• Review Article •

Viral mechanisms, tropism, and clinical relevance regarding the ophthalmic manifestations of SARS-CoV-2 infection

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Abstract

● To explore the mechanisms underlying ocular infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we conducted a comprehensive review of current literature, focusing on viral entry pathways, receptor expression in ocular tissues, and associated clinical manifestations. This review encompasses studies published within the last five years with a focus on original research and systematic reviews that provide molecular, histological, or clinical evidence. The findings show that SARS-CoV-2 can infect ocular tissues through multiple receptors beyond angiotensin-converting enzyme 2 (ACE2), including transmembrane serine protease 2 (TMPRSS2), CD147, alanyl aminopeptidase N (ANPEP), dipeptidyl peptidase 4 (DPP4), angiotensin II receptor type 2 (AGTR2), and polymeric immunoglobulin receptor (PIGR), which are expressed in retinal, conjunctival, corneal, limbal, and photoreceptor cells. The virus may also reach ocular structures *via* neurovascular invasion. Clinically, patients with coronavirus disease 2019 (COVID-19) may present with a broad spectrum of ophthalmic manifestations, including conjunctivitis, hyperreflective lesions in the inner retinal layers, flame-shaped hemorrhages, cotton-wool spots, retinal pallor, hard exudates, and various forms of maculopathy, such as paracentral acute middle maculopathy and acute macular neuroretinopathy (AMN). These signs reflect both direct viral damage and secondary effects of systemic inflammation and microvascular injury. Understanding the molecular and clinical spectrum of ocular involvement is essential for early diagnosis, appropriate ophthalmologic care, and the prevention of long-term visual sequelae in patients affected by COVID-19.

● **KEYWORDS:** SARS-CoV-2; ophthalmic infection; retinopathy; viral tropism; inflammation

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been a global public health challenge because of its multisystemic implications, infecting hundreds of millions of people (with severity ranging from asymptomatic cases to life-threatening pneumonia and multiple organ failure)[1-2]. Interestingly, SARS-CoV-2 exhibits tropism for various human tissues, particularly the eyes, making ophthalmic manifestations crucial in understanding its multi-organ impact, which is a topic central to this text. Remarkably, SARS-CoV-2 membrane proteins may cause direct ocular infection by interacting with human proteins such as transmembrane serine protease 2 (TMPRSS2), alanyl aminopeptidase N (ANPEP), dipeptidyl peptidase 4

Table 1 Summary of viral tropism and pathological mechanisms in SARS-CoV-2 infection

Type of article	Findings	Reference
Original investigation	SARS-CoV-2 detected in retinal tissues. Spike (S) and nucleocapsid (N) proteins are found in retinal endothelial and nuclear layer cells. Viral replication structures observed.	[18]
Original investigation	SARS-CoV-2 infects and replicates in photoreceptor and retinal ganglion cells. Infection causes retinal degeneration through the inflammatory cytokine interleukin-33.	[7], [19]
Original investigation	S protein promotes senescence of RPE cells *via* ROS/tumor protein P53/P21 pathway. Associated with AMD.	[20]
Original investigation	OCTA shows reduced vessel density in SCP, DCP, and CC. Increased density in FCC.	[13]
Original investigation	Dilated eye exam and retinography in hospitalized patients reveal retinal vascular lesions: flame-shaped hemorrhages, cotton-wool spots, and sectorial retinal pallor.	[21]
Brief research report	In 142 acute and 93 convalescent patients, no retinal lesions were observed during the acute phase; 5.38% of convalescent patients had cotton-wool spots.	[22]
Original investigation	Mendelian randomization reveals that COVID-19 is associated with increased thickness of the mRNFL and the mGCIPL. Hospitalization had no effect.	[23]
Original investigation	Low expression of ACE2 in ocular tissues may increase the potential for viral entry during inflammation.	[8]
Case report	A 24-year-old woman developed AMN after COVID-19. Stable vision. Imaging and immune link discussed.	[24]
Meta-analysis	Retinal microvascular damage and choroidal thinning were identified in COVID-19 patients compared to healthy controls.	[25]
Case report	ARN reactivated due to HSV-2 post-COVID-19, with a poor visual prognosis. Prophylaxis recommended.	[26]
Original investigation	Expression of ACE2, BSG, and TMPRSS2 in conjunctival and corneal cells suggests limited potential for viral ocular entry.	[27]
Original investigation	ACE2, TMPRSS2, and proprotein convertase furin are expressed in the retinal tissue of COVID-19-negative donors. Variability may relate to symptom severity.	[28]
Original investigation	S protein found in corneal, limbal, and scleral tissues; co-expressed with ACE2, TMPRSS2, and KRT markers. Supports possible ocular surface involvement.	[29]
Original investigation	In 232 severe COVID-19 patients, no significant retinal lesions were found. Suggests retinal findings are secondary to systemic comorbidities.	[6]

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RPE: Retinal pigment epithelium; ROS: Reactive oxygen species; P53: Tumor protein p53; P21: Cyclin-dependent kinase inhibitor 1A; AMD: Age-related macular degeneration; OCTA: Optical coherence tomography angiography; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris; FCC: Foveal choriocapillaris; COVID-19: Coronavirus disease 2019; mRNFL: Macular retinal nerve fiber layer; mGCIPL: Macular ganglion cell–inner plexiform layer; ACE2: Angiotensin-converting enzyme 2; AMN: Acute macular neuroretinopathy; ARN: Acute retinal necrosis; HSV-2: Herpes simplex virus type 2; BSG: Basigin; TMPRSS2: Transmembrane serine protease 2; KRT: Keratin.

