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REVIEW ARTICLE

Covid-19 and its relation to the human eye: transmission, infection, and ocular manifestations

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Abstract

Background The world is suffering from a new strain of the coronavirus family-Covid-19. This virus strain affected different organs in the human body with a wide range of mild symptoms and moderate signs to severe and deadly ones. Multiple organs can be infected, and one of these organs is the eye. The eye is a vital organ that consists of vascular tissues and is connected to the respiratory tract through the tears and the nasolacrimal duct.

Methods Recent papers and research from PubMed, Researchgate, and Google Scholar were cited and thoroughly discussed. These papers were chosen based on their relevancy, reliability, publication year, published journal, and ease of accessibility to the paper itself.

Results The theory concluded that the ocular surface might consider a pathway for the virus attack and infection causation through the tears and the angiotensin-converting enzyme 2 located in the eye. This article thoroughly reviewed the history, the existing aspects of Covid-19, the ocular system features, and the claims about the possible involvement of the eye in the virus transmission along with the eye infection. There was no consensus on the eye's involvement theory.

Conclusion The authors highlighted the extra work and research needed to be conducted to prove or deny these claims to provide a better understanding of the immune response of the eye to Covid-19 infection.

Keywords Covid-19 · Ophthalmology · Ocular manifestations · Covid-symptoms · CoV virus

Key Messages:

- The pandemic virus -Covid-19-its main form of human-to-human transmission occurs through respiratory droplets.
- Another way of CoV transmission through fomite transmission; is by contacting contaminated objects of infected patients.
- The novel hypothesis of the possible ocular infection and feasible transmission of the virus through the eye is probably high.
- Ophthalmologists and the health care system should take the necessary precautions to limit and control the possible transmission of Covid-19 through our ocular tissue.

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Introduction

In 2019, a new virus, commonly known as Coronavirus (CoV) — Covid-19— was first reported in Wuhan, China. From there, it spread globally and became the fifth reported flu pandemic since 1918. After 2 years of the identification of the pandemic, there had been more than 200 million confirmed cases and over 4.6 million death [46]. The virus is

highly spreadable and has infected almost all continents; as a consequence, the WHO declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020 [9, 44, 81]. CoV is a single, positive-strand RNA virus that has a severe effect on the respiratory system in humans. Also, the gastrointestinal and central nervous systems can be affected by it resulting in severe diseases and threats to human lives [86]. The impact of the virus can be extremely severe on special populations like the elderly and immunodeficient patients; it can be lethal [33]. The symptoms of the disease were categorized based on intensity. The most common symptoms are fever (43% when administered and 55.7% after being hospitalized), cough (67.8%), fatigue, and loss of taste or smell [18, 78]. The less common symptoms like sore throat, headache, diarrhea, rash on the skin, and red or irritated eyes. These two categories are not life-threatening, and patients can be recovered without hospitalization. It takes on average from 5 to 6 days for these symptoms to appear, but sometimes, it can take up to 14 days [18]. The last category is the serious symptoms exampled in difficulty breathing or shortness of breath, loss of speech or mobility, and chest pain. Immediate medical attention is needed in this case [8, 90]. The suggested mechanism of the virus's entrance into our cells is defined as receptor-mediated endocytosis, in which CoV uses angiotensin-converting enzyme 2 (ACE2), a cell-surface receptor that is present in the heart, blood vessels, kidneys, and importantly, in the alveolar respiratory tract; the epithelial cells of the lungs that ease the viral infection [25]. It binds to ACE2, using it as a cell entry receptor to conquer respiratory and lung epithelium tissues through the spike (S) protein causing serious damage to the lung and respiratory tract [72]. The main transmission mode of CoV is droplet transmission, in which the respiratory droplets of an infected person are transmitted to a healthy person if he becomes in contact with the infected person's belongings like clothes [18]. Other less-evidenced data suggested that the transmission can be aerosol through the airborne pathway. The tiny droplets < 5–10 μm are respirable and can remain airborne. These are capable of short- and long-range transfer, resulting in transmitting the virus to people [42, 71]. One way of preventing the transmission is keeping a distance of 2 m between people while putting on masks. Another way is the isolation of infected people to prevent any contact with them. CoV was detected in saliva, sputum, urine, and blood in infected patients. A problem arose when the virus detection test was positive for asymptomatic patients; they became a potential source of the infection and spread without displaying any symptoms. So, they are the rate-limiting step of the transmission of the pandemic [18, 65]. In the context of infectivity, the estimated average number of extra infectious cases that one infectious case can cause ranged from 2.2 to 2.7 in the early stages of the epidemic in China [44]. Later on, this number can be controlled due to better control measures, awareness of the people, and the isolation of the infected patients [44]. However, studies have shown that there are barriers to understanding the infection, and this is probably due to several reasons. Firstly, the basic characteristics of the viral infection along with the infection periods are still ambiguous. Secondly, the majority of the infected patients is asymptomatic and shows no symptoms at all but still has the ability to propagate the infection. Finally, the various susceptibility of the people to be infected affect the spreadability of the infection, and this relation is still vague [86].

