

Ocular and Systemic Complications of COVID-19: Impact on Patients and Healthcare

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Abstract: There is increasing information available about the effects of the SARS-CoV-2 virus on the systemic and ocular health of patients, as well as the effects of delayed health care. This mini-review summarizes the potential complications and treatments of COVID-19. Systemic findings include respiratory illness, risk of thromboembolic events, and neurologic findings. Some patients may develop persistent symptoms even after the infection resolves. Effective treatment options include glucocorticoids, antivirals, interleukin-6 antagonists, monoclonal antibodies, Janus kinase inhibitors and vaccines. Potential ocular findings of COVID-19 include conjunctivitis, cranial nerve palsies, and microvascular changes in the retina; most symptoms resolved over time. During the lockdown periods, teleophthalmology was utilized to triage non-urgent issues; patients who did present to emergency departments tended to have more severe disease with worse visual prognoses. While transient delays in outpatient ophthalmic care may be tolerated in some patients, others experienced significant vision loss with interruptions in treatments. Resumption of ophthalmic care as soon as possible may help mitigate the effects of delayed care due to the pandemic.

Keywords: COVID-19, SARS-CoV-2, quarantine, steroids, interleukin 6, tocilizumab, monoclonal antibodies, casirivimab, imdevimab, antiviral, remdesivir, teleophthalmology; vaccine; trauma

Introduction

What began as an infection in China in 2019 continues as a global pandemic into 2022. COVID-19 is characterized by fever and severe respiratory illness or pneumonia, but it can also affect the ophthalmic, neurological, cardiovascular, gastroenterological, and nephrological systems.^{1,2} As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus continues to mutate, the far-reaching effects of COVID-19 will likely persist. According to the World Health Organization, over 276 million people worldwide have had confirmed COVID-19 infection as of December 2021, and over 5 million people having died from the disease and its complications.³ Public health measures to curtail the pandemic include social distancing, wearing masks, and vaccinating the population.⁴

This mini-review seeks to summarize the current information on the complications of the COVID-19 pandemic on the systemic and ocular health of patients, review current treatment regimens shown to be efficacious in large meta-analyses and systemic reviews, evaluate the effects of delays in healthcare, review the efficacy and potential side effects of vaccines, and review the impact of the pandemic on ophthalmic practices, education, and research.

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Systemic Findings

COVID-19 Transmission and Infection

SARS-CoV-2 virus binds to the angiotensin converting enzyme (ACE2) receptors, which are present in lung alveolar cells, cardiac myocytes, vascular endothelium, and the retina.⁵ In patients whose immune responses are overloaded and/or those with high viral loads, apoptosis of pneumocytes and endothelial cells activate platelets and coagulation factors, leading to increased inflammation and further damage to the pneumocytes, which can lead to increased oxygen demand, cytokine storm, acute respiratory distress syndrome, activation of the coagulation cascade, and thromboembolic disease.⁶ Fortunately, the usage of ACE inhibitors and angiotensin receptor blockers has not been associated with an increased risk of severe COVID-19 infection.⁷

The virus is primarily transmitted via respiratory droplets,⁸ but rare cases of vertical transmission from pregnant mothers to their children have also been reported.⁹ A systemic review found that 6.3% of babies born to mothers with COVID-19 tested positive for the infection at birth.¹⁰

Mortality and Morbidity

Approximately 20% of infected patients required hospitalization and 6% required critical care.¹¹ The risk of fatality was up to 14% in those older than 75 years of age.⁶ In Sao Paulo, Brazil, there was an estimated 25% excess death in 2020, of which 94% was attributed to SARS-CoV-2.¹² COVID-19 was the third leading cause of death in the United States in 2020, with an age-related death rate of 0.83%.⁸ Mortality rates were similar in southern India, but overall estimates of infection-fatality rates may have been limited by underreporting of deaths, especially in migrant populations that may have had worse baseline health.^{12,13}

More than half of patients with COVID-19 have underlying comorbidities, including obesity, diabetes, hypertension, and cardiopulmonary diseases that may affect the severity and morbidity of the infection, the post-infection sequelae, and the risk of vaccine breakthrough.¹⁴ Diabetes is associated with chronic inflammation and endothelial dysfunction, and obesity is associated with upregulation of the interleukin (IL)-6 receptors and low-grade metaflammation.¹⁴ Endothelial dysfunction and hypoxia can lead to thrombin generation and fibrinolysis.¹⁵ Recently, there have been reports of increasing rates of opportunistic fungal infections like pulmonary

aspergillosis and rhino-orbital-cerebral mucormycoses in COVID-19 patients in India (15–27%), which may be due to underlying uncontrolled diabetes, impaired immune systems, corticosteroid use for the treatment of COVID-19, and/or prolonged stays in intensive care units (ICUs).^{16,17} Some studies have also found an increased risk of infection and mortality from COVID-19 in patients with age-related macular degeneration (ARMD), which was hypothesized to be due to complement and coagulation cascade dysfunction, elderly patients' exposure as they obtained medical care, and other health comorbidities; however, the association between macular degeneration and morbidity may have been present even before the pandemic.^{18,19}

