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Vitreoretinal abnormalities in corona virus disease 2019 patients: What we know so far

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Abstract

The coronavirus disease 2019 (COVID-19) has become a global pandemic since December 2019. Although COVID-19 primarily affects the respiratory systems, it has become abundantly clear that it involves multiple organs including the heart, kidney, skin, and brain. Neuro-ophthalmic signs and anterior segment inflammation of the eyes were documented in COVID-19 patients recently. Small but growing number of literatures has also reported the cases of new onset vitreoretinal disorders related to COVID-19 infection. A comprehensive search from four online databases was done. Findings show vitreoretinal involvement in COVID-19 patients including the central retinal vein occlusion, central retinal artery occlusion, reactivation of previous uveitis, chorioretinitis, macular hemorrhage, acute macular neuroretinopathy, paracentral acute middle maculopathy, vitritis with outer retinal abnormalities, varicella zoster virus-related acute retinal necrosis in immunocompromised patient, and other posterior segment pathological changes. The hypotheses for potential pathogenesis of these manifestations are direct viral ocular infection and thromboembolic complications secondary to the hyperinflammatory response. This is the first review article, which provides an overview of current evidence regarding the vitreoretinal manifestations in COVID-19 patients.

Keywords: COVID-19, funduscopy, posterior segment, SARS-CoV-2, vitreoretinal abnormalities

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) occurred in December 2019 and started in Wuhan, China.[1,2] COVID-19 is caused by single-stranded RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 can be transmitted through respiratory droplets. Clinically, coronavirus manifests as common cold, but it also could cause bronchitis, pneumonia, severe acute respiratory distress syndrome, multiorgan failure, or even lead to death.[3,4] Symptoms of COVID-19 are nonspecific including fever, nonproductive cough, myalgia, and fatigue. Less common symptoms are headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting. It has been reported

that COVID-19 can have several organ-specific involvements. Lung manifestations include diffuse pulmonary intravascular coagulopathy, silent hypoxia, and acute respiratory distress syndrome. Renal involvements range from mild proteinuria to severe acute kidney injury. Hematological involvements consist of blood count abnormalities and coagulopathy. Cutaneous manifestations include direct skin lesion and underlying vasculopathy. Neurological features comprise inflammation of the brain, cerebrovascular events, and encephalopathy. Finally, the cardiovascular involvements consist of Kawasaki-like syndrome, acute myocardial infarction, and decompensated heart failure.[3,5]

A number of studies have reported the ophthalmic signs associated with COVID-19 infection. A significant number of patients infected with COVID-19 experienced conjunctival congestion, chemosis, epiphora, and watery discharge, presenting similar classic features of conjunctivitis caused by the other viral forms. Several reports also mentioned the existence of SARS-CoV-2 RNA in the tears and conjunctival secretion of the infected patients, suggesting the possibility of ocular surface as the portal entry for the viral transmission.[6,7,8,9,10,11] Furthermore, new onset neuro-ophthalmic diseases in COVID-19 patients have also been documented in the literature recently including Miller Fisher syndrome,[9,10] isolated cranial nerve palsies,[11,12] ocular myasthenia gravis,[13] neuromyelitis optic spectrum disorder,[14] and Adie's syndrome.[15]