Coronavirus evolution

Coronavirus was first known in 1965; it appeared to target the respiratory system and caused different symptoms and signs. Different strains started to develop various conditions and illnesses. Coronavirus is deemed to infect both animals and human beings. It was able to affect cats, bats, rats, and camels. It caused several diseases in the multiple animal species affected [36]. This varies from gastroenteritis, hepatitis, and encephalitis in mice; to pneumonitis and sialo dacryoadenitis in rats; and infectious peritonitis in cats. These findings revealed that the virus pathogenesis is various, complex, and dangerous. Some recent studies suggested that bats are the main natural reservoir of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Covid-19 [24, 40, 74]. On the other hand, other investigations disclosed that SARS was transmitted from civet cats to humans, MERS from dromedary camel, and Covid-19 probably from pangolin [24, 74, 76].

For a while, coronavirus was silent till the most powerful attack occurred in 2019. Mainly in Wuhan, China, the first case of CoV was imitated [88]. It spread through the continents like a clap of thunder striking the sky. Till now, approximately 35 million people have been infected, and about 1 million deaths in 235 countries or areas [92]. Covid-19 causes symptoms like those of the flu but with higher severity and can be ameliorated by acute respiratory distress (ARDS), pneumonia, renal failure, and death [9, 78]. The most common symptoms are fever, cough, and dyspnea [11]. CoV is egg-shaped, with a crown-shaped appearance and an average diameter of ~ 64.8, 85.9, and 96.6 for the short, medium, and the long axis of the outer shell, respectively [38]. As mentioned previously, human coronavirus is transmitted mainly through respiratory droplets; also, aerosol, direct contact with contaminated surfaces, and fecal–oral transmissions were identified during previous coronavirus strains, SARS, and MERS [45, 54]. The first reports of patients with cough, lung opacities, and symptoms of progression to severe pneumonia suggested the spreadable capability of CoV via the respiratory route [31, 88]. Additionally, there is new evidence for

the non-symptomatic/pre-symptomatic spread of CoV, like the transmission dynamics of SARS [4]. This result suggests the ability of the virus to colonize and replicate in the throat during early infection [26, 56, 91]. Furthermore, asymptomatic CoV spreadability has been documented throughout the pandemic [9, 47, 65]. These transmission findings of the current Covid-19 pandemic were critical for public health authorities to make the most effective disease control measures like the applied ones as mask-wearing, contact tracing, and physical isolation [26]. The various modes of Covid-19 transmission that have been claimed, including aerosol, surface contamination, and fecal–oral route, are still being studied and investigated [26, 48].