Treatment

Multiple potential treatment regimens have been investigated for the prevention and treatment of COVID-19, including monoclonal antibodies, glucocorticoids, and antivirals. The effectiveness may be partly dependent on the stage of the disease and the ability to decrease the inflammatory response.

Patients with non-severe COVID-19 infections who are not at high risk for severe disease are primarily treated with supportive care. In those at risk for progression, clinical trials have found that monoclonal antibodies including ritonavir, casirivimab, imdevimab, bamlanivimab, etesevimab, CT-P59, and sotrovimab were associated with decreased rates of hospitalization compared to placebos; however, only casirivimab-imdevimab was found in a meta-analysis to have moderate certainty evidence for reducing hospitalizations.²⁰ The combination of nirmatrelvir (SARS-CoV-2 main protease inhibitor) and ritonavir (HIV-1 protease inhibitor and CYP3A inhibitor) has gained emergency use approval by the Federal Drug Administration (Paxlovid, PF-07321332, Pfizer, New York, USA) for use in non-hospitalized patients with COVID-19 at high risk for progressing to severe illness to decrease the risk of hospitalization and death; in the phase 2/3 randomized double blind study, there was an 89% reduction in hospitalization and deaths compared to placebo.²¹

In patients with severe or critical COVID-19, meta-analyses have found that glucocorticoids likely reduced the risk of death and mechanical ventilation and duration of hospitalization in admitted patients requiring oxygen support.²² There was moderate certainty that the antiviral remdesivir reduced the length of symptoms and duration of mechanical ventilation.²² IL-6 antagonists like tocilizumab were also associated with a lower risk of progression

to mechanical ventilation or death, especially in those who were receiving corticosteroids.²³ Janus kinase (JAK) inhibitors baricitinib and ruxolitinib were associated with lower rates of invasive mechanical ventilation and mortality compared to the standard of care.²⁴

Some therapies were unfortunately not found to be effective in large clinical trials. A systemic review and meta-analysis of 12 clinical trials involving 8569 patients found that hydroxychloroquine and chloroquine had little to no effect on decreasing the risk of death or progression to mechanical ventilation in patients with COVID-19; indeed, these medications were associated with a three-fold higher risk of any adverse events, though fortunately not serious adverse events like QT-interval prolongation, cardiac arrhythmia, or retinopathy.²⁵ A meta-analysis found that it was highly uncertain that prophylactic ivermectin with or without iota-carrageenan reduced the risk of infection given the serious risk of bias in the clinical studies.²⁶ In meta-analyses, antiviral antibodies and blood products like convalescent plasma and intravenous immunoglobulins were not associated with a reduction in mortality in those with severe disease.^{20,27,28} The benefits of other treatments like favipiravir, azithromycin, lopinavir-ritonavir, umifenovir are under investigation.²²

Thromboembolism and Prophylaxis

Severe COVID-19 may be associated with acute coronary syndrome, and 1.3% may develop acute cerebrovascular disease.^{6,15} Approximately 14% develop venous thromboembolisms (46% of those in the ICU compared to 23% in non-ICU patients).⁶ For the prevention of thromboembolic complications in non-critically ill patients hospitalized with COVID-19, a randomized control trial of 2219 patients found that therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge and decreased the need for ICU-level organ support when compared to usual-care thromboprophylaxis, such as low or intermediate-dose thromboprophylaxis with enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin; in contrast, there was no difference in the risk of thromboembolism based on the type of thromboprophylaxis for critically ill patients in the ICU.^{29,30}

Long-Term Systemic Effects of COVID

While most patients, especially those with milder symptoms, recovered from COVID-19, some may develop persistent or new symptoms four or more weeks after their infection. A large meta-analysis found that 80% of patients

developed one or more long-term symptoms, most commonly fatigue (58%), headache (44%), attention disorder (27%), dyspnea (24%), and anosmia (21%).³¹ Other symptoms included myalgias, hair loss (25%), digestive disorders (12%), sleep issues, fever, dizziness, rash, mood changes, autoimmune conditions, and post-traumatic stress disorder.^{8,31} A meta-analysis found that 39% of recovered patients had altered pulmonary diffusion capacity,¹¹ and 34% had abnormal chest X-rays or computerized tomography (CT) scans.³¹ Those who had severe disease with high inflammatory indicators were more likely to develop pulmonary fibrosis.¹¹ Former COVID-19 patients who were referred for rehabilitation services had poorer physical function than cancer patients;³² therefore, patients who recover from COVID-19 may need long-term follow-up care.

