to increase the risk of developing diabetes and other neurodevelopmental diseases, can also be linked to an increase in the levels of ACE receptors.[120] COVID-19 can target vascular pericytes that are expressing ACE-2, which could cause microvascular damage and ocular circulation involvement. This impairs the function of the vascular endothelial cells.[121]

1.5.NEURO-OPHTHALMOLOGICAL COMPLICATIONS

COVID-19 has been known to cause neuro-ophthalmological complications such as polyneuritis, Guillain-Barr e syndrome, and meningitis.Cases of individuals with COVID-19 have been reported in the literature. According to investigators, COVID-19 could be triggered by factors that contribute to the onset of Oculomotor nerve palsy.Although animal models suggest that optic neuritis could develop in COVID-19 patients, the literature has not yet revealed cases of this condition. Also, the prevalence of respiratory distress syndrome in COVID-19 patients is likely to increase.[122-123]

2. OCULAR COMPLICATIONS IN INTENSIVE CARE UNIT PATIENTS

A study conducted in Italy revealed that out of 1,591 COVID-19 patients, only 9% were admitted to intensive care units (ICUs).[124] These individuals tend to develop ocularcomplications.[123]Intensified care in an intensive care unit is associated with an increased incidence of eye- related complications.[125] In most cases, these complications occur in the posterior segment and ocular surface disorders.Only one case of central retinal artery occlusion has been reported during this review, and this was caused by COVID-19.[126] The role of thrombophilic factors in the pathogenesis of CVODs is still controversial.Future research may reveal an increased incidence of vascular occlusives during the COVID-19 pandemic.[127]

2.1.OCULAR SURFACE DISORDERS

Surface disorders are the most common ocular complications that occur in the intensive care unit (ICU). They can range from mild to severe infectious keratitis. Most critically ill patients in the intensive care unit (ICU) experience surface disorders, which can range from mild to severe infectious diseases. The most common causes of these conditions include exposure to various multiresistant bacteria, and the use of antibiotics.[128-129]

In ventilated patients, the main surface defense mechanisms of the eye are impaired. This impairs the ability of the orbicularis to contract. This leads to lagophthalmos.[130] Airway pressure and oxygen masks can dry the surface of the eye. In most cases, exposure keratopathy occurs in patients who have been sedated for more than 48 hours.[132] Airway Pressure and Oxygen masks can cause a drying effect on the eye surface. Exposure keratopathy occurs in up to 44% of intensive care unit patients and up to 60% of those sedated for longer periods.[133]

Conjunctival chemosis is usually seen in patients with acute respiratory distress syndrome (ARDS). It can cause lagophthalmos and reduce ocular surface lubrication. The risk factors for developing this condition include decreased venous return and increased hydrostatic pressure.[134]

In mechanically ventilated individuals, the increase in central venous pressure can also cause subconjunctiva hemorrhage. This condition is usually benign but can lead to surface disorders. An increase in the central venous pressure can also cause sub conjunctival hemorrhage, which is a benign condition that usually goes unnoticed. In mechanically ventilated individuals, the end-expulsive pressure can also increase and lead to subconjuctival hemorrhage.[135] A study published in the Journal of Allergy and Infectious Diseases revealed that among 134 patients who underwent respiratory support, at least 77% were colonized by at least a few bacterial species other than those with normal flora.[136]

2.2.RARE OCULAR COMPLICATIONS

It has been observed that prone position ventilation can prevent the development of acute ischemic optic neuropathy. However, prolonged exposure to a prolonged exposure to a high level of oxygen deprivation can lead to the development of this condition.[138-140] The prone position can also reduce the perfusion acting on two mechanisms. It can increase the IOP by up to 40 mmHg and increase venous pressure by up to 0.5 mmHg.[141] Other systemic conditions such as diabetes and arterial hypertension can also affect the blood flow to the ocular surface. This impairs the ability of the eye to perform its usual function. This condition is characterized by the sudden appearance of bilateral or uni-lateral macular pre-retinal hemorrhages. It usually appears due to the increasing intrathoracic pressure.[142] It has been known that valsalva can also occur due an intubation or a high end-expulsive pressure. An acute angle closure is a potentially sight-threatening condition that can be triggered by various factors.[143] Some of these include the usual medications and the prone position. An acute angle closure can occur in an ICU patient if the patient has underlying risk factors such as diabetes, high end-expulsive pressure, or an unstable or inverted heart rate.[144] Currently, anticholinergics and systemic drugs are known to cause this type of event. This syndrome has been reported to occur in 2% of central venous catheterization patients.[146-146] It was most likely caused by trauma to the central nervous system or an expanding hematoma. In patients with COVID-19, endophthalmitis has been considered a rare but significant clinical feature of the viral infection.[147]Staff members should be aware of the signs of possible eye-related complications, such as visual impairment and blindness, and should refer them to an ophthalmologist when needed.[148]

3. OCULAR SIDE EFFECTS OF DRUGS USED FOR THE TREATMENT OF COVID-19

Currently, there are no pharmacological treatments for COVID-19. However, some drugs are being studied for their potential use.[154]

