Oman J Ophthalmol. 2024 Jun 27;17(2):166–172. doi: 10.4103/ojo.ojo_212_22

Manifestations of COVID-19 in the posterior eye segment – Up-to-date

Basheer Abdullah Marzoog [1,✉]

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PMCID: PMC11309540 PMID: 39132129

Abstract

Since coronavirus disease infection-19 (COVID-19) entry to the cells is angiotensin enzyme receptor (ACEII) dependent, extrapulmonary manifestations have been suspected. Ocular manifestations reported in several studies to involve the anterior as well as posterior eye segments. However, the predominance of the anterior eye segment reduced the attention of the scientific community on the posterior eye segment. Our results showed that the incidence of changes in the posterior eye segment is 1/5 of the anterior eye segment. Posterior eye segment manifestations include acute macular neuroretinopathy and paracentral middle maculopathy, central retinal vein/artery occlusion, reactivation of previous uveitis, varicella zoster virus-related acute retinal necrosis in an immunocompromised patient, chorioretinitis, macular hemorrhage, paracentral acute middle maculopathy, retinal detachment, and vitritis with outer retinal abnormalities. The pathogenesis of posterior eye segment manifestations under COVID-19 includes viremia, autoimmune vasculitis, hyperimmune response, coagulopathy, and cytokine storm. A full ophthalmological examination is crucial for patients recovering from COVID-19. The paper provided up-to-date manifestations with potential underlying pathophysiological mechanisms of development, as well as pathogenetic therapy.

Keywords: ACEII and Transmembrane protease, serine 2 (TMPRSS), COVID-19, severe acute respiratory syndrome-corona virus 2, thrombosis, retinitis, visual acuity, visual field

Introduction

COVID-19 is a global catastrophic challenge that appeared first in Wuhan Province, China, in late 2019.[1] According to the World Health Organization (WHO), there were more than half a billion confirmed COVID-19 cases and 6,224,220 deaths by the evening of April 26, 2022.[2]

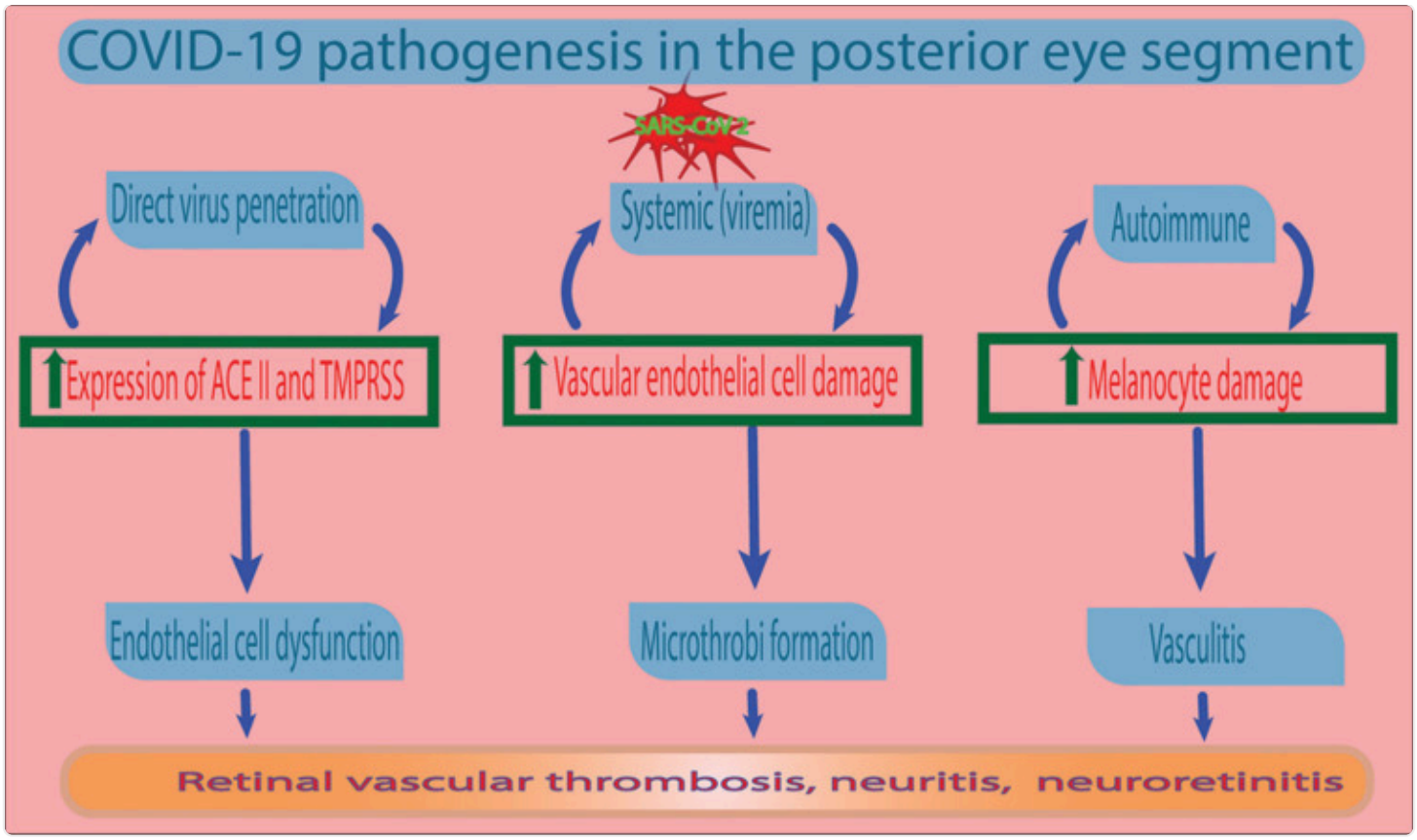
The presence of extrapulmonary manifestations during the first cases of COVID-19 suggested the politropism of the virus. The signs and symptoms of anterior eye segment