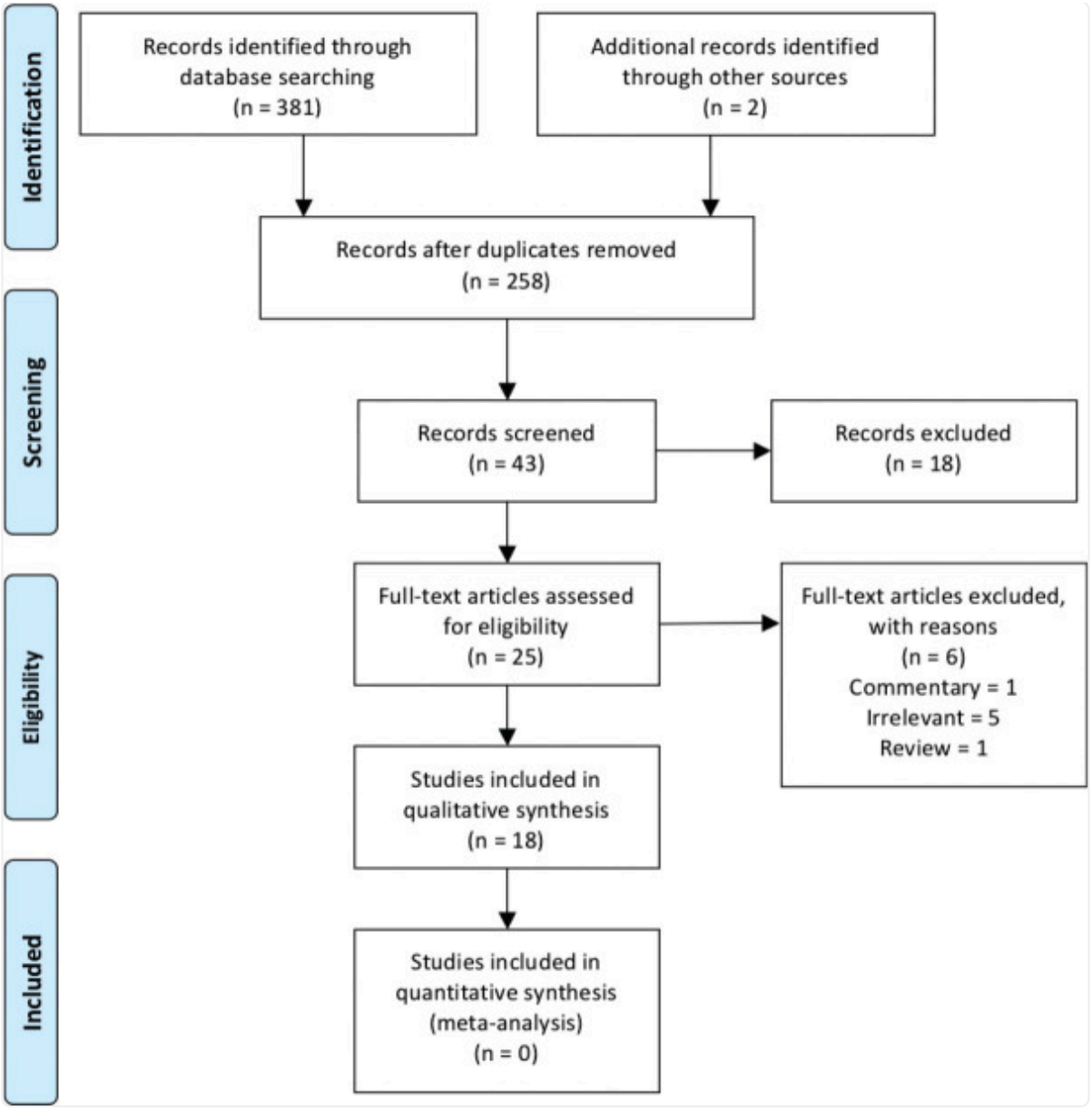
Given the ability of SARS-CoV-2 to cause neuro-ophthalmic manifestations and anterior segment inflammation of the eye, the possibility of the virus to manifest into vitreoretinal disorders should also be considered. Limited number of studies described the new onset vitreoretinal disorders in patients with COVID-19. This review article aims to gather the information regarding the vitreoretinal manifestations of COVID-19 patients that have been documented in the literature so far. To date, this is the first review article specifically evaluating this particular issue.

Methods

A systematic search of four databases including PubMed, Scopus, EBSCO, and Cochrane was performed on December 3, 2020 by two independent investigators. The following keywords were used “vitreoretina,” “retina,” “posterior segment,” “COVID-19,” “SARS-CoV-2,” and “coronavirus,” either individually or in combination. A manual search of relevant articles from reference lists was also conducted. Two investigators independently reviewed the title, abstracts, and full texts of the studies. The results were limited to original studies published in the English language and conducted on human subjects. Further narrowing of search results was conducted using the appropriate inclusion and exclusion criteria, as follows: Inclusion criteria were (i) original studies evaluating vitreoretinal manifestations in COVID-19 patients. Exclusion criteria were (i) studies evaluating other ocular manifestations in COVID-19 patients and (ii) review article.