Ocular Manifestations in Adults and Children

Ophthalmic manifestations of SARS-CoV-2 are not common, affecting approximately 6–12% of COVID-19 patients.^{2,33–35} The ocular symptoms can precede systemic symptoms by 3 hours to 5 days in 13% of patients.² Frequent hand-eye contact and more severe systemic illness may be more likely to be associated with ocular findings.³⁶

Anterior Segment Findings

In systemic reviews, the most common signs and symptoms were conjunctivitis (86%), ocular pain (31–34%), dry eyes (33%), discharge (19%), and redness (11%).^{2,33,37} The presence of COVID-19 in the tear film and anterior surface varied from 0% to 13%,² and approximately 4–24% had viral ribonucleic acid (RNA) detectable in conjunctival swabs.^{2,33,37} Eye protection and frequent hand hygiene may be considered to minimize the risks of transmission.³⁸ For those who develop conjunctivitis, some authors have proposed using topical eye drops with broad-spectrum antiviral activity, like povidone iodine and sodium hypochlorite.³⁹ Fortunately, most ocular symptoms were mild and resolved, with or without treatment.^{2,36}

In the ICU, ocular complications like exposure keratopathy and corneal abrasions may occur in patients who are on ventilators or respiratory masks; efforts to ensure adequate lubrication and closure of the eyelids may help prevent these ocular surface issues. In the outpatient setting, quarantine dry eye syndrome may occur as people

socially distance indoors and use technology more frequently; artificial tears and rest may help alleviate these symptoms.⁴⁰

Posterior Segment Findings

Histopathologic specimens from the retinas of deceased patients with COVID-19 have found presumed SARS-CoV-2 viral particles in the ganglion cell layer, inner plexiform, inner nuclear, outer plexiform, outer nuclear layer, retinal pigment epithelium, and choroid.⁴¹ A literature review found that COVID-19 was associated with an 8.86-fold risk of retinal vascular microvasculopathy, including retinal hemorrhages, cotton wool spots, infarcts at the internal plexus, and thinner ganglion cell layer and inner nuclear layer.⁴² More severe systemic disease was associated with lower vascular density on OCT angiography (OCTA).⁴³ Other potential posterior segment findings included possible hyperreflective lesions in the inner and outer retina and vitreous,^{1,2,44} uveitis-like multifocal evanescent white dot syndrome,⁴⁵ acute macular neuroretinopathy,⁴⁶ central retinal vein occlusion,⁴⁷ intraretinal hemorrhages,⁴⁸ and inflammatory multifocal chorioretinitis with Adie's pupil.⁴⁹ These changes may reflect the underlying systemic hypercoagulable, ischemic, inflammatory, and/or hypertensive state of the patient or direct invasion of the virus.^{1,2,44,46–48,50}

Neuro-Ophthalmic Findings

Up to 21% of patients with COVID-19 may have systemic neurologic signs, and 0.4% have cranial nerve impairment.¹⁵ Potential neuro-ophthalmic associations with COVID-19 include optic neuritis and myelitis, ischemic optic neuropathy, Guillain-Barre syndrome, Miller-Fisher syndrome, and cranial neuropathies like CNIII or CNVI palsies.⁵¹ These neurologic conditions may be related to hypoxia, ischemia, and/or inflammation.⁵² An immunologic response to peripheral nerve antigens may result in demyelination and nerve injury.¹⁵ A systemic review found a higher prevalence of Guillain-Barre syndrome in patients with COVID-19 than in the general population (0.15% vs 0.02%, respectively), which was believed to be due to an immune-mediated response rather than a direct viral infection.⁵³

Ocular Findings in Children

Children who are hospitalized with COVID-19 may be more likely than adults to have ocular manifestations (up to 23%), including conjunctival discharge (55%) and

conjunctival congestion (10%);⁵⁴ posterior segment findings include retinal hemorrhages (9%), cotton wool spots (7%), dilated veins (28%), and tortuous vessels (13%).⁵⁵ In Bergamo, Italy, there was a 30-fold increase in the number of children with severe Kawasaki-like disease compared to before the pandemic; the majority of these children had IgG and/or IgM to SARS-CoV-2, were older, had a higher rate of cardiac involvement, and had more severe disease.⁵⁶ A case series of 15 COVID-19+ newborns in Mexico found high rates of chemosis and hemorrhagic conjunctivitis (73%), ciliary injection (53%), and hyaline secretions (100%).⁵⁵ In contrast, a study of 165 newborns exposed to SARS-CoV-2 in Brazil found that only 6 patients had polymerase chain reaction (PCR)-confirmed COVID-19, and none had vascular abnormalities that were attributed to SARS-CoV-2.⁹ Some ocular findings in children with COVID-19 may be related to their underlying systemic health.