3.1.ANTIMALARIAL DRUGS

The anti-malarial drugs CQand HCQ are commonly used to treat various conditions, such as malaria and amebiasis. They have also been studied in animal models to develop an immunological response against SARS-CoV-2.A study in China showed that CQ reduced the exacerbations of pneumonia and promoted viral-negative seroconversion. In COVID-19, this treatment led to better clinical recovery and reduced hospitalizations.A study conducted by Gautret et al. showed that treating HCQ in patients with COVID-19 led to viral load reduction and disappearance.[155]In addition, these drugs have anti-SARSCoV-2 and anti-SARSCoV-2 effects. They can inhibit the growth of cells that are infected with SARSCoV-2 and SARSCoV-2 by suppressing the terminal glycosylation of the ACE-2 receptor.COVID-19 is an anti-SARSCoV-2 and SARSCoV-2 monoclonal antibody that blocks the terminal glycosylation of the ACE-2 receptor. It is administered at a dose of 1,000 mg daily for 4 or 7 days.[156,157]

The clinical picture of CQ and HCQ ocular toxicity shows whorl-like intraepithelial deposits and posterior subcapsular lens opacity. It is also characterized by a bilateral Maculopathy that shows progressive loss of visual acuity and RPE atrophy.The clinical picture of CQ and HCQ ocular toxicity shows whorl-like intraepithelial deposits that are usually reversible. There is also a bilateral Maculopathy that shows the presence of a ring of RPE depigmentation.CQ and HCQ maculopathy is not reversible, and it can progress even after stopping drug assumption. The most critical risk factor for developing these conditions is excessive daily dosage.Most of the patients treated with COVID-19 for COVID-19 receive higher-than-recommended doses of CQ and HCQ. This increased risk of ocular toxicity increases with prolonged use of HCQ.Most of the patients who received COVID-19 for COVID-19 received potentially toxic doses. The duration of therapy is also an important factor to consider when choosing a drug for treating ocular

toxicity.Two studies showed that patients receiving HCQ had a 25% to 40% increase in the incidence of retinopathy within 2 years. No reports of retinal toxicity have been reported in patients receiving CQ or HCQ.[158] A two-year study on patients receiving 800 to 1,000 mg/day of HCQ showed that 60% of them experienced vision problems within 1-2 years. The study did not find evidence of drug toxicity being observed under 2 weeks of CQ.[159]

3.2.ANTIVIRAL DRUGS

Both lopinavir and ritonavir are known to reduce the COVID-19 infection in humans.Lopidinavir and Ritonavir are commonly used as part of an HIV infection-fighting strategy known as COVID-19. These two drugs are formulated in a combination to inhibit the P450 3A4 enzyme.[155]Lopinavir/ritonavir is a therapy that can reduce the viral load in COV-19 patients. Although it has been shown to improve the efficacy of the virus, its safety has been limited.In one study, researchers described a rare but devastating vision loss caused by ritonavir. The drug was commonly used for treating HIV positive individuals with vision loss. It can also cause visual changes that can deceive people with compromised vision.There can also be changes in the pigments in the mid-peripheral retina. Intricate intraretinal deposits can also form. Pigment changes in the mid-peripheral retina can also occur. Also, loss of the ellipsoid zone and outer retinal layers can also cause OCT to be affected.The shortest time before diagnosis for COVID-19 patients is 19 months. The duration of treatment is usually 5 to 7 days. The shortest time before diagnosis for COVID-19 patients is 19 months. For HIV cases, the recommended dosage of lopinavir/ritonavir is 400/100 mg twice daily.[160]

3.3.IMMUNOMODULATORY DRUGS

Interferons are a class of drugs that can be used to treat COVID-19. Among the IFN subtype's most promising characteristics is their ability to trigger an immunological response against

COVID-19.[161-162] Interferon-associated retinopathy is a type of visual impairment that can manifest with various microvascular irregularities and cotton-wool spots. It usually appears 3 to 5 months after treatment.[163] Although the ocular findings of patients with interferon-associated retinopathy were reversed after cessation of treatment, they still exhibited significant deficits in visual quality.[164]

Currently, there are no published studies on the use of anti-IL-1 and anti-IL-6 inhibitors in patients with chronic wasting syndrome (COVID-19). However, some studies have shown an association between high doses of anakinra and progressive nystagmus.[165]

CONCLUSION

REFERENCES

1. W.-j. Guan, Z.-y. Ni, Y. Hu et al., "Clinical characteristics of coronavirus disease 2019 in China," New England Journal of Medicine, vol. 382, no. 18, pp. 1708–1720, 2020.
2. E. Petersen, D. Hui, D. H. Hamer et al., "Li Wenliang, a face to the frontline healthcare worker. The first doctor to notify the emergence of the SARS-CoV-2, (COVID-19), outbreak," International Journal of Infectious Diseases, vol. 93, pp. 205– 207, 2020.
3. R. Lu, X. Zhao, J. Li et al., "Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding,"
4. A. Gulati, C. Pomeranz, Z. Qamar et al., "A comprehensive review of manifestations of novel coronaviruses in the context of deadly COVID-19 global pandemic,
5. Seah and R. Agrawal, "Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals," Ocular Immunology and Inflammation, vol. 28, no. 3, pp. 391–395, 2020.