damage were reported in several studies, including keratitis, conjunctivitis, iridocyclitis, and corneal punctate epitheliopathy. According to a systemic review, approximately 7.5% have positive reverse transcriptase–polymerase chain reaction results for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) in their tears.[3] Therefore, according to the number of WHO COVID-19 sick people, there are 31,275 (7.5% of the average daily new cases; 417,000) each day someone producing the infection through their conjunctival secretions. Moreover, the meta-analysis demonstrated the highest risk of COVID-19-induced conjunctivitis, 10,008 (32% of the total daily infected COVID-19 patients; 31,275 will have conjunctivitis). For these reasons, the urgency of describing the ocular manifestations during COVID-19 was raised.

Unfortunately, the eye and, in particular, the cornea have been affected by multiple systemic diseases.[4] Involvement of the posterior eye segment has been reported in several studies.[5] Therefore, the incidence of ocular manifestations is frequently seen and requires immediate response due to the importance and value of vision.

The materials and methods involved searching PubMed and Embase databases from December 2019 to April 30, 2022. The search was carried out using the terms in combination, “posterior eye segment in coronavirus,” “COVID-19 in posterior eye segment,” and “COVID-19 and retina.” We found 155 papers; by title, we excluded 59 papers, and by abstract, we excluded 33–63 papers that were fully reviewed. The results show a dramatic increase in the number of published papers on ocular manifestation in the comparison of 2020–2021 (*t*-test 4.801960, $P < 0.040736$) [Figure 1].

Figure 1.