CoV is highly spreadable comparable to SARS and MERS. The incubation period is approximately 5 to 6 days [26]. For the coronavirus family, all shared some common flu-like symptoms including fever (≥ 38.0 °C), cough, sore throat, dyspnea, headache, myalgia or fatigue, and diarrhea [89].

Regarding Covid-19, with the previously mentioned common symptoms, gastrointestinal symptoms are very usual such as diarrhea, nausea, and vomiting [77]. Covid-19 sufferers predominantly exhibit mild symptoms, but those with compromised health diseases have worse clinical outcomes [32]. However, the case fatality rate of Covid-19 has unspectacularly increased as the growing figure of worldwide deaths is [89]. The asymptomatic patients carrying it have worsened the status, as they are able of spreading the virus through regular modes of transmission. The asymptomatic carrier rate is still difficult to calculate, which was a challenging obstacle in controlling the infection [27, 89].

Coronavirus genome

Genomic awareness of the coronavirus family facilitates the perceiving of the origin and pathogenesis (host immune response and viral virulence and transmission mode) of the virus [89]. Therefore, a full understanding of the genomic information is pivotal for beating the coronavirus outbreaks. The different genera of coronaviruses belong to the family Coronaviridae; they are classified into four genera, α-CoV, β-CoV, γ-CoV, and δ-CoV [40, 43, 76]. Coronavirus belongs to the genus β-CoV and is identified as a zoonotic virus that transmits between animals and humans [21, 76]. The microscopic images of covid-19 revealed that it is characterized by an envelope shape with a single positive-strand RNA and spike proteins projecting from the virion surface (Fig. 1) [21]. The genome structure consists of 5′ methylated caps and 3′ polyadenylated tails [85]. The first one (two-thirds) is the non-structural protein-coding region, comprising significant genes, which are essential for viral replication [83, 85]. While the latter one (one-third of the genome) is responsible for encoding structural proteins, known as spike protein, envelope protein, membrane protein, and nucleocapsid protein, which are critical for the viral life cycle [83, 89]. Among these structural proteins, spike one controls the entry of the virus into our cells [58]. Spike has a receptor-binding domain that plays an important role in direct contact with the cellular receptor, angiotensin-converting enzyme 2 (ACE2) [26].

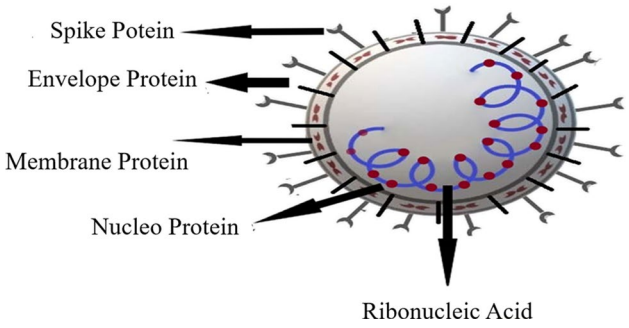

Fig. 1 Coronavirus's structure

Eye transmission mechanism

As mentioned above, the main form of human-to-human transmission occurs through respiratory droplets expelled by an infected individual through coughing or sneezing. Another way of CoV transmission through fomite transmission is by contacting contaminated objects of infected patients [72]. When the virus enters the body, it binds to human angiotensin-enzyme II (ACE2), using it as a cell entry receptor to invade respiratory and lung epithelium through the spike (S) protein [72]. But, CoV does not spread through droplets and fomites only; recent studies suggested that the eye is a possible source of transmission. The eye transmission route speculations involved using the droplets found in the eye as the supporter to enter the respiratory tract. Conjunctiva is inoculated by droplets, so the virus uses these droplets to enter the tears reaching the lacrimal duct, arriving at nasal and nasopharyngeal mucosa, and then causing respiratory tract infection [61]. Some studies reported that ACE2 is predominantly located in posterior tissues of the eye, such as the retina and the retinal pigment epithelium, so the possible transmission of the virus through the eye is less possible and most likely happens because of the relation between the respiratory tract and the eye through nasolacrimal duct [12, 61]. Another study emphasized the same idea and stated that the normal human conjunctiva contains ACE2 receptors but not the priming protease, so the virus would not be able to bind to the ocular surface of the eye and cause the infection. But the possible way is through the tears along the nasolacrimal ducts into the nasopharynx

and from there to the respiratory and gastrointestinal tracts [53, 70]. Figure 2 shows a diagrammatic presentation of the possible mechanisms [3].