(DPP4), angiotensin II receptor type 2 (AGTR2), polymeric immunoglobulin receptor (PIGR), adhesion G protein-coupled receptor F1 (ADGFR1), basigin (CD147) and cathepsin L (CTSL; Table 1), facilitating viral entry into retinal, conjunctival, and corneal cells[3-7]. These proteins are crucial for understanding the ophthalmic implications in severe SARS-CoV-2 patients, a topic that is thoroughly explained in the text.

Beyond direct infection, SARS-CoV-2 may spread through photoreceptors, retinal ganglion cells, and limbal cells, as well as through neurovascular invasion, underscoring the potential for direct eye damage and highlighting how viral systemic effects can exacerbate pre-existing ocular pathologies[3-7].

For instance, these processes explain ophthalmic implications in patients with severe acute respiratory syndrome caused by SARS-CoV-2, such as conjunctivitis, hyperreflective lesions within the ganglion cell and inner plexiform layers, flame-shaped hemorrhages with ischemic patterns, and microvascular derangement lesions, including cotton-wool spots, retinal sectorial pallor, intraretinal hemorrhages, hard exudates, paracentral acute middle maculopathy, acute macular neuroretinopathy (AMN), and retinal vein occlusions. Consequently, understanding these findings is crucial for healthcare professionals in the diagnosis and treatment of coronavirus disease 2019 (COVID-19)[5,8-12].

For instance, with this information, specific ophthalmic treatments can be applied, and the criteria for applying such therapies will depend directly on the signs and symptoms presented. If viral conjunctivitis is present, it will be treated with symptomatic relief methods, such as artificial tears, cool compresses, membrane peeling, non-steroidal anti-inflammatory drugs (NSAIDs), and topical steroids. On the other hand, if there are retinal microvascular abnormalities, anti-vascular endothelial growth factor (anti-VEGF) drugs (bevacizumab, ranibizumab, aflibercept, faricimab, brolucizumab) are used for macular degeneration to reduce retinal edema[13-14]. Additionally, non-pharmacological therapies are available, like retinal photocoagulation, surgical treatment, sclerotherapy, and micropulsed laser therapy, which prevent severe complications[15-17].

In summary, this review aims to highlight the ophthalmic pathological implications of SARS-CoV-2, focusing on its mechanism of tropism, infection, and pathological development in severe cases, particularly in conjunctivitis and retinopathy. Furthermore, recent discoveries in humans, animal models,

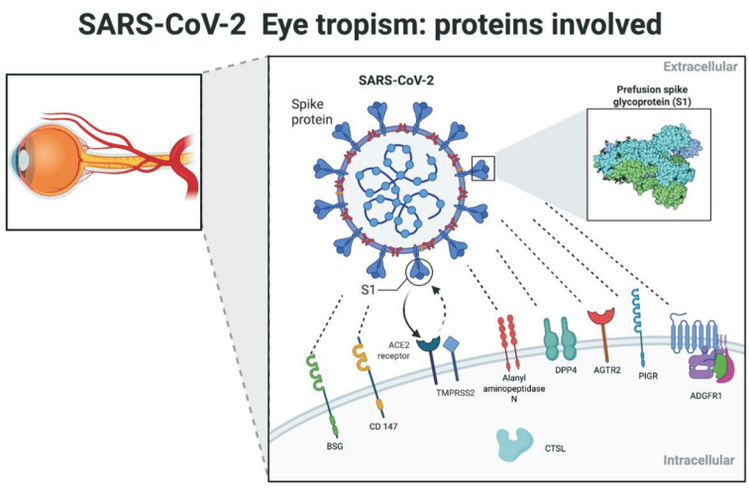

Figure 1 SARS-COV-2 eye tropism: proteins involved CTSL, DPP4, ADGFR1, and CD147 are present in the retinal and ocular tissue and surface; ACE2, BSG, and AGTR2 are found in both conjunctival and corneal cells. TMPRSS2, ANPEP, and PIGR are present in the conjunctival tissue. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; CTSL: Cathepsin L; DPP4: Dipeptidyl peptidase 4; ADGFR1: Adhesion G protein-coupled receptor F1; CD147: Cluster of differentiation 147; ACE2: Angiotensin-converting enzyme 2; BSG: Basigin; AGTR2: Angiotensin II receptor type 2; TMPRSS2: Transmembrane serine protease 2; ANPEP: Alanyl aminopeptidase N; PIGR: Polymeric immunoglobulin receptor. Created in https://BioRender.com.

and related coronaviruses will be explained, emphasizing the imperative importance of recognizing, diagnosing, and treating COVID-19 ocular pathologies adequately to preserve patients' health[13-14].

Data Retrieve The information in this text was obtained from databases such as PubMed, using search criteria related to SARS-CoV-2 infection mechanisms, pathophysiology, ocular involvement, and clinical implications. Only scientific peer-reviewed articles from the past five years were included, with critical findings and sources displayed in Table 1.