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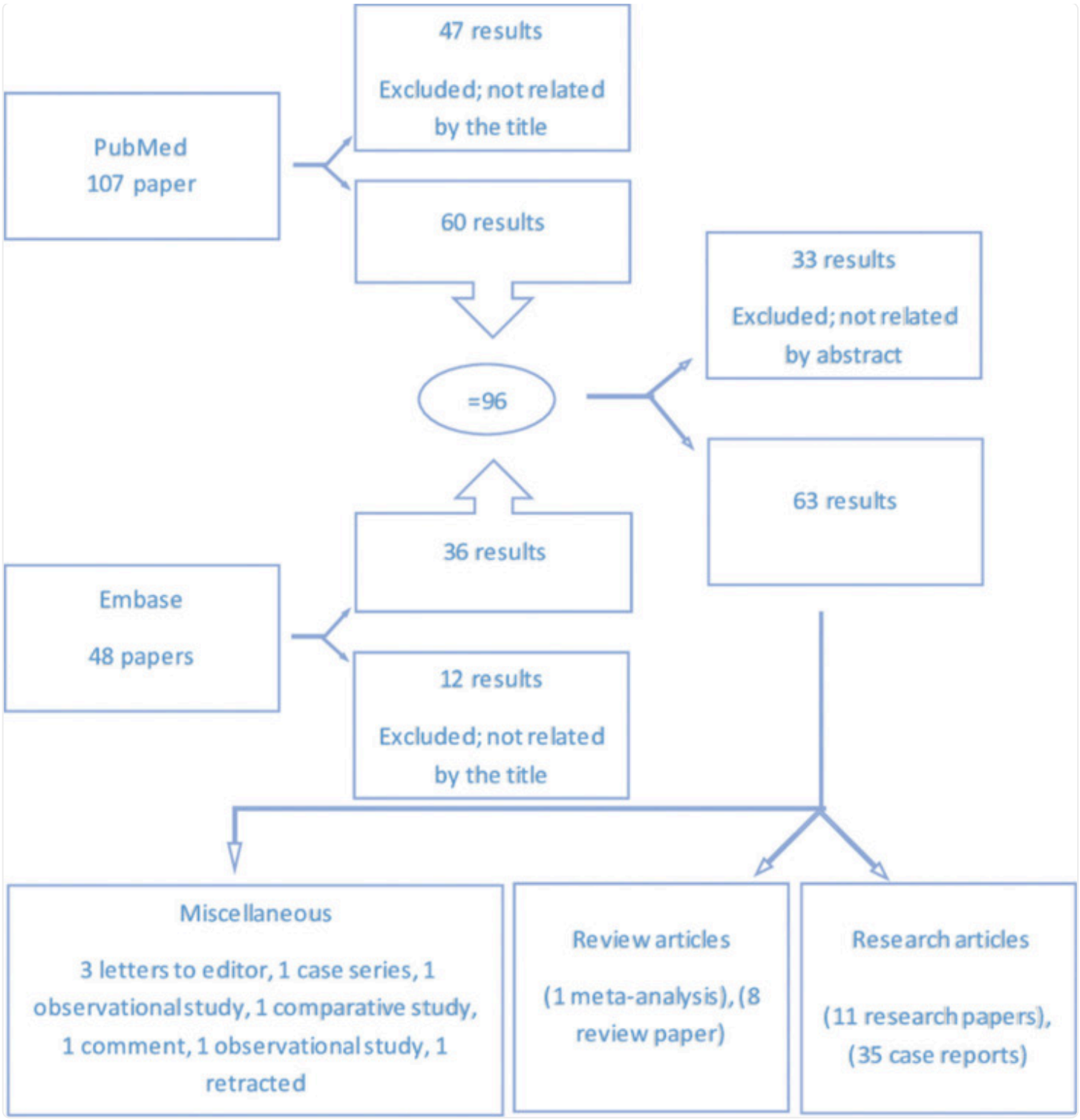
Data outflow from the period 2020–2021. A dramatic increase in the number of published papers on the posterior eye segment in the main databases research (MEDLINE 163–294 and Embase 172–348) shows the significance of COVID-19 on the posterior eye segment pathology

After searching MEDLINE and Embase, we inserted all the results into Mendeley and then checked for duplication. Then, we removed the nonadherent titles. Excluded studies do not directly show the incidence or prevalence of posterior eye segment manifestations. Thereafter, we read the abstract and determined which study was eligible for the criteria of posterior eye segment with COVID-19. Finally, we read the full paper text [Scheme 1].

Scheme 1.