Ophthalmic Clinical Services and Effects of Delayed Care

Even before the pandemic, there were barriers to health-care, with delayed care being associated with worse visual acuity outcomes. Patients who were older than 80 years old, non-white, and had lower incomes were more likely to be lost to follow-up.⁵⁷ Delays of 3 months or more in anti-vascular endothelial growth factor (VEGF) treatment were associated with persistently decreased visual acuities in patients with neovascular ARMD, even with resumption of treatment and return to baseline retinal thicknesses.⁵⁸

During the initial phases of the pandemic, many patients delayed seeking medical care, even for life-threatening conditions like myocardial infarctions and cerebrovascular accidents.^{59,60} Hospitals and outpatient clinics limited services to concentrate on combating COVID-19 and decreasing viral transmission. Adaptations to ophthalmic clinical and emergency services included referral for virtual consultations when possible, minimizing wait times, isolating care teams, and using triaging algorithms.^{1,61,62} The American Academy of Ophthalmology, Centers for Disease Control, World Health Organization, and American Society of Retina Surgeons released clinical guidelines.¹ At the National Center for Global Health and Medicine in Japan, flow-charts were created for hospitalists to determine whether to consult ophthalmology for hospitalized patients with COVID-19, based on the consciousness levels and ocular

signs and symptoms.⁶³ At the University of Michigan, a risk stratification tool was used to determine patients' glaucoma severity and risk of glaucoma progression using the Sight Outcomes Research Collaborative (SOURCE) ophthalmology electronic health data repository data to determine when the patients should be evaluated in clinic.⁶² The Royal College of Ophthalmologists released guidelines to prioritize urgent and emergent ophthalmic care, including maintaining anti-VEGF therapy every 8 weeks for patients with neovascular age-related macular degeneration and consider deferring injections for most patients with macular edema from diabetes mellitus or vein occlusions.⁶⁴

Ocular Emergencies and Effects of Delayed Care

Ophthalmic emergency room visits and outpatient office visits decreased by approximately 25–81% in March–April 2020 compared to the previous year.^{61,65–67} In Italy, there was a 59% reduction in patient visits to the ophthalmic emergency department, and in Spain, there was a 65% decrease during the lockdown.⁶⁸

Patients who did present to the emergency departments unfortunately had more delayed presentations, more trauma, more severe injuries like ruptured globes, lacerations, and orbital fractures, more at-home injuries, and were less likely to have health insurance.^{61,65,68} The greater proportion of severe injuries may have been associated with increased intimate partner violence and home improvement projects as people quarantined.⁶⁷

For the anterior segment, patients who presented during the pandemic in India were more likely to have more severe corneal ulcers (22% vs 60%, $P<0.001$), more frank perforations (4% vs 18%, $P=0.002$), poorer treatment successes (51% vs 71%, $P=0.007$), and a higher proportion of anatomical failure (24% vs 2%, $P<0.001$) compared to patients who presented in the prior year.⁶⁹ In Ireland, there was a 37% reduction in the number of infectious keratitis during the pandemic compared to the prior 2 years, but the patients who did present had less improvement in their visual recovery compared to prior years (0.45logMAR vs 0.26–0.67logMAR, $P=0.04$).⁷⁰ There was also an increased incidence of alcohol-based hand sanitizer injury to the corneal surface in children.⁷¹ While there was a 81% reduction in glaucoma outpatient visits in India, there was a 62% increase in the proportion of glaucoma emergencies.⁷²

Some studies found a 55–80% decrease in retinal detachment repairs during lockdown periods in 2020,^{73,74} but others found a 39% increase for urgent surgeries, such as retinal tears, retinal detachments, and trauma.⁷⁵ One study of 82 patients with rhegmatogenous retinal detachments at Wills Eye Hospital found that the patients in 2020 tended to present later than in prior years (20% within a day vs 37%, respectively, $P=0.005$), were less likely to have their maculas still attached (24% vs 50%, $P=0.001$), had worse presenting visual acuities (1.00logMAR vs 0.48logMAR, $P=0.008$), and were more likely to have grade C proliferative vitreoretinopathy (13% PVR vs 5%, $P=0.03$).⁶⁰ Similarly, Awad et al found that patients who presented with retinal detachments after lockdown measures were implemented in the United Kingdom were more likely to have PVR (10% vs 24%, $P=0.047$).⁷⁶ The initially decreased rates of retinal detachment surgeries may therefore reflect delays in care.