6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
7. World Health Organization. Coronavirus disease (COVID-2019) Situation reports. WHO (2020). Available online at: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/situation-reports.
8. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. (2003) 348:1986–94. doi: 10.1056/NEJMoa030685
9. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. (2012) 367:1814–20. doi: 10.1056/NEJMoa1211721
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. (2020) 579:270–3. doi: 10.1038/s41586-020-2012-7
11. Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet. (2020) 395:e39. doi: 10.1016/S0140-6736(20)30313-5
12. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. (2020) 138:575–8. doi: 10.1001/jamaophthalmol.2020.1291
13. Hong N, Yu W, Xia J, Shen Y, Yap M, Han W. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19.
14. Acta Ophthalmol. (2020). doi: 10.1111/aos.14445. [Epub ahead of print].

15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. (2020) 382:1708– 20. doi:
16. 10.1056/NEJMoa2002032 10. Chen L, Deng C, Chen X, Zhang X, Chen B, Yu H, et al. Ocular manifestations, and clinical characteristics of 534 cases of COVID19 in China: a cross-sectional study. medRxiv [Preprint]. (2020) 20034678. doi: 10.1101/2020.03.12.20034678
17. van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, et al. Identification of a new human coronavirus. Nat Med. (2004) 10:368–73. doi: 10.1038/nm1024
18. Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol. (2005) 79:884– 95. doi: 10.1128/JVI.79.2.884-895.2005
19. Vabret A, Mourez T, Dina J, van der Hoek L, Gouarin S, Petitjean J, et al. Human coronavirus NL63, France. Emerg Infect Dis. (2005) 11:1225– 9. doi: 10.3201/eid1108.050110
20. Loon SC, Teoh SC, Oon LL, Se-Thoe SY, Ling AE, Leo YS, et al. The severe acute respiratory syndrome coronavirus in tears. Br J Ophthalmol. (2004) 88:861–3. doi: 10.1136/bjo.2003.035931
21. Chan WM, Yuen KS, Fan DS, Lam DS, Chan PK, Sung JJ. Tears and conjunctival scrapings for coronavirus in patients with SARS. Br J Ophthalmol. (2004) 88:968–9. doi: 10.1136/bjo.2003.039461

22. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. (2020) 92:589–94. doi: 10.1002/jmv.25725
23. Seah IYJ, Anderson DE, Kang AEZ, Wang L, Rao P, Young BE, et al. Assessing viral shedding and infectivity of tears in coronavirus disease 2019 (COVID-19) patients. Ophthalmology. (2020) 127:977–9. doi: 10.1016/j.ophtha.2020.03.026
24. Zhang X, Chen X, Chen L, Deng C, Zou X, Liu W, et al. The evidence of SARS-CoV-2 infection on ocular surface. Ocul Surf. (2020) 18:360– 2. doi: 10.1016/j.jtos.2020.03.010
25. Ye Y, Song Y, Yan M, Hu C, Chen X, Yu J, et al. Novel coronavirus pneumonia combined with conjunctivitis: three cases report. Chin J Exp Ophthalmol. (2020) 38:242–4. doi: 10.3760/cma.j.issn.2095-0160.2020.0006
26. Zhou Y, Duan C, Zeng Y, Tong Y, Nie Y, Yang Y, et al. Ocular findings, and proportion with conjunctival SARS-COV-2 in COVID-19 patients. Ophthalmology. (2020) 127:982–3. doi: 10.1016/j.ophtha.2020.04.028
27. Chen L, Liu M, Zhang Z, Qiao K, Huang T, Chen M, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. Br J Ophthalmol. (2020) 104:748– 51. doi: 10.1136/bjophthalmol-2020-316304
28. Cheema M, Aghazadeh H, Nazarali S, Ting A, Hodges J, McFarlane A, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). Can J Ophthalmol. (2020) 55:e125– 9. doi: 10.1016/j.jcjo.2020.03.003
29. Colavita F, Lapa D, Carletti F, Lalle E, Bordi L, Marsella P, et al. SARSCoV-2 isolation from ocular secretions of a patient with COVID-19 in Italy with prolonged viral RNA detection. Ann Intern Med. (2020) 173:242– 3. doi: 10.7326/M20-1176

30. Khavandi S, Tabibzadeh E, Naderan M, Shoar S. Corona virus disease-19 (COVID-19) presenting as conjunctivitis: atypically high-risk during a pandemic.
31. Cont Lens Anterior Eye. (2020) 43:211–2. doi: 10.1016/j.clae.2020.04.010
32. Navel V, Chiambaretta F, Dutheil F. Haemorrhagic conjunctivitis with pseudomembranous related to SARS-CoV-2. Am J Ophthalmol Case Rep. (2020) 19:100735. doi: 10.1016/j.ajoc.2020.100735
33. Hu Y, Chen T, Liu M, Zhang L, Wang F, Zhao S, et al. Positive detection of SARS-CoV-2 combined HSV1 and HHV6B virus nucleic acid in tear and conjunctival secretions of a non-conjunctivitis COVID-19 patient with obstruction of common lacrimal duct. Acta Ophthalmol. (2020). doi: 10.1111/aos.14456. [Epub ahead of print].
34. Abrishami M, Tohidinezhad F, Daneshvar R, Omidtabrizi A, Amini M, Sedaghat A, et al. Ocular manifestations of hospitalized patients with COVID-19 in Northeast of Iran. Ocul Immunol Inflamm. (2020) 28:739– 44. doi: 10.1080/09273948.2020.1773868
35. Scalinci SZ, Battagliola ET. Conjunctivitis can be the only presenting sign and symptom of COVID-19. IDCases. (2020) 20:e00774. doi: 10.1016/j.idcr.2020.e00774
36. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R Jr. Retinal findings in patients with COVID-19. Lancet. (2020) 395:1610. doi: 10.1016/S0140-6736(20)31014-X
37. Daruich A, Martin D, Bremond-Gignac D. Ocular manifestation as first sign of Coronavirus disease 2019 (COVID-19): Interest of telemedicine during the pandemic context.
38. J Fr Ophtalmol. (2020) 43:389–91. doi: 10.1016/j.jfo.2020.04.002
39. Salducci M, La Torre G. COVID-19 emergency in the cruise's ship: a case report of conjunctivitis. Clin Ter. (2020) 171:e189– 91. doi: 10.7417/CT.2020.2212