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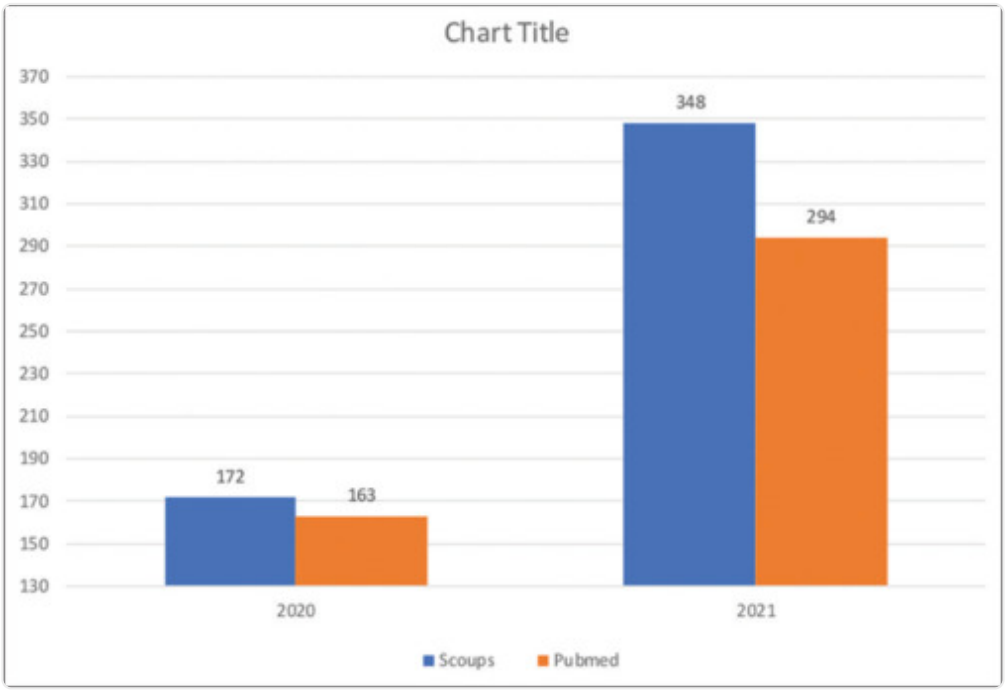
Systematic outflow of the database research of PubMed and Embase resources

Potential Mechanism of COVID-19 in Posterior Eye Segment Involvement

The pathogenesis of the posterior eye segment always arises in the background of systemic disease manifestations. Due to the topographical anatomy of the posterior segment, it is not suggested that direct virus penetration without open trauma reaches the posterior eye segment. COVID-19 has been found to cause damage to the microvascular retinal compartment.[6] The overwhelming immune response, cytokine storm, activation of tyrosine kinase, and hypercoagulation induce microthrombi formation of microthrombi.[6] Deposition of these microthrombi in the small vessels of the retina results in ischemia and necrosis of different parts of the retina[7,8] [Figure 2]. Moreover, central retinal vessel occlusion was reported in severe and critical patients aged <60 years. [5,9,10,11,12,13,14,15] The sudden loss of vision is manifested with retinal microangiopathy.[8,16] In addition, vitreous body damage (vitritis) with retinal detachment is potentially possible under COVID-19.[7,17] In rare cases, bilateral neuroretinitis and panuveitis may occur as an outcome of a severe course of COVID-19 ocular manifestations. [18,19]

Figure 2.



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Graphical presentation showing the ocular manifestations that may occur as a result of COVID-19 and their possible underlying pathogenesis. The pathogenesis of ocular manifestations involves several aspects. The manifestations of the posterior eye segment include acute macular neuroretinopathy and paracentral middle maculopathy, central retinal vein occlusion, reactivation of previous uveitis, central retinal artery occlusion, acute retinal necrosis in immunosuppressed patients, chorioretinitis, macular hemorrhage, paracentral acute middle maculopathy, acute macular neuroretinopathy, retinal

detachment, and vitritis with outer retinal abnormalities. However, the pathogenesis is multifactorial. Viremia and autoimmune pathways are the primary pathogenetic mechanisms of the development of posterior eye segment manifestations. The overall result of hyperimmune response is endothelial cell dysfunction of the eye microvascular network. This leads to hypercoagulation and the formation of microthrombi that culminate in occlusion of the small retinal vessels and the central retinal artery and vein