Several studies have found worse outcomes in patients whose anti-VEGF treatments were delayed. There was an approximately 10–75% decrease in intravitreal injections in 2020 compared to 2019, with at least 42% directly attributed to the pandemic.⁷⁷ In the United Kingdom, Stone et al found that in 981 eyes of 858 patients, patients with wet ARMD lost a mean of 5.18 ETDRS letters, vein occlusion patients 5.15 letters, and diabetics 2.37 letters; even after resuming anti-VEGF treatments, less patients with wet ARMD and vein occlusions returned to baseline than diabetics (75–77% vs 90%, respectively).⁶⁴ Fortunately, 27% of patients with wet ARMD did not develop recurrent subretinal fluid despite an average 13 weeks delay.⁶⁴ Rush et al similarly found that their patients in Texas with an average of 12 weeks delay in treatment had worse visual acuities that did not recover back to baseline, despite resuming anti-VEGF treatments for at least 6 months.⁷⁸ In a study of 109 patients in Turkey, 58% of whom had delayed care (on average 98 days), patients had worse visual acuity and more activity on follow-up OCTs.⁷⁹ In Jordan, a mean delay of 61 days was associated with worse visual acuities.⁸⁰ In Turkey, 7 of 106 patients (7%) developed submacular hemorrhages during the restriction period.⁸¹ While the central macular thickness improved to pre-restriction levels, the vision at the last follow-up did not significantly improve; linear logistic regression found that the time interval between the injections was correlated with the visual acuity.⁸¹ In Cleveland, Song et al found that patients with an average of 5 weeks delay also had vision loss, more pronounced in

those with diabetes and/or vein occlusions than neovascular ARMD.⁸² In Italy, patients who were evaluated in retina clinics during or immediately after the quarantine period had worse visual acuities compared to prior visits; in multiple regression analyses, the time period between visits showed the greatest association with changes in visual acuity.⁸³ In Miami, patients whose intravitreal injections were delayed by an average of 3 weeks were more likely to have at least a 3 letter visual loss.⁷⁷ Indeed, a study in Minnesota found that even a 2-week delay was associated with worse central subfield thicknesses and worse visual acuities, with a difference of approximately 5 letters.⁸⁴ A theoretical model found that patients could lose vision as quickly as 1 letter per month of deferred treatment, outpacing the potential 0.17–0.56 letter visual gain per month that patients could gain with anti-VEGF therapy for ARMD.⁸⁵ While some patients may therefore be able to tolerate a short delay in treatment, it is important to try to restart treatment as quickly as feasible for patients once lockdown restrictions have lifted in order to improve the visual potential. Importantly, masks did not appear to increase the risk of ocular infections after intravitreal injections. A large multicenter retrospective study of over 500,000 intravitreal injections found that the rates of presumed endophthalmitis were similar when there was universal masking of the physician, ancillary staff, and patients (with or without tape across the top of the mask) compared to no face masks by the physician or patient; however, the rates of culture-positive endophthalmitis were lower in the universal masking group.⁸⁶

Uveitis and Immunosuppressive Therapy

The initiation or continuation of immunosuppressive therapy for non-infectious uveitis has been debated. Approximately 6–15% of patients with non-infectious uveitis may contract COVID-19.⁸⁷ In a survey of 150 uveitis patients, 20% of respondents had stopped their medications during the pandemic, and 34% reporting worsening of their ocular condition.⁸⁸ In a national claims-based database search of 29,869 patients with non-infectious uveitis, uveitis patients had higher rates of COVID-19 infections (5.7% VS 4.2%, $P<0.001$), hospitalizations (1.2% vs 0.6%, $P<0.001$), and death (0.3% vs 0.1%, $P<0.001$), but this association was attributed to the patients' comorbidities and medication use rather than the uveitis itself. After adjusting for demographics and comorbidities like autoimmune disease, cardiovascular disease, diabetes, and chronic kidney disease,

systemic steroids were associated with an increased risk of COVID-19 infection (hazards ratio for 1.19, 95% CI, 1.18–1.20, $P<0.001$), hospitalization, and death.⁸⁷ While tumor necrosis-alpha (TNF- α) inhibitors like infliximab were also associated with an increased risk of infection, there have been conflicting reports in the literature as to whether they might have a protective effect by mitigating the inflammatory response.^{87,89}