Tropism A well-proven fact is that SARS-CoV-2 virus has a specific mechanism of infection based on its tropism. SARS-CoV-2 is part of the *Coronaviridae* family, a single-stranded, non-segmented RNA virus enveloped by surface proteins embedded in its membrane. The spike (S) protein is the key factor in the virus's infection process and tropism for human tissues, attaching to the angiotensin-converting enzyme 2 (ACE2) receptor, which promotes viral transport into the host cell[18-19]. The ACE2 receptor is found in human tissues, such as the airway, kidneys, heart, bladder, gastrointestinal system, and testes; however, it is also present in human cornea and aqueous humor, which is meaningful in this text because of the relationship between the virus and the ophthalmic infection[20-21].

After infection, the virus may inhibit heme synthesis by competing for porphyrin's iron-binding capacity. Additionally, it produces an inflammatory response mediated by the innate immune system through inflammatory mediators, leading to dysregulation of DNA replication and activation of apoptotic pathways[5]. These processes and their consequences have been studied in relation to respiratory abnormalities; however, the purpose of this article is to review the ophthalmic implications in affected patients[5].

THEORIES

Conjunctivitis: Direct Infection The first theory of infection addressed in this text is that the SARS-CoV-2 virus can infect the human eye directly through the conjunctiva. This is because the virus, in addition to the ACE2 receptor, employs other proteins to infect human cells, such as transmembrane serine protease TMPRSS2, ANPEP, DPP4, AGTR2, PIGR, ADGFR1, CD147 and CTSL[3,5]. These proteins, as shown in Figure 1, are relevant because of their presence in the ocular tissues: CTSL and CD147 are present in the retinal and ocular surface; ACE2, BSG, and AGTR2 are found in conjunctival and corneal cells; on the other hand, TMPRSS2, ANPEP, and PIGR are present in the conjunctival tissue. Therefore, it can be suggested that the virus may have a direct inoculation route to the eye if it comes into direct physical contact with the ocular surface through aerosols and droplets[4].

Moreover, identifying the function of the previously mentioned proteins is crucial to comprehending the pathophysiological processes of SARS-CoV-2 ocular abnormalities. First, TMPRSS2 facilitates SARS-CoV-2 entry by cleaving the ACE2 receptor and the coronavirus S glycoproteins, thereby promoting viral entry[22].

Regarding ANPEP, it is involved in peptide digestion through the hydrolysis of proteins by gastric and pancreatic proteases, as well as in processing peptide hormones, such as angiotensin III and IV, neuropeptides, and chemokines, thereby linking it to inflammatory processes[23]. Additionally, it acts as a receptor

for human coronavirus 229E (HCOV-229E), serving as a receptor for the viral S glycoprotein[24].

Additionally, DPP4 is a cell surface glycoprotein receptor involved in T-cell receptor (TCR)-mediated T-cell activation[25-26]. Also, it is a positive regulator of T-cell coactivation, binding to adenosine deaminase (ADA), caveolin-1 (CAV1), insulin-like growth factor 2 receptor (IGF2R), and protein tyrosine phosphatase receptor type C (PTPRC), thereby inducing T-cell proliferation, NF-κB activation in a TCR/CD3-dependent manner, regulating lymphocyte-epithelial cell adhesion, and in association with fibroblast activation protein (FAP), participating in the pericellular proteolysis of the extracellular matrix (ECM), the migration and invasion of endothelial cells into the ECM[25-27].

Next, AGTR2 has vasoconstriction effects *via* non-canonical G-protein and beta-arrestin-independent pathways and cooperates with microtubule associated scaffold protein 1 (MTUS1) to inhibit extracellular signal-regulated kinase 2 (ERK2) activation and cell proliferation, which is directly related to inflammatory processes and states that favor viral infection and the ocular abnormalities presented in SARS-CoV-2 patients[28-30].

Furthermore, PIGR mediates selective transcytosis of polymeric IgA and IgM across mucosal epithelial cells and binds polymeric IgA and IgM at the basolateral surface of epithelial cells, forming secretory IgA (sIgA). Its secretory component through N-linked glycans, anchors sIgA to mucus, lining the epithelial surface, neutralizing extracellular pathogens and acting as a microbial scavenger to prevent interaction of pathogens with epithelial cells[31-33].

Regarding BSG/CD147/EMMPRIN, it is essential for normal retinal maturation and development, and it acts as a retinal cell surface receptor for nucleoredoxin-like 1 (NXNL1) and is crucial in NXNL1-mediated survival of retinal cone photoreceptors[34]. Additionally, in conjunction with glucose transporter solute carrier family 16 member 1 (SLC16A1)/glucose transporter 1 (GLUT1) and NXNL1, it promotes retinal cone survival by enhancing aerobic glycolysis and facilitating the entry of glucose into photoreceptors[34]. Additionally, it stimulates interleukin-6 (IL-6) secretion in monocytes and other cell lines; also, it acts as a signaling receptor for cyclophilins [peptidylprolyl isomerase A (PPIA/CyPA) and peptidylprolyl isomerase B (PPIB/CyPB)] related to chemotaxis and adhesion of immune cells, serving as a co-receptor for VEGF receptor 2 [kinase insert domain receptor (KDR)/VEGFR2] in endothelial cells, enhancing its VEGFA-mediated activation and downstream signaling, promoting angiogenesis; and finally, it can facilitate SARS-CoV-1 and SARS-CoV-2 infection[35-37].