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The autoimmune mechanism of development is associated with self-autoantibodies against myelin oligodendrocyte glycoprotein.[20] The damage to the vascular sheath exposes the underlying tissue, including immune privilege. Manifestations of autoimmune damage to the posterior eye segment include optic neuritis and myelitis.[21,22,23,24,25,26,27,28,29]

Furthermore, ocular manifestations of COVID-19 are usually reported in patients with severe and critical COVID-19. At the retinal level, a discrete white–yellow spot in the posterior pole has been visualized. In the result, hyporeflective alterations occur in the retinal pigment epithelium, as well as at the outer segment and the ellipsoid layers.[30] Further fundus manifestations are observed in severe and critical patients that involve cotton wool spots, tortuosity, and retinal hemorrhages with disc edema and hyperemia.[13,31,32] Furthermore, due to the inflammatory process in the retinal nerve, thickening of the retinal nerve has been reported in some studies,[33] suggesting the severity of ocular manifestations and the virulence of SARS-CoV2.

Choroid involvement in pathogenesis is due to the expression of high numbers of viral entry receptors in the endothelial vasculature. The presence of ACEII suggests a high risk of choroiditis, even involvement of the retinal pigment epithelium and the choriocapillaris (serpiginous choroiditis).[34]

Interestingly, patients with concomitant diseases such as beta-thalassemia and COVID-19 or acute myeloid leukemia and COVID-19 have an increased risk of macular neuroretinopathy.[35,36] In addition, patients with systemic diseases such as hypertension and diabetes have more pronounced retinal microvascular disorders, especially in elderly patients.[6,14] On optical coherence tomography (OCT), acute macular neuroretinopathy findings include a hyperreflectivity band in the outer nuclear layer (ganglion cell) and outer plexiform layer as well as a hyperreflective patch in outer retina segmentation.[36,37]

Antivascular endothelial growth factor (anti-VEGF) therapy has been investigated for its role in preventing vein occlusion post-COVID-19. Lin and Sun reported a case of bilateral simultaneous central retinal vein occlusion (CRVO) in a patient with COVID-19, who received intravitreal anti-VEGF therapy and showed resolution of symptoms and improvement of retinal vascular appearance.[38] In addition, Napal and Castillo Hernández found that vaccination and COVID-19 infection may be involved in the development of retinal vein occlusion in some cases, particularly in patients without vascular risk factors or

thrombophilia, especially within the 1st month after vaccination or infection.[39] These findings suggest that anti-VEGF therapy may play a role in managing vein occlusion post-COVID-19. However, further research is needed to fully understand the effectiveness and safety of this treatment approach.

COVID-19 has been observed to infect several organs, including gastrointestinal, and is associated with multiple complications in pregnancy as well as brain injury and myocardiocytes injury.[40,41,42,43,44]

Current Perspective for a Future Therapeutic Approach

The current approaches for the management of the posterior eye segment are identical to that of nonviral etiology. For the management of acute eye pathologies, usually, conservative treatment or surgery is required. The requirement for subconjunctival injections of corticosteroids is crucial in the conservative plan of treatment.[45] The treatment of occlusion of the central retinal vessels includes thrombolytics and prophylactic anticoagulants.[46] Outcomes of CRVO are usually favorable.[15] However, surgical treatment is required for retinal detachment, including pars plana vitrectomy and scleral buckling.[47]

However, planned regenerative therapeutic strategies are currently in rapid development for the management of retinal degenerative diseases. The ability to induce stem cells into the retinal cells is of particular interest. However, the lack of the sources of stem cells in the adult period remains problematic. A surrogate strategy exists by direct reprogramming of Müller glia into the retinal neural cells by ATOH7 transcription factor.[48] Moreover, the application of retinal-specific transcription factors to nonretinal cells can induce retinal cell regeneration. The use of transcription factors can induce the proliferation of retinal cells, and can also lead to the danger of tumor formation. The retinal cell functionality is impaired with aging and depends on the degree of expression of retinal-specific genes, confirmed by the degree of the epigenetic markers. With aging, cellular transdifferentiation of retinal cells is crucial. To prevent cell lineage reprogramming, maintain the expression of retinal cell-specific transcription factors and maintain the epigenetic markers of the retinal cell.[49,50] Regeneration plan of retinal cells involves transcription factors (Tailless-X-Receptor transcription factor), epigenetics, DNA methylation/demethylation, microRNAs, autophagy, and microenvironment.[51,52] The usage of the autologous retinal pigment epithelium and fetal retina cells is more acceptable in clinical trials.[53,54]