40. Wu P, Liang L, Chen C, Nie S. A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis. Graefes Arch Clin Exp Ophthalmol. (2020) 258:1565–66. doi: 10.1007/s00417-020-04708-6
41. Tong TR, Lam BH, Ng TK, Lai ST, Tong MK, Chau TN. Conjunctiva-upper respiratory tract irrigation for early diagnosis of severe acute respiratory syndrome. J Clin Microbiol. (2003) 41:5352. doi: 10.1128/JCM.41.11.5352.2003
42. Yuen KS, Chan WM, Fan DS, Chong KK, Sung JJ, Lam DS. Ocular screening in severe acute respiratory syndrome. Am J Ophthalmol. (2004) 137:773– 4. doi: 10.1016/S0002-9394(03)01148-6
43. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. (2013) 310:1721–9. doi: 10.1001/jama.2013.280318
44. Grixti A, Sadri M, Edgar J, Datta AV. Common ocular surface disorders in patients in intensive care units. Ocul Surf. (2012) 10:26–42. doi: 10.1016/j.jtos.2011.10.001 Frontiers in Medicine | www.frontiersin.org 8 November 2020 | Volume 7 | Article 569126 Chen et al. Ocular Involvement in COVID-19
45. Siedlecki J, Brantl V, Schworm B, Mayer WJ, Gerhardt M, Michalakis S, et al. COVID-19: ophthalmological aspects of the SARS-CoV 2 global pandemic.
46. KlinMonblAugenheilkd. (2020) 237:675–80. doi: 10.1055/a-1164-9381
47. Senanayake P, Drazba J, Shadrach K, Milsted A, RunggerBrandle E, Nishiyama K, et al. Angiotensin II and its receptor subtypes in the human retina. Invest Ophthalmol Vis Sci. (2007) 48:3301–11. doi: 10.1167/iovs.06-1024

48. Holappa M, Valjakka J, Vaajanen A. Angiotensin(1-7) and ACE2, “The Hot Spots” of renin-angiotensin system, detected in the human aqueous humor. Open Ophthalmol J. (2015) 9:28–32. doi: 10.2174/1874364101509010028
49. Seah I, Agrawal R. Can the coronavirus disease 2019 (COVID19) affect the eyes? a review of coronaviruses and ocular implications in humans and animals. Ocul Immunol Inflamm. (2020) 28:391–5. doi: 10.1080/09273948.2020.1738501
50. Yan Y, Chang L, Wang L. Laboratory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): status, challenges, and countermeasures.
51. Rev Med Virol. (2020) 30: e2106. doi: 10.1002/rmv.2106 42. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. (2020) 26:845–8. doi: 10.1038/s41591-020-0897-1
52. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. (2020) 25:2000045. doi: 10.2807/1560-7917.ES.2020.25.3.2000045
53. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARSCoV-2 in different types of clinical specimens. JAMA. (2020) 323:1843– 4. doi: 10.1001/jama.2020.3786
54. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients.
55. N Engl J Med. (2020) 382:1177–9. doi: 10.1056/NEJMc2001737
56. Sun CB, Wang YY, Liu GH, Liu Z. Role of the eye in transmitting human coronavirus: what we know and what we do not know. Front Public Health. (2020) 8:155. doi: 10.3389/fpubh.2020.00155

57. Peng Y, Zhou YH. Is novel coronavirus disease (COVID-19) transmitted through conjunctiva? J Med Virol. (2020). doi: 10.1002/jmv.25753. [Epub ahead of print].

58. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. (2020) 27:325–8. doi: 10.1016/j.chom.2020.02.001

59. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus.

60. J Virol. (2020) 94:e00127–20. doi: 10.1128/JVI.00127-20 50. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. (2020) 367:1260–3. doi: 10.1126/science.abb2507

61. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. (2020) 181:271– 80.e8. doi: 10.1016/j.cell.2020.02.052 cleanPredict

62. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. (2020) 581:465–9. doi: 10.1038/s41586-020-2196-x

63. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus a first step in understanding SARS pathogenesis. J Pathol. (2004) 203:631– 7. doi: 10.1002/path.1570

64. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. (2020) 26:681– 7. doi: 10.1038/s41591-020-0868-6

65. Zhang BN, Wang Q, Liu T, Dou SQ, Qi X, Jiang H, et al. [Expression analysis of 2019-nCoV related ACE2 and TMPRSS2 in eye tissues]. Zhonghua Yan Ke Za Zhi. (2020) 56:438–46. doi: 10.3760/cma.j.cn112142-20200310-00170

66. Ma D, Chen CB, Jhanji V, Xu C, Yuan XL, Liang JJ, et al. Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea. Eye. (2020) 34:1212– 9. doi: 10.1038/s41433-020-0939-4

67. Hui KPY, Cheung MC, Perera R, Ng KC, Bui CHT, Ho JCW, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. Lancet Respir Med. (2020) 8:687– 95. doi: 10.1016/S2213-2600(20)30193-4

68. Lange C, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, et al. Expression of the COVID-19 receptor ACE2 in the human conjunctiva. J Med Virol. (2020). doi: 10.1002/jmv.25981. [Epub ahead of print].