Finally, CTSL is related to protein degradation in lysosomes, which is pertinent in viral infections. In cells lacking TMPRSS2 expression, it facilitates human coronaviruses SARS-CoV and SARS-CoV-2 infections *via* a slow, acid-activated route, involving the proteolysis of coronavirus S glycoproteins in lysosomes for entry into host cells[38].

Overall, the SARS-CoV-2 virus may have a direct method of infection, thanks to the proteins already explained, which implicates direct infective mechanisms, inflammatory processes, and dysregulation of normal ocular physiology. However, it does not mean that there is only one possible method of infection, which will be explained below.

Photoreceptor and Retinal Ganglion Cells Interestingly, SARS-CoV-2 exhibits infective and replicative potential in invading photoreceptor and retinal ganglion cells. Menuchin-Lasowski *et al*[7] conducted a study with human retinal organoids derived from human pluripotent stem cells. They demonstrated that the virus can replicate in retinal cells, including ganglion cells and photoreceptors. Also, the virus had a greater presence in younger retinal organoids because TMPRSS2 decreased over time, underscoring age-related susceptibility. Additionally, inflammatory genes, such as interleukin 33, were expressed, which is associated with acute COVID-19 and retinal degeneration[7,19]. This information is crucial for understanding viral infections and identifying practical clinical approaches and opportunities.

Neurovascular Invasion This theory could have a massive impact on the patient's health because SARS-CoV-2 infection produces a massive inflammatory state in the host's organ systems, dysregulating the immune response and causing systemic hyperinflammation. The ocular tissues are no exception[39]. Hyperinflammation can cause central retinal artery/vein occlusion and AMN, disrupt the blood-retinal barrier, producing an inflammatory state, and increase vascular permeability, allowing immune cells and cytokines to enter the ocular tissue. Consequently, other ocular pathological changes occur, including a procoagulant state and inflammation of the endothelial cells, with the recruitment and presence of inflammatory cells, resulting in vascular-derived lesions such as microthrombosis, cell apoptosis, and retinal thickening and degeneration[39].

To achieve inflammation, SARS-CoV-2 must colonize the target epithelium. Jackson *et al*[40] reviewed several investigations to characterize such colonization using methods such as infection and viral culture in human cells *in vitro*, X-ray crystallography of the crystal structure of the C-terminal domain of the SARS-CoV-2 S-protein in complex with the human ACE2 receptor (hACE2), binding affinity analyses, and antibody reactivity assays. While these tools offer significant advantages, their limitations in reproducing complete human

physiology must be acknowledged; however, they provide a clinically relevant understanding of the viral infection.

Furthermore, SARS-CoV-2 neurovascular invasion involves several steps, beginning with the recognition and adhesion of S protein to host ACE2 receptors, facilitated by TMPRSS2-mediated host and viral membrane fusion[40]. Then, viral entry occurs by clathrin-mediated endocytosis or by TMPRSS2-facilitated direct fusion. The endocytic process involves the internalization of the virus in vesicles that then fuse with endosomes. Next, viral material is released into the acidic environment, causing endosomal-viral membrane fusion and the release of viral RNA into the cytoplasm. Ultimately, viral replication and exocytosis result in epithelial disruption, inflammation, and neurovascular invasion[40].

A crucial point is that this inflammatory process and neurovascular disease may result in direct damage to ophthalmic tissue, with vascular involvement, leading to visual deficits[8]. Thus, a deep comprehension by clinicians is mandatory to ensure adequate diagnosis and treatment in patients with ophthalmic abnormalities who are infected.

Limbal Cell Infection as a Portal of Entry Notably, the SARS-CoV-2 virus exhibits remarkable tropism flexibility, with limbal cells serving as another infectious target. Eye limbal cells could undergo epithelial–mesenchymal transition (EMT) with a decrease in cell junctions, downregulation of genes that mediate normal limbus functions (KRTs, mucins, aquaporins, and tight junctions), and an increase in injury response genes as a recovery mechanism from viral infection[6]. High TMPRSS4 expression in limbal cells suggests that it may play a more critical role than TMPRSS2 in viral entry, given its high prevalence in this region[6].

In addition, ocular inflammation following SARS-CoV-2 invasion may be enhanced by NF-κB activation and reduced type I/III interferon signaling, resulting in impaired inflammatory cell recruitment and severe disease progression[6]. Thus, limbal cells serve as a crucial viral port of entry into ocular tissue. For more details, Table 1 summarizes the research evidence on viral tropism and the pathological mechanisms of SARS-CoV-2.

Clinical Relevance, Manifestations, and Diagnostics As discussed, this investigation highlights the clinical relevance of ocular involvement in SARS-CoV-2-infected patients. For instance, multiple studies have been performed regarding the clinical manifestations, signs, symptoms, and diagnoses in affected individuals.

Conjunctivitis According to Szczęśniak and Brydak-Godowska[5], SARS-CoV-2 may cause ophthalmic abnormalities in patients with severe acute respiratory syndrome, with conjunctivitis being the most prevalent finding, which aligns with the detection of viral RNA material in the patients' tear film[9]. In addition, Szczęśniak and Brydak-Godowska[5] suggest that systemic inflammation and thromboembolic complications could directly damage the cornea, retina, and ocular blood vessels.