The study selection PRISMA flow diagram can be seen in Figure 1. A total of 258 titles were screened for eligibility, whereas only 43 papers were suitable for abstract screening. After excluding another 18 abstracts with irrelevant topics, 25 full text papers were assessed, with seven papers excluded with reasons as follows: one review article, one commentary paper, and five papers with irrelevant subject (one paper discussing the retinal biopsy in deceased COVID-19 patient, two papers with the absence of vitreoretinal findings in COVID-19 patients, and two papers evaluating the quantitative OCT imaging in COVID-19 patients). Eighteen studies were included in the data synthesis. The following variables were extracted from the included studies: name of the first author, year of publication, country of origin, study design, number of patients, gender, age, duration between COVID-19 symptoms/diagnosis and ophthalmic symptoms, systemic condition, severity of COVID-19 diagnosis, ocular signs and symptoms, vitreoretinal abnormalities, management, and outcomes. COVID-19 disease severity was graded as mild, moderate, or severe according to WHO COVID-19 clinical management guideline.[16]

Figure 1.



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PRISMA diagram for study selection process. Meta-analysis was not performed due to the nature of the studies included

Vitreoretinal Abnormalities in COVID-19 Patients

Currently, it is challenging to provide information regarding the prevalence of vitreoretinal abnormalities in COVID-19 patients. Limited reports regarding this topic have been published, as detailed in Table 1. A total of 14 case reports, two cross-sectional studies, and two prospective cohorts were included. Consequently, COVID-19 has been associated with several vitreoretinal abnormalities including central retinal vein occlusion (CRVO),[19,22,23,30,32] central retinal artery occlusion (CRAO),[17] serpiginous choroiditis,[29]

chorioretinitis,[28] macular hemorrhage,[18] acute macular neuroretinopathy (AMN),[22,32] paracentral acute middle maculopathy (PAMM),[22,32] vitritis,[19] acute retinal necrosis (ARN),[21] and posterior segment anatomical changes[24,26,27,28,30] Summary of patients' ocular manifestations were listed in [Table 2].

Table 1.

Patients' baseline characteristics and COVID-19 systemic manifestations

Study	Design	Country	Number of patient (s)	Gender	Age	COVID-19 systemic manifestation (s)	COVID-19 severity
Acharya *et al*., 2020[17]	Case report	USA	1	Male	60	Fever, cough, acute respiratory distress syndrome	Severe
D'Aloisio *et al*., 2020[18]	Case report	Italy	1	Male	46	Fever, cough, acute respiratory distress syndrome	Severe
Filho *et al*., 2020[19]	Case report	Brazil	1	Female	57	Fever, cough, asthenia, anosmia	Mild
Gaba *et al*., 2020[20]	Case report	United Arab Emirates	1s	Male	40	Shortness of breath, fever, cough (severe pneumonia), pain in right calf (deep vein thrombosis in right femoral vein)	Severe
Gupta *et al*., 2020[21]	Case report	United Kingdom	1	Female	75	Persistent cough	Mild
Gascon *et al*., 2020[22]	Case report	France	1	Male	53	None	Mild
Insausti-García *et al*., 2020[23]	Case report	Spain	1	Male	40	Fever, cough, myalgia	Mild