The consensus opinion from a survey of uveitis specialists from the International Uveitis Study Group, the International Ocular Inflammation Society, the Uveitis Society of India, and the Foster Ocular Immunology Society was to try local therapy rather than systemic steroids when possible and to avoid starting systemic steroids or immunosuppressive therapy (IMT) in those with suspected or confirmed COVID-19.⁹⁰ Patients already on immunomodulatory therapy, biologics, or non-steroidal anti-inflammatory drugs without signs of COVID-19 may continue their medications but should practice hand hygiene, social distancing, and wear masks.⁹⁰ In a study of 59 patients on biologic agents like infliximab, adalimumab, and rituximab, 15% tested positive for COVID-19 but none exhibited symptoms; the biologics were held temporarily until the viruses cleared, and 2 patients (22%) developed flares that were successfully treated by resuming their biologic agents. Immunocompromised patients may therefore be asymptomatic carriers, and their IMTs may be held temporarily if they contract COVID-19.⁸⁹

Teleophthalmology

Teleophthalmology has been used for years to remotely screen for diabetic retinopathy, retinopathy of prematurity (ROP), macular degeneration, glaucoma, and anterior segment pathologies. The pandemic highlighted the importance of developing the infrastructure for telehealth options.

Approximately 22–73% of ophthalmic emergency department visits before the pandemic were estimated to be for non-urgent issues. At Moorfields Eye Hospital, approximately 57% of cases presenting to the emergency departments were referred for virtual consultations, with 21% being referred to the emergency department or a subspecialty service.⁶¹ In Pittsburgh, only 8% of those with telehealth visits required urgent, in-person evaluations; the majority of telehealth visits were for routine postoperative visits, followed by conjunctivitis.⁹¹

Ways to expand telehealth include developing secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant programs, increasing access to the internet and technological devices, improving patient education device usage, quickly and accurately reviewing screenings, and ensuring appropriate and timely in-person examinations and treatments.⁹² Home OCTs and smart phone apps measuring vision, contrast sensitivity, ocular alignment, subretinal fluid, and metamorphopsia may be used for at-home monitoring and earlier detection of disease.^{93–95} Fundus photographs, slit lamp photography, laser flare photometry, fluorescein angiography, OCTs, and OCTAs can be obtained with minimally trained staff, be remotely operated, or be self-operated.^{93,96}

Artificial intelligence (AI) or a remote screener can help evaluate the images. Current AI screenings have sensitivities ranging from 75–95% for diabetic retinopathy, 87–100% for macular degeneration, 95% for ROP, 67–93% for glaucoma, and 70% for cataracts.^{92,93} Those with unreadable images (approximately 5–20%) or abnormalities detected remotely can then be referred in for in-person evaluations.⁹³ In areas where there may be a dearth of subspecialties like uveitis, hybrid visits may be considered where a general ophthalmologist can perform the exam and imaging, then consult a uveitis specialist electronically.⁹⁶ As the pandemic continues, hybrid visits where patients get imaging in person and counseling virtually may help ease patient concerns while still maintaining ophthalmic care.

Vaccine Effectivity and Potential Side Effects

Vaccine Effectiveness

Over 7 billion doses of COVID-19 vaccines have already been administered.³ In a multicenter study of 64,400 hospital or emergency department (ED) and urgent care (UC) visits between January 1–June 22, 2021, the messenger RNA (mRNA)-based BNT162b2 (Comirnaty, Pfizer–BioNTech, United States) and mRNA-1273 vaccine (Moderna, United States) vaccines were found to be 89% effective against laboratory-confirmed SARS-CoV-2 infections leading to hospitalizations, 90% effective against ICU admissions, and 91% against ED/UC visits.⁹⁷ Comparing the mRNA-based vaccines in July 2021, when the delta variant was more prevalent in Minnesota, the mRNA-1273 vaccine (Moderna) was estimated to be slightly more effective than the BNT162b2 (Pfizer)

vaccine in preventing infections (86% vs 76% $P<0.001$), hospitalizations (92% vs 85%, $P<0.001$), and ICU admissions (93% vs 87%, $P=0.0005$), but both were highly effective in preventing deaths (0% in both groups).⁹⁸ The BNT162b2 vaccine was found to be 91–95% effective in children over 5 years old.⁹⁹