Impact on the Retinal and Choroidal Microvasculature As demonstrated by Kal *et al*[21], SARS-CoV-2 also impacts the retinal and choroidal microvasculature, as shown in COVID-19 bilateral pneumonia-hospitalized patients using optical coherence tomography angiography (OCTA), finding decreased vessel density (VD) in the superficial capillary plexus (SCP), the deep capillary plexus (DCP), and the choriocapillaris (CC), with increased VD observed in the choriocapillaris in the foveal area (FCC). In addition, the foveal avascular zone in DCP (FAZd) was enlarged[21].

Notably, marked sex-based differences were observed, potentially affecting clinical results and accentuating the necessity for clinicians to contemplate these distinctions in their diagnosis and treatment. First, the foveal VD in SCP and DCP was decreased in women compared to men. The FAZ area in SCP (FAZs) and superior VD in the choriocapillaris (SCC) were increased in women. Additionally, Wang *et al*[41] reported that the alterations in retinal microvasculature and choroidal vessels, resulting in lower foveal VD in deep capillary plexus and thinner subfoveal choroidal thickness (SCT), may be a medium to long-term process; for instance, ophthalmic surveillance in such individuals is necessary.

Obviously, the changes in VD have several structure-specific implications. First, decreased VD in the SCP reduces oxygenation in the retinal ganglion cell layer, causing loss of central and peripheral vision, visual acuity defects, and a predisposition to optic neuropathy[10-11]. Additionally, decreased VD of the DCP reduces oxygen supply to the inner nuclear layer of the retina and bipolar neurons, thereby damaging contrast perception and color sensitivity, and may progress to macular edema or retinal ischemia[10-11]. Additionally, decreased VD of the CC lowers blood flow to the outermost layer of the retina (pigmentary epithelium and photoreceptors), affecting regeneration of photoreceptors, contributing to macular degeneration or progressive impairment of night vision[10-11]. Moreover, the rise in FCC VD increases blood flow in the fovea, triggering inflammatory or compensatory processes that can lead to choroidal neovascularization, ultimately resulting in macular edema or subretinal hemorrhages[10-11]. Finally, the enlarged FAZd expands the area without blood vessels in the fovea, reducing the supply of oxygen and nutrients to the foveal cones, producing visual acuity reduction, difficulty in reading or seeing fine details, progression to macular ischemia, or even foveal atrophy in severe cases[10-11].

Retinopathy Addressing the retinal abnormalities, Schnichels *et al*[42] reported that high ACE2 and TMPRSS2

expression in retinal and ocular tissues renders them highly susceptible to SARS-CoV-2 ocular involvement. Also, neuropilin-1 (NRP-1) interacts with SARS-CoV-2, resulting in angiogenesis, neuronal development, and regulation of immune responses[43]. NRP-1 facilitates the virus entry into the central nervous system through the olfactory epithelium of the nasal cavity, increasing the viral spread and infection, causing pathological changes in the human eye, specifically the retina, among other neurological manifestations[42].

Expanding the previous information, Kennedy *et al*[20] mention that SARS-CoV-2 retinopathy is characterized by hyperreflective lesions within the ganglion cell and inner plexiform layers, flame-shaped hemorrhages with ischemic patterns and microvascular derangement lesions including cotton-wool spots, retinal sectorial pallor, intraretinal hemorrhages, hard exudates, paracentral acute middle maculopathy, AMN, or retinal vein occlusions[44-45]; thus, Figure 2 illustrates the hallmarks of such retinopathy. Conversely, in convalescent patients, there were isolated cotton-wool spots with or without retinal hemorrhage, with no other retinal abnormality, and no visual symptoms, insinuating a potential relationship between ocular manifestations and the disease severity of infected patients[46-51].

Importantly, there are more pathological abnormalities in infected patients, as Abdolrahimzadeh *et al*[12] mention peripapillary, macular retinal nerve fiber layer (mRNFL), and ganglion cell layer thickness alterations, which were observed using spectral domain optical coherence tomography (OCT). Also, Pan *et al*[8] proposed that genetically predisposed patients to COVID-19 infection have a higher risk of mRNFL and macular ganglion cell-inner plexiform layer (mGCIPL) thickness changes *via* the previously mentioned viral neurovascular invasion.

Age-Related Macular Degeneration Furthermore, SARS-CoV-2 could be related to age-related macular degeneration (AMD) because SARS-CoV-2 S protein promotes retinal pigment epithelium (RPE) cell senescence *via* the reactive oxygen species (ROS)/tumor protein p53 (P53)/cyclin-dependent kinase inhibitor 1A (P21) pathway, inducing cellular senescence of ARPE-19 cells *in vitro* and expression of senescence-associated cytokines in zebrafish retina *in vivo*, likely by activating endoplasmic reticulum (ER) stress, ROS, and NF-κB. This results in inflammation and a potential association between SARS-CoV-2 and development of AMD[20]. Another outlook is that the alterations of the retina could be accompanied by pathological abnormalities in the optic nerve, like anterior and posterior non-arteritic ischemic optic neuropathy, optic neuritis, central or branch vascular occlusion, paracentral acute middle maculopathy, neuroretinitis, as well as concomitant diagnoses such as possible Vogt-Koyanagi-Harada disease, among others[44,52].