69. Belser JA, Rota PA, Tumpey TM. Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev. (2013) 77:144–56. doi: 10.1128/MMBR.00058-12

70. Garaszczuk IK, Montes Mico R, Iskander DR, Exposito AC. The tear turnover and tear clearance tests - a review. Expert Rev Med Devices. (2018) 15:219– 29. doi: 10.1080/17434440.2018.1435271

71. Deng W, Bao L, Gao H, Xiang Z, Qu Y, Song Z, et al. Rhesus macaques can be effectively infected with SARS-CoV-2 via ocular conjunctival route. bioRxiv [Preprint]. (2020) 990036. doi: 10.1101/2020.03.13.990036

72. Lawler JV, Endy TP, Hensley LE, Garrison A, Fritz EA, Lesar M, et al. Cynomolgus macaque as an animal model for severe acute respiratory syndrome. PLoS Med. (2006) 3:e149. doi: 10.1371/journal.pmed. 0030149
73. de Wit E, Rasmussen AL, Falzarano D, Bushmaker T, Feldmann F, Brining DL, et al. Middle east respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. Proc Natl Acad Sci USA. (2013) 110:16598–603. doi: 10.1073/pnas.1310744110
74. Munster VJ, de Wit E, Feldmann H. Pneumonia from human coronavirus in a macaque model. N Engl J Med. (2013) 368:1560– 2. doi: 10.1056/NEJMc1215691
75. Olivia Li JP, Shantha J, Wong TY, Wong EY, Mehta J, Lin H, et al. Preparedness among ophthalmologists: during and beyond the COVID-19 pandemic.
76. Ophthalmology. (2020) 127:569–72. doi: 10.1016/j.ophtha.2020.03.037
77. Hu VH, Watts E, Burton M, Kyari F, Mathenge C, Heidary F, et al. Protecting yourself and your patients from COVID-19 in eye care. Community Eye Health. (2020) 33:S1–6.
78. Lai THT, Tang EWH, Chau SKY, Fung KSC, Li KKW. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong.
79. Graefes Arch Clin Exp Ophthalmol. (2020) 258:1049–55. doi: 10.1007/s00417-020-04641-8
80. Qiao C, Zhang H, He M, Ying G, Chen C, Song Y, et al. Symptomatic COVID-19 in eye professionals in Wuhan, China. Ophthalmology. (2020) 127:1268–70. doi: 10.1016/j.ophtha.2020.04.026
81. Li JO, Lam DSC, Chen Y, Ting DSW. Novel coronavirus disease 2019 (COVID-19): the importance of recognising possible early ocular manifestation and using protective eyewear.

82. Br J Ophthalmol. (2020) 104:297– 8. doi: 10.1136/bjophthalmol-2020-315994 70. Seah I, Su X, Lingam G. Revisiting the dangers of the coronavirus in the ophthalmology practice. Eye. (2020) 34:1155– 7. doi: 10.1038/s41433-020-0790-7
83. Jayaram H, Strouthidis NG, Gazzard G. The COVID-19 pandemic will redefine the future delivery of glaucoma care.
84. Eye. (2020) 34:1203– 5. doi: 10.1038/s41433-020-0958-1
85. Chandra A, Haynes R, Burdon M, Laidlaw A, Neffendorf J, Eames I, et al. Personal protective equipment (PPE) for vitreoretinal surgery during COVID-19. Eye. (2020) 34:1196–9. doi: 10.1038/s41433-020-0948-3
86. Shih KC, Wong JKW, Lai JSM, Chan JCH. The case for continuing elective cataract surgery during the COVID-19 pandemic.J Cataract Refract Surg. (2020) 46:921. doi: 10.1097/j.jcrs.00000000000 00225
87. Desautels JD, Moshirfar M, Martheswaran T, Shmunes KM, Ronquillo YC. Risks posed to corneal transplant recipients by COVID-19-affected donors. OphthalmolTher. (2020) 9:371–9. doi: 10.1007/s40123-020-00254- w.
88. The L. tabet, S. Mhalla, H. Naija et al., “SARS-CoV-2 infection virological diagnosis,” La TunisieMedicale, vol. 98, no. 4, pp. 304–308, 2020.
89. C. W. Lu, X. F. Liu, and Z. F. Jia, “2019-nCoV transmission through the ocular surface must not be ignored,” <e Lancet, vol. 395, no. 10224, p. e39, 2020.
90. L. Zhou, Z. Xu, G. M. Castiglione et al., “ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection,” <e Ocular Surface, vol. 18, no.4, pp. 537–544, 2020.