Study	Design	Country	Number of patient (s)	Gender	Age	COVID-19 systemic manifestation (s)	COVID-19 severity
Invernizzi *et al*., 2020[24]	Case report	Italy	1	Female	54	Fever, cough, myalgia	Mild
Invernizzi *et al*., 2020[25]	Cross-sectional	Italy	54 in total 15 with ocular symptoms and 37 with funduscopic abnormalities	16 female, 38 male	49.9±15.6	Fever (50), cough (41), pneumonia (45), deep vein thrombosis (1)	Mild, moderate, severe
Landecho *et al*., 2020[26]	Prospective cohort	Spain	27 in total 6 with funduscopic abnormalities	13 female, 20 male	N/A	Fever, cough (pneumonia)	Mild, moderate
Marinho *et al*., 2020[27]	Prospective cohort	Brazil	12	6 female, 6 male	25-69	Fever, asthenia, dyspnea, anosmia	Mild, moderate, severe
Ortiz-Seller *et al*., 2020[15]	Case report	Spain	1	Female	51	Fever, dry cough, fatigue, headache	Mild
Pereira *et al*., 2020[28]	Cross-sectional	Brazil	18 in total 10 with funduscopic abnormalities	2 female, 8 male	62.5 (12)	Fever, cough (pneumonia), acute respiratory distress syndrome	Severe
Providência *et al*., 2020[29]	Case report	Portugal	1	Female	41	Anosmia, hypogeusia, headache	Mild
Ruiz-Medrano *et al*., 2020[30]	Case report	Spain	1	Male	42	Ageusia	Mild
Sheth *et al*., 2020[31]	Case report	India	1	Male	52	N/A	N/A
Virgo and Mohamed *et al*., 2020[32]	Case report	United Kingdom	1	1 female, 1 male	37 and 32	Fever, cough, and anosmia	Mild
Walinjkar *et al*., 2020[33]	Case report	India	1	Female	17	Fever, cough	Mild

N/A=Not available, COVID-19=Corona virus disease 2019

Table 2.

Vitreoretinal abnormalities in patients with COVID-19 infection

Study	Duration between COVID-19 symptoms/diagnosis and ocular symptoms (days)	Ocular signs and symptoms	Vitreoretinal abnormalities	Management	Outc
Acharya *et al*., 2020[17]	12	Acute vision loss of the right eye	CRAO	N/A	N/A
D'Aloisio *et al*., 2020[18]	12	Acute vision loss of the left eye	Bilateral macular hemorrhages (beneath the internal limiting membrane)	None given	1 mo visua and abno reso
Filho *et al*., 2020[19]	12	Redness in both eyes	Vitritis, hyperreflective lesions of IPL and GCL, and disruption of outer retina layer (suggestive of/AZOOR)	N/A	2 mo visua and abno impr
Gaba *et al*., 2020[20]	4	Acute vision loss of both eyes	CRVO	Low molecular weight heparin, rivaroxaban injection (2×15 mg for 21 days and 1×20 mg for 3 months)	2 we com reso
Gupta *et al*., 2020[21]	Presented with ocular symptoms	Floaters and reduced vision of the left eye	VZV-related panuveitis with vitritis and extensive peripheral and mid-peripheral necrotitsing retinitis	Foscarnet injection 2.4 mg/0.1 ml, valganciclovir 2×900 mg - changed to valaciclovir 3×1 g	2 mo OCT abno impr
Gascon *et al*., 2020[22]	Presented with ocular symptoms	Acute vision loss, negative scotoma,	Acute macular neuroretinopathy	N/A	2 we visua

Study	Duration between COVID-19 symptoms/diagnosis and ocular symptoms (days)	Ocular signs and symptoms	Vitreoretinal abnormalities	Management	Outc
		and dyschromatopsis of the left eye	and paracentral acute middle maculopathy		and abnc reso
Insausti-García *et al*., 2020[23]	42	Decrease contrast sensitivity of the left eye	Papillophlebitis	Sustained release dexametasone implant intravitreal	2 we visu impr
Invernizzi *et al*., 2020[24]	9	Multiple violet scotoma of the right eye	CRVO	Oral prednisolone 60 mg/day for 3 days then reduced to 30 mg/day	1 we com reso
Invernizzi *et al*., 2020[25]		Near vision difficulties, redness, burning sensation, and photobia	Other posterior segment pathological changes: Retinal haemorrhages, retinal nerve fiber layer infarction, stasis retinopathy	N/A	N/A
Landecho *et al*., 2020[26]	N/A	None	Other posterior segment pathological changes: Retinal nerve fiber layer infarction	N/A	N/A
Marinho *et al*., 2020[27]	11-33	None	Other posterior segment pathological changes: Retinal nerve fiber layer infarction, micro-retinal hemorrhage, hyper-reflective lesions at the level of GCL and IPL	N/A	N/A
Ortiz-Seller *et al*., 2020[15]	2	Retroocular pain and near vision difficulty	Chorioretinitis (suggestive of/APMPPE) and Adie's syndrome	Oral prednisone 60 mg/day	1 we symp visu and abnc reso