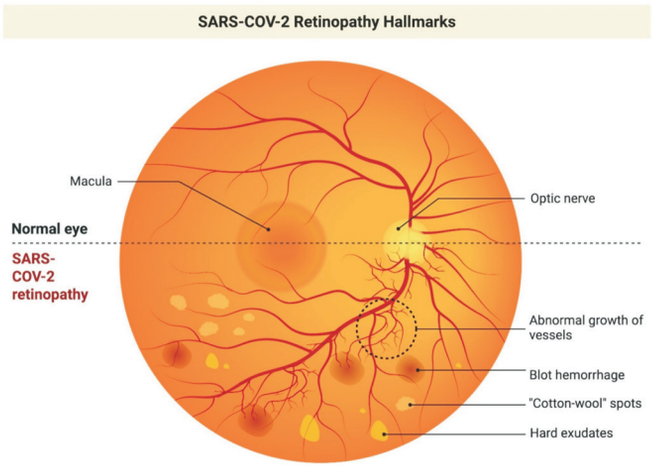

Figure 2 SARS-CoV-2 retinopathy hallmarks SARS-CoV-2 infection can cause several retinopathy hallmarks, such as abnormal blood vessels, hemorrhages, cotton-wool spots, and hard exudates. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Created in https://BioRender.com.

Similarities with Other Viruses of the Same Family Notably, equivalent ocular abnormalities have been documented with other coronaviruses in animal and human models, which is particularly interesting because it can provide valuable insights into the infection based on the viral family history. Kennedy *et al*[20] and Abdul-Kadir and Lim[9] report that the murine hepatitis coronavirus (MHV) can cause retinal vasculitis, degeneration, demyelination, and optic neuritis in mice. Also, Kennedy *et al*[20] and Abdul-Kadir and Lim[9] say that feline coronavirus (FCoV) causes pyogranulomatous inflammation and phlebitis in the uvea, sclera, conjunctiva, retina, and optic nerve, choroiditis with retinal detachment and retinal vasculitis in cats. Finally, HCoV-NL63 can cause conjunctivitis in humans[30]. These concepts support the idea that the similarities between SARS-CoV-2 virus and coronaviruses may result in relevant clinical characteristics in infected hosts. Thus, Table 2 summarizes the most prevalent SARS-CoV-2 ocular manifestations[3,5,9,53-57].

TREATMENT

Treatment of the Viral Infection After establishing the clinical ocular manifestations of SARS-CoV-2 patients, therapeutic options must focus on systemic viral infection management to achieve adequate ophthalmic treatment. Additionally, such treatment relies on pharmacological and non-pharmacological strategies. Non-pharmacological strategies are applied as needed, in conjunction with hemodynamic therapies, such as intravenous fluid therapy. Additionally, oxygen therapy includes high-flow nasal cannula, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). However, there are three primary pharmacological strategies: antivirals, glucocorticoids, and immunosuppressants[58-60].

Table 2 Known prevalent SARS-CoV-2 ocular manifestations

Target host receptor	Ocular manifestation	Cellular/tissue target
ACE2	Conjunctival hyperaemia, chemosis, and secretions	Corneal epithelial cell
	Epiphora, eyelid oedema, tarsal pseudomembranous	Conjunctival epithelial cells
	Eye discomfort, follicular and haemorrhagic conjunctivitis	RPE
	Photophobia, superficial punctate keratitis	Müller cells
	Corneal epithelial defect, subepithelial infiltrates	Endothelial cells of the retinal vasculature
	Pseudodendrite, dry eyes	Ciliary body epithelium
	Asymptomatic retinal lesions, cotton-wool spots, and retinal microhemorrhages	Choroidal vascular endothelial cells
CTSL, CD147	Retinopathy, keratitis, conjunctivitis	RPE cells, conjunctival and corneal epithelial cells
BSG, AGTR2	Conjunctivitis, keratitis, corneal inflammation	Corneal and conjunctival epithelial cells, retinal cells
TMPRSS2, ANPEP, PIGR,	Conjunctivitis, conjunctival inflammation	Conjunctival cells, corneal tissue
DPP4	Uveitis, keratoconjunctivitis	Retinal endothelial cells, uveal tissue, conjunctival cells, corneal tissue
PDGFRα (ADGFR1)	Ocular surface inflammation, conjunctivitis	Conjunctival cells

ACE2: Angiotensin-converting enzyme 2; CTSL: Cathepsin L; CD147: Cluster of differentiation 147; BSG: Basigin; AGTR2: Angiotensin II receptor type 2; TMPRSS2: Transmembrane protease serine 2; ANPEP: Alanyl aminopeptidase N; PIGR: Polymeric immunoglobulin receptor; DPP4: Dipeptidyl peptidase 4; PDGFRα/ADGFR1: Platelet-derived growth factor receptor alpha; RPE: Retinal pigment epithelium.

Besides, the antivirals with evidence of effectiveness and widely used are remdesivir (ATP analog) and molnupiravir (beta-D-N4-hydroxycytidine), both being RNA dependent RNA polymerase (RdRp) inhibitors of the virus, resulting in the decrease of the viral RNA production and future survival/replication. In addition, dexamethasone is the most used glucocorticoid in these cases, and the implementation of immunosuppressants such as baricitinib or tocilizumab improves the patients' health and outcome because of the decrease in the exacerbated inflammatory response[61].