91. C. Lange, J. Wolf, C. Auw-Haedrich et al., “Expression of the COVID-19 receptor ACE2 in the human conjunctiva,” Journal of Medical Virology, 2020.
92. D. Ma, C.-B. Chen, V. Jhanji et al., “Expression of SARS-CoV2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea,” Eye,
93. vol. 34, no. 7, pp. 1212–1219, 2020.
94. F. Colavita, D. Lapa, F. Carletti et al., “SARS-CoV-2 isolation from ocular secretions of a patient with COVID-19 in Italy with prolonged viral RNA detection,” Annals of Internal Medicine, vol. 173, no. 3, pp. 242-243, 2020.
95. P. Wu, F. Duan, C. Luo et al., “Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID19) in Hubei Province, China,” JAMA Ophthalmology, vol. 138, no.5, pp. 575–578, 2020.
96. M. Cheema, H. Aghazadeh, S. Nazarali et al., “Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19),” Canadian Journal of Ophthalmology, vol. 55, no. 4, pp. e125–e129, 2020. Journal of Ophthalmology 7
97. V. Navel, F. Chiambaretta, and F. Dutheil, “Haemorrhagic conjunctivitis with pseudomembranous related to SARSCoV-2,” American Journal of Ophthalmology Case Reports, vol. 19, Article ID 100735, 2020.
98. I. Y. J. Seah, D. E. Anderson, A. E. Z. Kang et al., “Assessing viral shedding and infectivity of tears in coronavirus disease 2019 (COVID-19) patients,” Ophthalmology, vol. 127, no. 7, pp. 977–979, 2020.
99. L. Loffredo, F. Pacella, E. Pacella, G. Tiscione, A. Oliva, and F. Violi, “Conjunctivitis and COVID-19: a meta-analysis,” Journal of Medical Virology, vol. 10, 2020.

100. S. Khavandi, E. Tabibzadeh, M. Naderan, and S. Shoar, “Corona virus disease-19 (COVID-19) presenting as conjunctivitis: atypically high-risk during a pandemic,” Contact Lens & Anterior Eye, vol. 43, no. 3, pp. 211-212, 2020.

101. S. Z. Scalinci and E. Trovatobattagliola, “Conjunctivitis can be the only presenting sign and symptom of COVID-19,” IDCases, vol. 20, Article ID e00774, 2020.

102. P. Wu, L. Liang, C. Chen, and S. Nie, “A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis,” Graefe’s Archive for Clinical and Experimental Ophthalmology, vol. 258, no. 7, pp. 1565-1566, 2020.

103. L. Chen, M. Liu, Z. Zhang et al., “Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease,” British Journal of Ophthalmology, vol. 104, no. 6, pp. 748–751, 2020.

104. J.-F. Korobelnik, A. Loewenstein, B. Eldem et al., “Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic,” Graefe’s Archive for Clinical and Experimental Ophthalmology, vol. 258, no. 6, pp. 1149–1156, 2020.

105. D. Veritti, V. Sarao, F. Bandello, and P. Lanzetta, “Infection control measures in ophthalmology during the COVID-19 outbreak: a narrative review from an early experience in Italy,” European Journal of Ophthalmology, vol. 30, no.

106. L. Verdoni and A. Mazza, “An outbreak of severe Kawasakilike disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study,” <e Lancet, vol. 395, no. 10239, pp. 1771–1778, 2020.

107. S. Riphagen, X. Gomez, C. Gonzalez-Martinez, N. Wilkinson, and P. Theocharis, “Hyperinflammatory shock in children during COVID-19 pandemic,” <e Lancet, vol. 395, pp. 1607-1608, 2020.

108. V. G. Jones, M. Mills, D. Suarez et al., “COVID-19 and Kawasaki disease: novel virus and novel case,” Hospital Pediatrics, vol. 10, no. 6, pp. 537–540, 2020.

109. L. Jacob, R. C. Polomeno, Z. Chad, and N. Lapointe, “Ocular manifestations of Kawasaki disease (mucocutaneous lymph node syndrome),” Canadian Journal of Ophthalmology. Journal CanadienD’ophtalmologie, vol. 17, no. 5, pp. 199–202, 1982.

110. R. Krogh-madsen, J. P.)yfault, C. Broholm et al., “A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity,” Journal of Applied Physiology, vol. 108, no.5, pp. 1034–1040, 2010.

111. P. M. Marinho, A. A. A. Marcos, A. C. Romano et al., “Retinal findings in patients with COVID-19,” Lancet, vol. 395, no. 10237, p. 1610, 2020.

112. D. G. Vavvas, D. Sarraf, S. R. Sadda et al., “Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication,” Eye, pp. 1-2, 2020.

113. Y. Zhang, M. Xiao, S. Zhang et al., “Coagulopathy and antiphospholipid antibodies in patients with COVID-19,” New England Journal of Medicine, vol. 382, no. 17, pp. e3–8, 2020.

114. G. Greenwood, “Case report of atypical hemolytic uremic syndrome with retinal arterial and venous occlusion treated with eculizumab,” International Medical Case Reports Journal, vol. 8, pp. 235–239, 2015.

115. K. L. Rasmussen, B. G. Nordestgaard, and S. F. Nielsen, “Complement C3 and risk of diabetic microvascular disease: a cohort study of 95202 individuals from the general population,” Clinical Chemistry, vol. 64, no. 7, pp. 1113–1124, 2018.