Study	Duration between COVID-19 symptoms/diagnosis and ocular symptoms (days)	Ocular signs and symptoms	Vitreoretinal abnormalities	Management	Outc
Pereira *et al.*, 2020[28]		None	Other posterior segment pathological changes: Flamed-shaped haemorrhages, retinal nerve fiber layer infarction, acute retinal ischemia, peripheral retinal haemorrhages, and macular haemorrhages	N/A	N/A
Providência *et al.*, 2020[29]	28	Reduced vision of the left eye	Reactivation of previously diagnosed serpiginous choroiditis	Methylprednisolone injection 1 g/day for 3 days and methotrexate 12.5 mg weekly	1 mo activ and acuit impr
Ruiz-Medrano *et al.*, 2020[30]	21	Temporal relative scotoma of the left eye	Other posterior segment pathological changes: Hyper-reflective lesions at the level of GCL and IPL	None given	1 mo symp pers OCT abno wors
Sheth *et al.*, 2020[31]	10	Reduced vision of the left eye	Vasculitic RVO	Oral methylprendisolone 40 mg/day and intravitreal ranibizumab 0.5 mg/0.05 ml	1 mo visua OCT abno reso
Virgo and Mohamed *et al.*, 2020[32]	35 and 16	Paracentral scotoma of the left eye	Paracentral acute middle maculopathy and acute macular neuroretinopathy	N/A	N/A
Walinjkar *et al.*, 2020[33]	21	Acute vision loss of the right eye	CRVO	3 doses intravitreal ranibizumab	3 mo visua impr to 6/

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N/A=Not available, COVID-19=Corona virus disease 2019, CRVO=Central retinal vein occlusion, RVO=Retinal vein occlusion, IPL=Inner plexiform layers, GCL=Ganglion cell layers, AZOOR=Acute zonal occult outer retinopathy, APMPPE=Acute posterior multifocal placoid pigment epitheliopathy, CRAO=Central retinal artery occlusion, VZV=Varicella zoster virus, OCT=Optical coherence tomography

Central Retinal Vein Occlusion

CRVO was one of the most common vitreoretinal disorders reported in COVID-19 patients. *Walinjkar et al*.[33] demonstrated a case of a 17-year-old girl with chief complaint of decrease vision in the right eye for 2 days before hospital admission. On eye examination, her right BCVA was 6/24, N24 and her left BCVA was 6/6. Funduscopic examination revealed disc swelling accompanied with splinter hemorrhages and multiple flame-shaped hemorrhages in all quadrants. The optical coherence tomography (OCT) result showed neurosensory detachment and cystoid macular edema. Patient's chest computed tomography (CT) scans revealed ground-glass appearance indicating COVID-19. The reverse transcription-polymerase chain reaction (RT-PCR) testing was negative in this case. The patient was suggestive of COVID-19 past infection due to the positive immunoglobulin G (IgG) result in the immunoglobulin test.

There was another CRVO case with positive confirmation of COVID-19. Invernizzi *et al*.[24] reported a case of a 54 year-old female tested positive for COVID-19, with complaints of reduced vision and scotomas in her right eye for 3 days prior. Eye examination showed visual acuity of 20/40 in the right eye and 20/20 in the left eye. Funduscopic findings were consistent with impending CRVO, which were retinal hemorrhages, diffuse fern-like retinal whitening, and increased venular tortuosity. In addition, the result of spectral domain OCT (SD-OCT), auto fluorescence (AF), and fundus fluorescein angiography (FFA) examination confirmed this diagnosis.

Another case of CRVO was reported by Gaba *et al*.[20] A male aged 40 years old presented with blurred vision on both eyes after being admitted for 1 day. The patient was tested positive for COVID-19 through RT-PCR of the nasopharyngeal swab. In addition, the patient also had deep vein thrombosis and possible pulmonary embolism. Visual acuity was 6/9 and 6/18 in the right and left eye, respectively. Funduscopic examination showed dilated tortuous veins, cotton wool spots, dot and blot intraretinal hemorrhages, and optic disc edema on both eyes. These findings concluded CRVO on both eyes.