Discussion

Despite that most of the referrals of patients to the hospital are due to the anterior eye segment, most of the examinations are done to the posterior eye segment.[55] The frequent

ocular manifestations are usually resolved with treatment or by self.[56,57] However, more rare and severe ocular changes can persist for lifelong.[58,59]

Interestingly, COVID-19 posterior eye segment manifestations have been reported in several cases which suggest the possibility of post-COVID-19 ocular syndrome.[6,30,33,60,61,62,63] In addition, post-COVID ocular manifestations include reduced vascular density and enlarged foveal avascular zone, suggesting impaired retinal vascular circulation and increasing the risk of future retinal complications.[64,65] Unfortunately, early vascular retinal changes are silent and can be identified by OCT angiography. Missing of vascular retinal changes culminates in vision deterioration and blindness.[66]

In severe and critical patients with impaired immune status, the risk of superinfection of the eyeball is increased that leads to physio-anatomical changes in the eyeball.[45,67] Interestingly, postmortem autopsy findings show the presence of SARS-CoV2 in the intraocular tissue,[68,69] suggesting the tropism of the virus to the ocular tissue. The onset of ocular manifestations can precede the pulmonary changes.[70] Therefore, the susceptibility of COVID-19 can be based on the ocular findings.

Moreover, some posterior ocular alterations, like choroiditis, have been reported after COVID-19 vaccination.[71] Furthermore, the Pfizer and Sinopharm vaccines have been reported to induce retinal detachment and choroiditis.[72,73,74] However, mRNA vaccines, like the Moderna vaccine, have been reported to induce choroiditis as well as dacryoadenitis.[75,76]

Ocular manifestations have been reported following COVID-19 vaccination. These manifestations include uveal effusion syndrome, posterior ocular adverse events, ocular adverse effects, ocular inflammatory events, and ocular motility disorders. Uveal effusion syndrome, a rare ocular disease, has been reported following COVID-19 vaccination.[77] Posterior ocular adverse events such as posterior scleritis, paracentral acute middle maculopathy, herpes panuveitis, and Vogt–Koyanagi–Harada (VKH)-like uveitis have also been observed.[78] Ocular adverse effects after COVID-19 vaccination commonly appear in the uvea and retina, but can also affect the eyelid, cornea, ocular surface, and cranial nerves innervating the eye.[79] Ocular inflammatory events following vaccination have included acute anterior uveitis, multiple evanescent white dot syndrome, VKH disease, anterior scleritis, idiopathic panuveitis, and central retinal artery occlusion.[80] Ocular motility disorders such as internuclear ophthalmoplegia, cranial nerve palsy, myasthenia gravis, orbital diseases, and comitant vertical strabismus have also been reported.[81,82,83]

Conclusions

Ocular manifestations are often observed during COVID-19, particularly in the anterior eye segment.[69] However, posterior eye segment manifestations are more severe but less

frequent.[84] The pathogenesis involves autoimmune damage to the immune privilege compartment of the eye, endothelial dysfunction that leads to edema and potential retinal detachment, as well as hypercoagulation that leads to microthrombi formation.[20] ACEII overexpression in the choroid and retinal vasculature is the primary route of the viral entrance.[85,86] The poor prognosis of the posterior eye segment is associated with the severity of the systemic manifestations of COVID-19. In light of the presented reports, a full ophthalmological examination is recommended for COVID-19-recovered patients.

Financial support and sponsorship

The work of Basheer Abdullah Marzoog was financed by the Ministry of Science and Higher Education of the Russian Federation within the framework of state support for the creation and development of the World-Class Research Center “Digital Biodesign and Personalized Health Care” № 075-15-2022-304.

Conflicts of interest

There are no conflicts of interest.

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