116. W. D. Strain and N. Chaturvedi, “Review: the renin-angiotensin-aldosterone system and the eye in diabetes,” Journal of the Renin-Angiotensin-Aldosterone System, vol. 3, no. 4, pp. 243–246, 2002.

117. E. Gavriilaki and R. A. Brodsky, “Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily,” British Journal of Haematology, vol. 189, no. 6, 2020.

118. S. Acharya, M. Diamond, S. Anwar, A. Glaser, and P. Tyagi, “Unique case of central retinal artery occlusion secondary to COVID-19 disease,” IDCases, vol. 21, Article ID e00867, 2020.

119. M. C. Janssen, M. den Heijer, J. R. Cruysberg et al., “Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis?” <rombosis and Haemostasis, vol. 93, no. 6, pp. 1021–1026, 2005.

120. M. Dinkin, V. Gao, J. Kahan et al., “COVID-19 presenting with ophthalmoparesis from cranial nerve palsy,” Neurology, vol. 95, no. 5, pp. 221–223, 2020.

121. H. Wei, H. Yin, M. Huang, and Z. Guo, The 2019 novel coronavirus pneumonia with onset of oculomotor nerve palsy: a case study,” Journal of Neurology, vol. 267, no. 5, pp. 1550–1553, 2020.

122. N. Chen, M. Zhou, X. Dong et al., “Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study,” <e Lancet, vol. 395, no.

123. G. Grasselli, A. Zangrillo, A. Zanella et al., “Baseline characteristics and outcomes of 1591 patients infected with SARSCoV-2 admitted to ICUs of the Lombardy Region, Italy,” JAMA, vol. 323, no. 16, p. 1574, 2020.

124. C. Huang, Y. Wang, X. Li et al., “Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China,” <e Lancet, vol. 395, no. 10223, pp. 497–506, 2020. [42] T. B. Saritas, B. Bozkurt, B. Simsek et al., “Ocular surface disorders in intensive care unit patients,” Scientific World Journal, vol. 2013, Article ID 182038, 2013.

125. E. K. Mela, E. G. Drimtzias, M. K. Christofidou, K. S. Filos, E. D. Anastassiou, and S. P. Gartaganis, “Ocular surface bacterial colonisation in sedated intensive care unit patients,” Anaesthesia and Intensive Care, vol. 38, no. 1, pp. 190–193, 2010.

126. F. Mercieca, P. Suresh, A. Morton, and A. Tullo, “Ocular surface disease in intensive care unit patients,” Eye, vol. 13, no. 2, pp. 231–236, 1999.

127. E. V. Hernandez and M. J. Mannis, “Superficial keratopathy in intensive care unit patients,” American Journal of Ophthalmology, vol. 124, no. 2, pp. 212–216, 1997.

128. L. Herbert, “Ophthalmology in anaesthesia and intensive care,” Anaesthesia& Intensive Care Medicine, vol. 5, no. 9, pp. 304–307, 2004.

129. P. Ghelichkhani and M. Esmaeili, “Prone position in management of COVID-19 patients; a commentary,” Archives of Academic Emergency Medicine, vol. 8, p. e48, 2020. 8 Journal of Ophthalmology

130. C. Guerin, J. Reignier, J.-C. Richard et al., “Prone positioning ´ in severe acute respiratory distress syndrome,” New England Journal of Medicine, vol. 368, no. 23, pp. 2159–2168, 2013.

131. L. A. Lee, “Risk factors associated with ischemic optic neuropathy after spinal fusion surgery,” Anesthesiology, vol. 116, pp. 15–24, 2012.

132. P. N. Nair and E. White, “Care of the eye during anaesthesia and intensive care,” Anaesthesia& Intensive Care Medicine, vol. 15, no. 1, pp. 40–43, 2014.

133. A. Abbas and G. Hyman, “Macular hemorrhage secondary to increased intrathoracic pressure and difficult intubation,” JPMA. <e Journal of the Pakistan Medical Association, vol. 52, no. 6, pp. 265-266, 2002.

134. T. Panchabhai, D. Bandyopadhyay, A. Kapoor, O. Akindipe, C. Lane, and S. Krishnan, “Acute ischemic optic neuropathy with extended prone position ventilation in a lung transplant recipient,” International Journal of Critical Illness and Injury Science, vol. 6, no.1, pp. 45–47, 2016.

135. M. S. Ozcan, C. Praetel, M. T. Bhatti, N. Gravenstein, M. E. Mahla, and C. N. Seubert, The effect of body inclination during prone positioning on intraocular pressure in awake volunteers: a comparison of two operating tables,” Anesthesia & Analgesia, vol. 99, no. 4, pp. 1152–1158, 2004.

136. M. A. Cheng, A. Todorov, R. Tempelhoff, T. McHugh, C. M. Crowder, and C. Lauryssen, The effect of prone positioning on intraocular pressure in anesthetized patients,” Anesthesiology, vol. 95, no. 6, pp. 1351–1355, 2001.

137. B. I. Atwater, E. Wahrenbrock, J. L. Benumof, and W. J. Mazzei, “Pressure on the face while in the prone position: proneview versus prone positioner,” Journal of Clinical Anesthesia, vol. 16, no. 2, pp. 111–116, 2004.