Most of the vaccines had lower efficacies when administered as a single dose or against the COVID-19 variants. The single-dose adenovirus-based Ad26.COV2 (Johnson & Johnson/Janssen, Netherlands) was 54% effective in preventing hospitalization and 68% effective against ED/UC visits.⁹⁷ One dose of the BNT162b2 (Pfizer) or the adenovirus vector-based ChAdOx1 nCoV-19 (AstraZeneca, United Kingdom) vaccines was 49% effective against the alpha variant and 31% against the delta variant.¹⁰⁰ After two doses, however, the BNT162b2 vaccine was 94% effective against the alpha and 88% against the delta while the ChAdOx1 nCoV-19 vaccine (AstraZeneca) was 75% effective against the alpha and 67% against the delta variant.¹⁰⁰ The spike protein-based NVX-CoV2373 vaccine (Novavax, United States) was 51% effective against the beta variant.¹⁰⁰ The two-dose inactivated whole-virion SARS-CoV-2 vaccine CoronaVac (SinoVac Life Sciences, China) had an 84% efficacy in preventing symptomatic COVID-19 and 100% against hospitalizations in Phase 3 clinical trials,¹⁰¹ and the two-dose heterologous recombinant adenovirus-based Gam-COVID-Vac (Sputnik V, Gamaleya National Centre for Epidemiology and Microbiology, Russia) had a reported 92% efficacy in phase 3 clinical trials.¹⁰²

Potential Systemic and Ocular Side Effects

Common vaccine side effects include myalgia and pain at the injection site.^{8,98} Very rare but serious adverse effects include anaphylaxis, myocarditis, pericarditis, and “vaccine-induced thrombotic thrombocytopenia” (VITT). Patients with VITT have anti-platelet factor 4 (PF4) antibodies, which activate platelet aggregation, leading to systemic thromboses. In contrast to other hypercoagulable disorders, thrombosis in VITT can occur in atypical sites such as the splanchnic, adrenal, cerebral, and ophthalmic veins.¹⁰³ The current criteria for diagnosis of VITT include COVID vaccination 4 to 42 days prior to symptom onset, any venous or arterial thrombosis, thrombocytopenia, positive anti-PF4 antibodies, and D-dimer levels greater than 4 times the upper limit of normal.¹⁰⁴

The prothrombotic state induced by COVID vaccination may affect ocular and neurologic perfusion as well. Bayas

et al reported a case of bilateral superior ophthalmic vein thrombosis, ischemic stroke, and thrombocytopenia after ChAdOx1 nCoV-19 (AstraZeneca) vaccination, and other unilateral case reports have also been published.^{105–107}

Acute macular neuroretinopathy has been reported following the ChAdOx1 nCoV-19 vaccination,^{108,109} and CNVI palsy has been reported 2 days after BNT162b2 mRNA vaccine (Pfizer), which resolved after 3 months.¹¹⁰ Fan et al reported a case of branched retinal artery occlusion with features of paracentral acute middle maculopathy in a pediatric patient after BNT162b2 vaccination (personal communication). As of May 2021, the Royal College of Ophthalmology has issued a safety alert soliciting reports of vaccine-related retinal vascular occlusions due to an increased incidence of central venous sinus thrombosis and other anecdotal reports of RVO after vaccination.¹¹¹ Given the rarity of such cases, further study is required before a causative link can be established.

Although rare, uveitis and graft rejections have previously been associated with vaccines against influenza, hepatitis B, tetanus, toxoid, and yellow fever. The proposed mechanisms of action include molecular mimicry, delayed hypersensitivity, or other immune responses.^{112–114} In a multi-center study of 23 eyes of 21 patients that developed an acute episode of uveitis after the BNT162b2 vaccine (Pfizer), 8 patients (38%) had a known history of uveitis, the median time to onset was approximately 8 days, and most patients (86%) had mild to moderate anterior uveitis that significantly improved with topical therapy or intravitreal steroids.¹¹⁵ The authors suggested that the vaccine may have triggered a type I interferon secretion, leading to an autoimmune reaction.¹¹⁵ There have also been case reports of acute corneal graft rejections occurring after vaccination, which may be due to allorecognition by the direct pathway or incitation of the antibody response; fortunately, most rejection episodes resolved with topical and/or systemic steroids.^{105,112,116–120} Physicians may therefore consider reviewing the potential signs of graft rejection with corneal transplant recipients in order to improve earlier detection and treatment.