The lacrimal sac lies in the lacrimal fossa located in the anterior part of the medial orbital wall. It has got three parts: the fundus (the portion above the opening of canaliculi), the body (middle part), and the neck (the lower small part which is narrow and continuous with the nasolacrimal duct). Then, the final part of our lacrimal drainage is the nasolacrimal duct which extends from the neck of the lacrimal sac to the inferior meatus of the nose. It is about 15–18 mm long and lies in a bony canal formed by the maxilla and the inferior turbinate. This apparatus is the connection between the eye and the respiratory tract which leads to the main transmission mode of COVID-19 through the eye [57].

Coronavirus and ocular manifestations

Although previous studies postulated that Covid-19 ocular symptoms were generally low, reporting that only 9 out of 1099 patients across China were recorded to have conjunctival congestion [30]. More recent studies and meta-analyses have supported a higher incidence of ocular signs and symptoms with a prevalence ranging from 2 to 32% [30]. Common symptoms reported in patients comprised conjunctivitis, ocular pain, redness, swelling, and discharge. Follicular conjunctivitis was the first seen symptom as a result of eye involvement in the CoV manifestations [80]. In 2020, a systematic study of 2347 confirmed cases revealed that 11.64% of patients had ocular surface manifestations like pain, redness, and discharge, with pain being the most prevalent at 31.2% [80]. Another meta-analysis conducted by Nasiri et al. in 2021 published a pooled prevalence of all the possible ocular symptoms among 7300 Covid-19 patients as 11.03% [49]. In the meta-analysis, the most frequent ocular signs were conjunctivitis, dry eye or foreign body sensation, redness, tearing, and itching: 88.8%, 16%, 13.3%, 12.8%, and 12.6%, respectively [30, 49].

A case series study of 38 patients conducted by Ping Wu et al. [82] outlined that 12 of the hospitalized patients experienced conjunctivitis hyperemia, chemosis, epiphora, or increased secretions. Only 2 patients out of the 12 had a positive CoV test result after a conjunctival and nasopharyngeal swab [30, 82]. Notably, one patient presented with epiphora as the first symptom, and only one patient in this study showed conjunctivitis as the first symptom. The authors pointed out that patients with ocular manifestations had higher white blood cells, neutrophils, and C-reactive protein compared to patients with no ocular symptoms [82]. In Wuhan, a cross-sectional study was conducted on a total of 535 confirmed Covid-19 patients. The study found that 5% (27) of the patients had conjunctival congestion, and 4 of those patients had congestion; there were other ocular symptoms noted like ocular pain, discharge, Epiphora, and photophobia [10, 28]. Another cross-sectional study was done in Iraq on 186 Covid-19 patients from June 2020 to December 2020. The article stated that conjunctivitis was found in 13.4% of patients with a higher prevalence of ocular affection in the more severe cases of Covid-19 [39].