138. T. D. Duane, “Valsalva hemorrhagic retinopathy,” Transactions of the American Ophthalmological Society, vol. 70, pp. 298–313, 1972.

139. C. H¨onemann and L. Brandt, “Valsalva retinopathy,” A & A Case Reports, vol. 5, no. 12, pp. 231–233, 2015.

140. A. Petsas, G. Chapman, and R. Stewart, “Acute angle closure glaucoma—a potential blind spot in critical care,” Journal of the Intensive Care Society, vol. 18, no. 3, pp. 244–246, 2017.

141. M. S. Singer and S. Salim, “Bilateral acute angle-closure glaucoma as a complication of facedown spine surgery,” <e Spine Journal, vol. 10, no. 9, pp. e7–e9, 2010.

142. Z. Butty, J. Gopwani, S. Mehta, and E. Margolin, “Horner’s syndrome in patients admitted to the intensive care unit that have undergone central venous catheterization: a prospective study,” Eye, vol. 30, no. 1, pp. 31–33, 2016.

143. H. Li, L. Liu, D. Zhang et al., “SARS-CoV-2 and viral sepsis: observations and hypotheses,” <e Lancet, vol. 395, no. 10235, pp. 1517–1520, 2020.

144. D. Dawson, “Development of a new eye care guideline for critically ill patients,” Intensive and Critical Care Nursing, vol. 21, no. 2, pp. 119–122, 2005.

145. J. B. Rosenberg and L. A. Eisen, “Eye care in the intensive care unit: narrative review and meta-analysis,” Critical Care Medicine, vol. 36, no. 12, pp. 3151–3155, 2008.

146. COVID-19 Treatment Guidelines Panel, Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines, National Institutes of Health, Bethesda, MD, USA, 2020, https:// www.covid19treatmentguidelines.nih.gov/.

147. EUA Hydroxychloroquine Sulfate Health Care Provider Fact Sheet, https://www.fda.gov/media/136537/download.

148. EUA Chloroquine Phosphate Health Care Provider Fact Sheet, https://www.fda.gov/media/136535/download.

149. J. Gao, Z. Tian, and X. Yang, “Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies,” BioScience Trends, vol. 14, no. 1, pp. 72-73, 2020.

150. Z. Chen, J. Hu, Z. Zhang et al., “Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial,” 2020.

151. P. Gautret, J.-C. Lagier, P. Parola et al., “Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial,” International Journal of Antimicrobial Agents, vol. 56, no. 1, Article ID 105949, 2020.

152. T. J. Stokkermans and G. Trichonas, Chloroquine and Hydroxychloroquine Toxicity, StatPearls Publishing, Treasure Island, FL, USA, 2020, https://www.ncbi.nlm.nih.gov/books/NBK537086/.

153. M. F. Marmor, U. Kellner, T. Y. Y. Lai, R. B. Melles, and W. F. Mieler, “Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision),” Ophthalmology, vol. 123, no. 6, pp. 1386–1394, 2016.

154. E. V. Navajas, H. Krema, D. S. Hammoudi et al., “Retinal toxicity of high-dose hydroxychloroquine in patients with chronic graft-versus-host disease,” Canadian Journal of Ophthalmology, vol. 50, no. 6, pp. 442–450, 2015.

155. L.-S. B. Leung, J. W. Neal, H. A. Wakelee, L. V. Sequist, and M. F. Marmor, “Rapid onset of retinal toxicity from high-dose hydroxychloroquine given for cancer therapy,” American Journal of Ophthalmology, vol. 160, no. 4, pp. 799–805, 2015.

156. M. F. Marmor, “COVID-19 and chloroquine/hydroxychloroquine: is there ophthalmological concern?” American Journal of Ophthalmology, vol. 213, pp. A3–A4, 2020.

157. R. H. Roe, J. M. Jumper, V. Gualino et al., “Retinal pigment epitheliopathy, macular telangiectasis, and intraretinal crystal deposits in HIV-positive patients receiving ritonavir,” Retina, vol. 31, no. 3, pp. 559–565, 2011.

158. Lopinavir/ritonavir: a rapid review of effectiveness in COVID-19,)e Center for Evidence-Based Medicine, https://www.cebm.net/covid-19/lopinavir-ritonavir-a-rapid review-of-the-evidence-for-effectiveness-in-treating-covid/.

159. https://www.aifa.gov.it/documents/20142/0/lopinavir_ritonavir_ 02.04.2020.pdf/64b8cf03-acf1-e9fa-80fa-c6d3ecba5f7d.

160. J. A. Schulman, C. Liang, L. M. Kooragayala, and J. King, “Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin,” Ophthalmology, vol. 110, no. 2, pp. 437–442, 2003.

161. S. Kadayifcilar, S. Boyacioglu, H. Kart, M. Gursoy, and P. Aydin, “Ocular complications with high-dose interferon alpha in chronic active hepatitis,” Eye, vol. 13, no. 2, pp. 241–246, 1999.

162. A. Tada, N. Hashida, T. Tanaka, and K. Nishida, “Anti-interleukin-6 receptor antibody therapy-induced retinopathy in a patient with rheumatoid arthritis,” Case Rep Rheumatol, vol. 2012, Article ID 270315, 4 pages, 2012.