Conjunctivitis Treatment Meanwhile, Muto *et al*[13] established that the viral conjunctivitis treatment is aimed at symptomatic relief, including lubrication with artificial tears, use of cool compresses, peeling of membrane or pseudomembrane if present with jeweler's forceps or a cotton swab soaked with topical anesthetic, use of topical NSAID (ibuprofen), and use of topical steroids (fluorometholone acetate, prednisolone acetate 1%, dexamethasone 0.1%) in patients with decreased vision due to their subepithelial infiltrates or severe conjunctival injection causing more discomfort.

Microvascular Abnormalities and Retinopathy Treatment Furthermore, treating retinal microvascular abnormalities is crucial, as they are prevalent in SARS-CoV-2 patients and have several clinical implications. Such microvascular retinopathies, as described by Reddy *et al*[15] and Sinclair and Schwartz[16], are treated by addressing the leading cause. Then, several strategies are implemented to treat the retinopathies. First, anti-VEGF drugs such as bevacizumab and ranibizumab target AMD, macular edema following retinal vein occlusion, improve visual acuity, and reduce retinal thickness due to edema.

Besides, several drugs are being studied and tested for their use, as illustrated in Table 3. These therapies have several targets: decreasing macular thickness, improving visual acuity, reducing leukostasis and retinal vascular leakage, protecting blood-retinal barrier integrity, inhibiting retinal neovascularization, regulating the formation of abnormal blood vessels in the retina, reducing vascular leakage, and protecting against loss of retinal ganglion cells. Finally, another target is the reduction of retinal inflammation, oxidative stress, VEGF production, and capillary degeneration[15].

Furthermore, several studies performed by Reddy *et al*[15] and Sinclair and Schwartz[16] suggest that other non-pharmacological therapies such as retinal photocoagulation, accomplished by xenon arc or laser applications, surgical therapy (enucleation), sclerotherapy (laser therapy or cryotherapy), and micropulsed laser therapy are used to treat and prevent the vision-destructive complications in severe cases of retinopathy. Therapeutic choices depend on the patient's clinical state and evolution. Regarding conjunctivitis, treatment focuses on symptom relief.

Remarkably, retinopathy treatment criteria depend directly on the disease stage. In mild non-proliferative retinopathy, the therapeutic actions are strict control of the underlying cause (SARS-CoV-2 infection) and ophthalmologic monitoring[62-63]. In moderate non-proliferative retinopathy, the therapy is based on the application of anti-VEGF drugs (bevacizumab, ranibizumab, among others) if there is macular edema. Also, focal laser photocoagulation could be used if there is significant retinal ischemia[62-63]. In cases of severe non-proliferative retinopathy, anti-VEGF drugs are also used if edema is present; thus, panretinal photocoagulation can be performed to minimize the risk of progression to proliferative retinopathy[62-63].

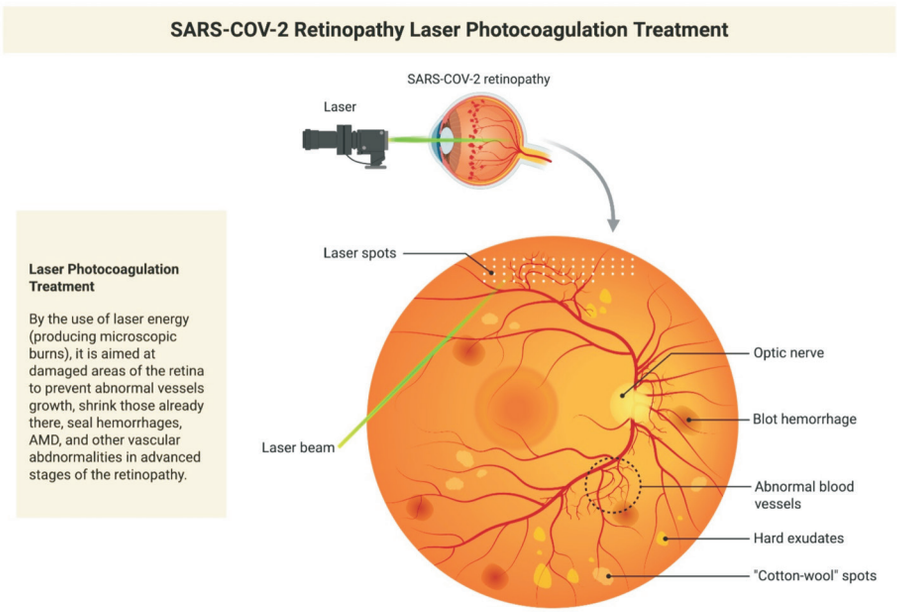

Figure 3 SARS-CoV-2 retinopathy laser photocoagulation treatment Laser photocoagulation is a therapeutic intervention done to counteract SARS-CoV-2 retinopathy pathological abnormalities. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Created in https://BioRender.com.