A paper comprised 20 case series and reports where 2228 patients were diagnosed with Covid-19. Of these patients, 95 suffered from ocular manifestations during the disease. Adding to this, 21 out of the 95 subjects experienced ocular manifestations as the first complaint or sole manifestation [14, 18, 28, 67, 82, 87]. Moreover, out of 30 hospitalized patients inspected by Xia et al., one patient presented with conjunctivitis and was also the sole patient in the study to test positive for the virus in ocular secretions by a conjunctival swab. Worth noting, this patient did not have a severe

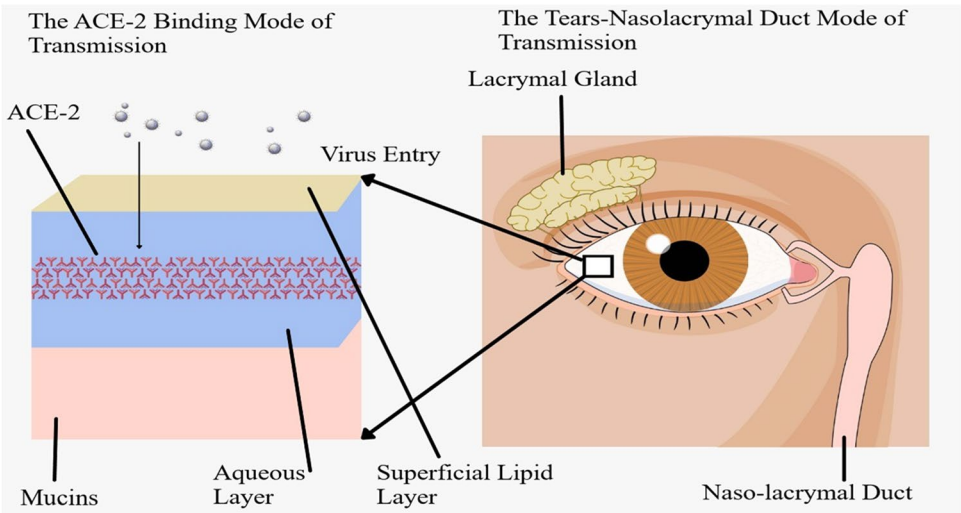

Fig. 2 Possible transmission mechanisms diagram (Armstrong et al.)

fever or respiratory symptoms at the time of testing [84]. An interesting case report showed that a healthcare worker presented with signs of conjunctivitis, but there were no other symptoms. After his examination, the CT chest was normal. After a couple of days, the PCR test came back positive for CoV. His conjunctival swab was negative, but blood results and nasopharyngeal swab showed a positive. This suggested the possible theory that conjunctivitis can be the only symptom of Covid-19 [55].

Cao et al. conducted a systematic review and meta-analysis that comprised 12 studies with 1930 participants included for meta-analysis [7]. The net prevalence rate of conjunctivitis/conjunctival congestion was 8%, whereas only 1% of Covid-19 patients have been diagnosed with conjunctivitis/conjunctival congestion as the initial symptom. The positive rate of conjunctival swab samples was 3%. Other assessed ocular symptoms were reported in the 12 studies, like foreign body sensation, higher secretions, and eye itching. The net rates were 6%, 10%, and 9%, respectively. The prevalence of positive conjunctival swab samples and the propagation incidence of ocular symptoms were suggested evidence of the possible ocular transmission of coronavirus but with a limited rate [7].

The neuro-ophthalmology era drew the attention of some scientists as there has been suggested evidence that Covid-19 affects the eye as it comprises neurons and fibers. As stated in some papers, the authors claimed that there have been reports of cranial nerve palsy, polyneuritis cranialis, and Miller-Fisher syndrome associated with Covid-19 [15, 23]. An interesting case study done by Greer et al. [22] showed that CoV can affect a single cranial nerve as the patient developed isolated abducent nerve palsy only with no identifiable lesion on the imaging study, and no unclear etiology was described [22].

Optic neuritis was one of the neuro-symptoms that has been proven in a study done in Spain [20]. The study showed that a patient developed optic neuritis in the recovery phase of the disease. The study also stated that these neuro-symptoms and signs are varied and may extend through the recovery phase of the infection [20]. Another case report was discovered in a patient in Southern California who found out that he had bilateral optic nerve affection with the spotting of retinal hemorrhages [5]. The authors called for some inquiries about the recent history of Covid-19 and should be aware of the possible concurrent SARs-CoV-2 infection in patients. There was a suggestion for using corticosteroid treatment as it provides excellent outcomes with minimal complications in all patients [5].