Systemically, the vaccines have fortunately not been associated with a significantly high risk of transplant rejection. A large study of 741 solid organ transplant recipients (STOR) who received either the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccines found that only 1 person developed a graft rejection after the second dose.¹²¹ In patients with graft-versus-host disease, there was no evidence that the vaccines triggered or worsened the disease.¹²² SOTR and hematopoietic stem cell patients, who are typically on

immunosuppressants and are at higher risk for developing infections, are encouraged to receive the vaccines and boosters, even if they mount less of an antibody response.^{122,123}

Impact on Ophthalmic Business, Research, and Education

While the primary focus of physicians during the pandemic has been on providing quality medical care in a safe environment, medical practices have also had to deal with the financial burdens of the pandemic. Clinical and surgical volumes were decreased as patients socially distanced, personal protective equipment was in short supply, and medical resources were diverted to caring for hospitalized patients.

In March 2020, the United States Congress passed the Coronavirus Aid, Relief and Economic Security (CARES) Act, which provided for accelerated Medicare payments for providers, tax relief for medical practices, no cost testing for COVID-19, and payroll tax credits. The Small Business Administration's Paycheck Protection Program (PPP) offered zero-fee loans as part of the efforts to help small business severely impacted by the pandemic with payroll support. Approximately 88% of physicians responded to a survey asking if they had applied for federal financial aid, and 96% had successfully obtained funding.¹²⁴ Physicians are reporting a rebound in clinical volume, but there may still be a lag.¹²⁴ In terms of medicolegal liabilities, the CARES Act provided some legal protection to health-care workers when they were volunteering, but similar legal protections were not universal and did not apply to employed health-care workers.¹²⁵ Additional liability protection should be considered as physicians manage the complications of delayed care and continued clinical and surgical restrictions. While the Centers for Medicare and Medicaid Services (CMS) paid for telemedicine visits during the pandemic, the additional growth of teleophthalmology may be partly dependent on how those telehealth visits will be reimbursed in the future.

As hospital systems try to recoup loss revenue, financial support from academic institutions for research may be shifted elsewhere. Some research staff were furloughed during the pandemic, some experimental cell lines and animal models that took months or years to establish were adversely affected, and grants were delayed. Basic science research projects were halted, and clinical data was significantly affected by the pandemic restrictions and delays in care. Scientists have advocated for additional

government research support as they try to recover and restart their research.¹²⁶

In medical education, universities and hospitals cancelled clinical electives and away rotations, leaving future physicians with decreased clinical exposure and confidence about their preparedness, which can lead to missed diagnoses or over-referrals.¹²⁷ Students interested in ophthalmology, especially those without an associated ophthalmology department in their medical school, may have had greater difficulty obtaining clinical exposure, research, mentorship, and letters of recommendation when applying for residency.¹²⁷ The advent of teleophthalmology, online computer-based learning, videoconferencing, and virtual simulators have been used to try to increase medical student exposure to ophthalmology.¹²⁷

Discussion

COVID-19 has caused significant complications on the systemic and ocular health of patients and strained the global healthcare system. The SARS-CoV-2 virus is highly infectious, and patients with diabetes, immunosuppression, cardiopulmonary diseases, and metabolic syndromes may be more susceptible. Preventative methods include social distancing, masks, and vaccinations. For those who do contract the virus, systemic treatment options include monoclonal antibodies and antiviral agents in those at risk for severe disease, therapeutic dose heparin in non-critically ill hospitalized patients, JAK inhibitors to decrease the risk of invasive mechanical ventilation and mortality, IL-6 antagonists in patients with severe or critical COVID-19, and steroids in hospitalized patients requiring oxygen support. Most patients recover from the respiratory illness, but some may develop persistent pulmonary disease and fatigue. While the SARS-CoV-2 virus and the vaccines may both be associated with inflammatory or neurologic issues, the benefits of vaccinations far outweigh the rare potential complications.

In the eyes, the SARS-CoV-2 virus has been found in the conjunctiva, tear film, and retina, and it can cause conjunctivitis, microvascular disease, and cranial neuropathies. Fortunately, most ocular issues resolved, with or without treatment.

During the initial wave of the pandemic and quarantine period, there was a significant reduction in the clinical and surgical volumes. Teleophthalmology helped to minimize the risks of in-person evaluations for non-urgent issues. Those who did present to the emergency

departments tended to have more severe disease and worse visual outcomes, and patients who had delayed their routine outpatient ophthalmic care had difficulty returning to their baseline statuses even after restarting treatments. Resumption of ophthalmic treatments as soon as possible may therefore help decrease the risk of vision loss. Continued financial support of ophthalmic businesses and research will help preserve the availability of ophthalmologists and prevent the loss of scientific advancement. Supplemental virtual didactics may help prepare the next generation of physicians and ophthalmologists.

Ongoing research has shed greater insight into how the virus affects the human body, potential treatment options, and the effects of delayed care for ophthalmic diseases. The lessons and insights gained from researchers around the world will hopefully help improve patient care as the pandemic continues.

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