Table 3 Investigational therapies for SARS-CoV-2-associated microvascular retinopathies[16]

Therapeutic goal	Drug used	Molecular target
Decrease macular thickness and improve visual acuity	Infliximab	TNF-α
Reduce leukostasis and retinal vascular leakage	SAR 1118	LFA-1 antagonist
Reduction of retinopathy progression	Losartan	AT1R blocker–RAS
Reduction of retinopathy progression	Enalapril	ACEI
Inhibition of retinal neovascularization and regulation of abnormal retinal blood vessel formation	miR-182-5p	Angiogenin and BDNF
Stabilization of blood vessels and reduction of vascular leakage	ANGPTL4	ANGPTL4 protein
Protection against retinal ganglion cell loss	Syn3	BDNF enhancer
Action against retinal inflammation and vascular impairment	Anti-IL17A	IL-17A
Protection of blood-retina barrier integrity and prevention of neovascularization	UPARANT	uPAR-derived peptide inhibitor
Reduction of retinal inflammation, oxidative stress, VEGF production, capillary degeneration, and vascular leakage	XMD8-92 {2-[2-Ethoxy-4-(4-hydroxy-1-piperidinyl)-5,11-dihydro-5,11-dimethyl-6H-pyrimido[4,5-b][1,4]benzodiazepin-6-one]}	ERK5

VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-alpha; LFA-1: Lymphocyte function-associated antigen-1; AT1R: Angiotensin II type 1 receptor; RAS: Renin-angiotensin system; ACEI: Angiotensin-converting enzyme inhibitor; BDNF: Brain-derived neurotrophic factor; IL-17A: Interleukin-17A; uPAR: Urokinase plasminogen activator receptor; ERK5: Extracellular signal-regulated kinase 5.

Regarding more severe pathology, the treatment for proliferative retinopathy is based on anti-VEGF drugs to reduce neovascularization and panretinal photocoagulation to eliminate angiogenic stimuli. Additionally, if persistent vitreous hemorrhage or retinal detachment occurs, pars plana vitrectomy is recommended[64-65]. Finally, if there is advanced or end-stage retinopathy and vitreous hemorrhage or retinal detachment, urgent vitrectomy must be performed. Also, intraocular endolaser therapy or cryotherapy can resolve cases of severe ischemia. As a consequence, visual rehabilitation and pain management might be necessary in terminal cases[62-63]. For more details, refer to Figure 3, which illustrates the therapeutic processes mentioned earlier.

Long-term Ocular Sequelae of Viral Infection of SARS-CoV-2 Furthermore, beyond clinical oversight, it is crucial to consider the potential sequelae of the disease. For instance, retinal microvascular abnormalities are some of the most severe complications and sequelae in patients. Retinal microvascular abnormalities increase the risk of total stroke and MRI-defined subclinical cerebral infarcts independent of stroke risk factors[64-65]. In addition, retinopathy complications include partial or complete vision loss, retinal hemorrhage, retinal detachment, and retinal holes. For instance, SARS-CoV-2-related retinopathy should be promptly treated to prevent further complications and preserve patients' health and quality of life[66-67].

CONCLUSIONS AND FUTURE PERSPECTIVES

As demonstrated, this study provides compelling evidence that multiple SARS-CoV-2 structural and non-structural proteins orchestrate key mechanisms underlying viral entry, replication, immune evasion, host cell immunological reaction, and ocular inflammation through their tropism and activity in ophthalmic tissues. Therefore, proposing an appropiate diagnostic method supported by clinical findings, is crucial for infected patients with ocular abnormalities. Such diagnostic screening is based on imaging studies, such as fluorescein angiography and OCT, in conjunction with molecular techniques, including polymerase chain reaction (PCR), to enhance diagnostic specificity.

For instance, several recommendations have been proposed for appropriate diagnosis of ocular abnormalities in SARS-CoV-2 patients. First, fluorescein angiography is a crucial diagnostic method that uses a fluorescent dye to visualize retinal and choroidal circulation, whose alterations are pivotal for the development of retinopathy and other ocular pathologies. Consequently, this tool is crucial for detecting vascular alterations, inflammation, and hemorrhages associated with COVID-19. Additionally, it allows early identification of retinal complications in immunocompromised and chronic patients, enabling timely intervention[68].

Additionally, OCT is a tool that provides high-resolution images of retinal layers, detecting SARS-CoV-2-related structural changes, which is particularly useful for monitoring chronic disease progression and treatment response. In COVID-19 patients, OCT has been used to identify macular edema, hemorrhages, and other retinal alterations caused by the virus[69]. Moreover, molecular diagnosis is as important as imaging; with nucleic acid amplification, like PCR, being crucial to detect viral RNA in ocular secretions, confirming the etiology of SARS-CoV-2 conjunctivitis. In immunocompromised patients, accurate identification of the causative agent is vital for initiating appropriate treatment and preventing viral spread and serious complications[68-69].

Additionally, the retinal tropism of SARS-CoV-2 has been widely investigated to clarify ocular involvement and enhance diagnostic and treatment strategies. Combining fluorescein angiography, OCT, and nucleic acid amplification represents a comprehensive approach to addressing COVID-19 ocular complications[68-69].

Finally, SARS-CoV-2 infection in humans has several systemic implications beyond respiratory involvement, with ocular abnormalities proven subjects of study, representing significant health complications in moderate to severe cases, as retinopathy and the mechanisms involved: viral tropism, entry mechanisms, susceptible populations, clinical manifestations, diagnostic tools, and potential therapies.

As demonstrated in the previous data collection, these key points are essential for proper patient care and health preservation. Of course, further studies should be performed to broaden understanding of the aforementioned pathological process, emphasizing to the scientific community to need to focus on this topic due to its global clinical importance.

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