Some rare cases of central retinal artery occlusion have been reported that are associated with Covid-19 infections. Acharya et al. presented the first case of isolated central retinal artery occlusion secondary to the virus [1]. It was suggested that the retinal artery is occluded from a platelet–fibrin thrombus or embolism from an atherosclerotic lesion or hypercoagulable state as in Covid-19 infection [1]. In these cases, the visual recovery is usually very poor with a lot of controversies about the use of intraocular hypotensive agents or anterior chamber paracentesis that are used to dislodge the blood clot. For now, no definitive treatment therapy is available. Another two studies have demonstrated the same theory: in severe Covid-19 infections, patients may develop central retinal artery occlusion due to the hypercoagulability state caused by the virus [17, 68].

A cross-sectional cohort study was conducted by Rodríguez-Ares et al. to investigate the presence of CoV in conjunctival secretions and tears [64]. The trial included 56 hospitalized infected patients whose conjunctival secretions and tears were collected using flocked swabs. Assessment of ocular surface manifestations included an Ocular Surface Disease Index questionnaire. 7.1% (four) patients of 56 had shown positive conjunctival swabs, and 30% (17) patients presented ocular symptoms. The results demonstrated that coronavirus can be detected in the conjunctiva and tears of patients; it was found on the ocular surface [64].

A recent multicenter study done by M. Gijs et al. showed that the RNA of the virus was detected in the conjunctival swabs from 17 (7.0%) of 243 Covid-19 patients and that they were positive for the virus's RNA for almost 12 days after the disease onset [19]. The study revealed that the viral strain found in the nasopharynx swabs of the infected patients was the same as that found in the conjunctival swabs. The author suggested that the availability of the virus's viral RNA and the elevated cytokines found in the tear fluid confirm the involvement of the ocular surface in Covid-19 disease [19].

Another prospective study was conducted by Karabela et al. The study included a total of 83 patients experiencing mild-severe pneumonia, in which two conjunctival swabs were done. The first conjunctival swabs were positive in 5 out of 83 clinically confirmed patients or 33 laboratory-confirmed patients expressed as 6.02% and 15.15%, respectively. However, there were no positives detected in the second conjunctival swabs [37]. On the other hand, the nasopharyngeal swabs tested positive in 31 (37.35%) patients in the first nasopharyngeal swabs and 19 (22.89%) in the second swabs. Karabela et al. mentioned that coronavirus can be detected in the conjunctival swabs of patients with Covid-19 pneumonia [37].

Besides the effect of the virus on the eye, its medications and vaccines followed the same path. The medications used in managing Covid-19 are suspected to have ocular toxicities. Chloroquine and hydroxychloroquine's long-term use might lead to retinal toxicity but it is not seen in short-term use [70]. Ribavirin is known to cause retinopathy, retinal vein occlusion, serous retinal detachment, and non-arteritic ischemic optic neuropathy [29]. Retinopathy, conjunctivitis, optic neuropathy, corneal ulcers, and epithelial defects were

major symptoms associated with the use of interferons [70]. Systemically used corticosteroids possess cataracts, glaucoma, and central serous chorioretinopathy [16].

Coronavirus's different vaccines have been linked to some of the ocular manifestations reported in various case studies and reports around the world. As reported by Sen et al. [69], the eyelid, ocular surface, and cornea were presented as the first symptoms as they are accessible to the patient. Corneal graft rejection was the vaccine's most common anterior segment manifestation [79]. All the cases that showed eyelid involvement were transient and related to the Pfizer-mRNA vaccine [69]. The mRNA vaccine can also induce some immune reactions like antigen-specific cell- and antibody-mediated hypersensitivity reactions which play an important role in the formation of uveitis [13, 63]. Two cross-sectional studies conducted on healthcare workers who received the mRNA vaccines reported that few experienced rare ocular symptoms like blurred vision, eye pain, and flashes with percentages of 0.5%, 0.87%, and 0.25% respectively [34, 35]. The posterior segment, the retinal vasculature, and the uvea are most frequently affected. Microangiopathy, localized vasculitis, and demyelination were other possible effects induced by mRNA vaccines [69]. The possible mechanisms include the similarity between the vaccine components' molecules and the host ocular tissue's molecules, antigen-specific cell, and antibody-mediated hypersensitivity reactions to viral antigens and adjuvants present in the vaccines [41, 51, 52, 69]. Although there may be an associated relationship between the vaccines and some of the ocular manifestations, the side effects are rare, mild, and temporary. This relation is not well established, and further long-term, comprehensive multicenter studies are necessary to prove the co-related ocular symptoms and CoV vaccine. Table 1 summarizes the prevalence of some ocular manifestations.

Lockdown and ophthalmology care

The impact of Covid-19 was not limited to the severe symptoms and health problems, but the actions taken to limit the spread of the virus such as the lockdown had significantly affected the healthcare systems. Ophthalmological care was hurt by the lockdown. The lockdown of the population increased electronic use and boosted the stress while following the virus news. These new circumstances led to the growth of dry eye syndrome in the population, especially the young. Some people turned down going to the hospitals and refused to pass through the long screening tests and manifestations. Furthermore, the coronavirus loaded the healthcare system with tension and strain in finding treatments and vaccines; thus, the eye services were either significantly delayed or in other places stopped leading to exacerbation of the medical conditions and complications in rather easily manageable eye diseases.

Table 1 Prevalence of ocular manifestations

No	Symptoms	Prevalence	Reference
1	Conjunctivitis	88.8%	[30, 49]
2	Ocular Pain	31.2%	[2, 80]
3	Dry eye	16%	[30, 49]
4	Redness	13.3%	[30, 49]
5	Tearing	12.8%	[30, 49]
6	Itching	12.6%	[30, 49]
7	Conjunctival congestion	5%	[10, 28]

A retrospective cross-sectional observational study conducted in India to study the effect of the lockdown on ophthalmology care discovered that after the lockdown was initiated, the number of people attending the rural centers for eye care decreased from 1100 to 1200 patients daily to only 263 patients due to the restrictions. It also affected the higher centers because the rate of referral to it increased from 5.34 to 9% leading to delays in service and long travel for many of these patients [62].

Emergency eye care was also negatively affected by the virus as claimed in a study conducted by Poyser et al. [59] to study the ocular pathologies presented to an emergency eye department during the Covid-19 pandemic in 2020. There was a decrease in the attendance to emergency eye care approximately 53%. There was a higher percentage of retinal detachment and a lower number of retinal tears, suggesting the possibility of delayed presentation. Although, the authors noted that the measures taken to stop Covid-19 spread such as hand hygiene practices, social distancing, and school closures played an indirect role in minimizing the spread of infective conjunctivitis [59].

The ocular surface diseases were increased due to the excessive digital screen use during the lockdown; this was mentioned in a cross-sectional study. An online survey through social media between June and July 2020 showed that about 37.2% has been diagnosed with dry eye. It also showed that dry eye was worse in young adults compared to middle and old age. The reason was explained as young adults use electronic devices more frequently, exacerbating dry eye symptoms [60]. Additional online surveys were conducted, and 388 responded to the survey. Showing that 54% had severe dry eye symptoms, 25% had mild symptoms, and 21% had moderate symptoms. All of them reported an increase in the usage of electronic devices [50, 66].

A study conducted in the UK aimed to discuss the effect of Covid-19 on ophthalmic care. The results showed that there was a backlog and significant delay in the elective procedures and operations in the eye care units. Additionally, the protocols limiting the number of patients per day and the triage

system to screen any possible Covid-19 patients caused a delay in the eye service provided [6]. Thus, the health authorities tried to overcome these obstacles and manage the lockdown effect. For example, the National Health Service in the UK instructed all hospitals to increase capacity within acute medicine for the different virus case waves. The Royal College of Ophthalmologists issued guidance on Ophthalmology services during the pandemic. This guidance weighed the risk of patients experiencing Covid-19 by attending hospital dates against the risk of harm by delaying treatment [6].

Stone et al. guided a study to examine the effect of the lockdown delays on visual acuity outcomes and optical coherence tomography features for patients receiving an anti-vascular endothelial growth factor therapy treatment for neovascular age-related macular degeneration, retinal vein occlusions, and diabetic macular edema. The data of 858 patients' medical records were analyzed and revealed that in 36.9%, there was a delay in their appointment for follow-up for 8 weeks or more. Unfortunately, their visual acuity was different between the delayed and non-delayed groups [75]. This demonstrates the damage that the lockdown had on the eye care system was significant and needs further studies, precautions, and actions. Worldwide ophthalmologists should use this pandemic to discover new ways of working, streamline services, increase capacity, and enhance the positive patient experience. They will need to be stringently implemented in ophthalmic settings.

Conclusion and future directions

Literature approves the possible ocular infection and feasible transmission in animals during the previous coronavirus strains. This suggests the high probability of ocular implications during the current pandemic. Although the mechanisms might differ between those adopted by human and animal CoVs, basic domains are to be considered carefully while understanding the virus mechanisms and infections. CoV is capable of causing a wide spectrum of ocular manifestations, from conjunctivitis and anterior uveitis to sight-threatening conditions like retinitis and optic neuritis. It can also develop in vivo mutations which will alter the manifestations of the disease. The suggestions are that the intraocular renin-angiotensin system of the human eye plays the main role in the ocular implications, as the virus can bind to the ACE-2 receptors that are found in the aqueous humor of the eye. However, the eye-associated risk remains low which is explained as follows: the number of the demonstrated receptors in the conjunctival and corneal epithelia is faint compared to the respiratory tract tissues. The other reason is the open surface of the ocular environment that might take the virus away from the eye via the tears to the nose or the respiratory tract, so render the ocular system less vulnerable to the virus infection. In addition to the effect of the virus on the eye, ophthalmologists should consider the possible effect of the medications and vaccines used to treat CoV on the eye as they can cause serious ocular manifestations if not early reported. However, as reported by Sopp et al., the incidence rate of ocular manifestations after receiving the vaccine is considerably lower than the prevalence rate of ocular symptoms in Covid-19 patients [73]. Nevertheless, the benefits of CoV treatments and vaccines outweigh the rarely reported risks and should not hinder the vaccination road. It would help to pinpoint the high-risk characteristics of the patients developing ocular incidences in response to CoV infection or vaccination and prospectively follow up.

These controversies emphasize the need for more research to explore these different assumptions in the human eye Covid-19 relation and its ocular pathogenic mechanisms. On the other hand, studying the ocular manifestations of various Covid strains in animal species might be valuable and direct the research and studies in the right direction providing insights into the spectrum of ocular diseases that CoV can cause. This comprehension will lay out some infection control guidance and open the door for the probability of using the ocular tissue or tears as a medium of diagnosis. For now, ophthalmologists and the health care system should continue to take the necessary precautions to prevent the possible transmission of coronavirus through ocular tissue. WHO and other organizations have adopted considerable protocols, guidelines, and etiquette that should be implemented during pandemics to assure safety and minimize any possible risk to human beings. Plans and schemes are to be considered by global health and economical authorities for future contagion and any impacts on health and the economies of the world. Covid-19 is gradually becoming an endemic disease, so it would help to use a global registry for compiling rare ocular adverse effects of CoV, and post-CoV vaccination could facilitate our understanding of the virus.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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