Sheth *et al*.[31] reported a case of a 52-year-old male tested positive for COVID-19, who came with reduced vision in the left eye. Patient's visual acuity was 6/60 and 6/6 in the left

and right eye, respectively. His left eye had inferior hemiretinal vein occlusion with superonasal branch retinal vein occlusion, alongside with macular edema. The FFA showed significant taining and leakage in late phase, which was suggestive of phlebitis. Further multimodal imaging including OCT and AF was also in line. This patient was diagnosed with vasculitic retinal vein oclusion.

Papillophlebitis, a variant of CRVO, which occurred in patient with no history of vascular disorder, was also reported in COVID-19 patient. Garcia *et al*.[23] demonstrated a case of a 40-year-old man, who presented with reduced contrast sensitivity of his left vision. Visual acuity was normal bilaterally. Left eye funduscopy revealed optic disc edema, accompanied with tortuous and dilated veins, cotton-wool spots, and superficial hemorrhages in all quadrants. Visual field test confirmed decreased contrast sensitivity that was diffuse, with mild central scotoma and rise in the blind spot. OCT revealed papillary edema. The patient was diagnosed with papillophlebitis. The patient was tested positive for SARS-CoV-2 antibodies (IgG and IgM).

Central Retinal Artery Occlusion

CRAO is an ophthalmic emergency, which could be associated with the spectrum of thromboembolic events in COVID-19. Acharya *et al*.[17] demonstrated a case of a 60-year-old male, who presented with sudden complaint of painless vision loss in the right eye after being diagnosed with pneumonia. The patient was tested positive for SARS-CoV-2 by PCR and was admitted to the intensive care unit (ICU) for several days. The neurological examination showed irresponsive pupillary reflex an accommodation reflex of the right eye. The CT imaging of the head showed no sign of infarct. The posterior segment examination showed indistinct margin of the right optic nerve and a cherry red spot with retinal whitening, suggestive of a CRAO.

Serpiginous Choroiditis and Chorioretinitis

SARS-CoV-2 infection was proposed to have played role in initiating choroidal inflammation. A case report by Providencia *et al*.[29] described a case of a 41-year-old woman with blurred vision in the left eye 1 month following a mild COVID-19 infection. At the time of examination, the patient was already considered cured for COVID-19 as she was tested negative for PCR tests 2 weeks following the COVID-19 diagnosis. On examination, the visual acuity of the left eye was counting fingers at 2 m. The left eye fundus examination was consistent with her older lesions, showing multiple peripapillary atrophic lesions, alongside a diffuse, yellow-whitish patch in the peripapillary and foveal region. Further multimodal imaging including OCT, FF, and angiography was also suggestive of serpiginous choroiditis, which were already present in 2016. The patient was tested negative for Tuberculosis workup. This suggested the possibility of serpiginous choroiditis reactivation in the patient,

which was mediated by SARS-CoV-2 infection. The lesion was shown to be responsive to high-dose corticosteroid.

Another case report by Ortiz-Seller *et al*.[15] demonstrated the case of a 51-year-old woman with ocular pain and reading difficulty. The BCVA was 20/25 in both eyes with abnormal pupillary response consistent with bilateral Adie tonic pupil. The funduscopic examination demonstrated multiple bilateral white-yellowish placoid lesions in the posterior pole and midperipheral retina. Ultra-wide-field fundus autofluorescence and OCT-A revealed ischemic areas at the level of choriocapillary layers, with EZ and IZ disruption and hyperreflectivity of the outer retinal layers as shown in SD-OCT. These findings were consistent with the presentation of inflammatory chorioretinal disease, especially acute posterior multifocal placoid pigment epitheliopathy/APMPPE. The patient was tested negative for sarcoidosis, syphilis, and tuberculosis. The patient was tested positive for SARS-CoV-2 infection through RT-PCR of the nasopharyngeal swab.

Macular Hemorrhage

A case of macular hemorrhage with positive confirmation of COVID-19 was reported by D'Aloisio *et al*.[18] A 46-year-old African male was treated in the ICU due to respiratory failure and vision loss in the left eye. RT-PCR on nasopharyngeal swab confirmed COVID-19 infection. The patient had a history of hereditary spherocytosis with chronic hemolytic anemia. Patient's visual acuity was 20/20 and 20/70 in his right and left eye, respectively. There were some bilateral hemorrhages from fundus examination, involving parafoveal and foveal. SD-OCT revealed hemorrhages under the internal limiting membrane bilaterally, resulting in the left foveal dip to be obliterated. No treatment was given and the hemorrhage improved within 1 month with visual acuity of 20/20 in both eyes.

Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy

Gascon et al.[22] reported a case of AMN and PAMM. A 53-year-old male came to an ophthalmology department with decreased visual acuity in his left eye. He had negative scotoma in his left eye and inability to distinguish colors. His visual acuity was 20/63 in his left eye. Humphrey visual field 10–2 test revealed paracentral scotoma. The SD-OCT findings suggested AMN and PAMM. Patient's RT-PCR further confirmed the viral presence. Two weeks later, the patient's BCVA in the left eye increased to 20/32 with resolution of SD-OCT findings.

Virgo *et al*.[32] reported two cases of maculopathy associated with COVID-19 infection. First case was a 37-year-old pregnant woman (week 14) with complaint of paracentral scotoma in her left eye. She was tested positive for SARS-CoV-2 IgG antibody. Findings in OCT were

consistent with PAMM. Second case reported was a 32-year-old male, who came to ophthalmology department with paracentral scotoma in the right eye. Sixteen days prior, the patient was tested positive for COVID-19 through RT-PCR of the nasopharyngeal swab. OCT findings were consistent with AMN.

Vitritis and Acute Retinal Necrosis

Vitritis, an inflammation of the vitreous humor, has been observed in a newly diagnosed COVID-19 patient. Filho *et al*.[19] reported a unique case of a patient with intraocular inflammation (vitritis) and outer retinal layers abnormalities 12 days following COVID-19 symptoms onset. A 57-year-old woman presented to the outpatient clinic with symptoms of redness in both eyes. Her visual acuity was 20/25 in the right eye and 20/20 in the left eye. Posterior segment examination showed vitreous opacities in both eyes. Fundus photograph demonstrated a yellowish lesion of the macular area, consistent with the AF and SD-OCT result, which was suggestive of acute zonal occult outer retinopathy/AZOOR. The patient has been tested positive for SARS-CoV-2 antibodies.

A rare case of ARN resulted from severe vitreoretinitis was reported in a COVID-19-positive immunosuppressed patient. Gupta *et al*.[21] demonstrated a case of a 75-year-old female who came to the clinic with symptoms of floaters and reduced vision in her left eye over 3-week period. The visual acuity was 6/12 in the right eye and counting fingers in the left eye. The anterior and posterior segment examinations were consistent of left panuveitis, vitritis, peripheral, and midperipheral necrotizing retinitis and superior retinitis with minimal vitreous retinitis of the right eye. The intravitreal sample was tested positive for varicella zoster virus (VZV) and negative for COVID-19. The patient also had cough and therefore was tested for COVID-19. The PCR test of the nasopharyngeal swab was positive for COVID-19. The patient was immunocompromised with relapsed diffuse large cell B-cell lymphoma and had completed chemotherapy 2 months ago. This should be taken into consideration that the presence of ARN with such level of inflammation is uncommon, suggesting the possibility that COVID-19 might have a role in developing the VZV-related ARN by affecting the patient's immune system.

Other Posterior Segment Pathological Changes

A number of studies have reported patients with vitreoretinal anatomical changes, subsequent with COVID-19 diagnosis. These findings were obtained on the posterior segment examinations, including the funduscopic examination and SD-OCT.

Recently, a case report by Ruiz-Medrano *et al*.[30] described a 42-year-old male presented to the clinic with temporal relative scotoma in his left eye. SD-OCT result showed hyperreflective lesions at the level of ganglion cell layer (GCL) and inner plexiform layer (IPL). The patient was tested positive for SARS-CoV-2 antibody.

Consistent with these findings, Marinho *et al*.[27] presented a report of 12 patients examined with fundus photograph and OCT 11–33 days after the COVID-19 symptoms onset. Nine patients were tested positive for SARS-CoV-2 infection by RT-PCR of the nasopharyngeal and oropharyngeal swabs. Two patients were tested positive for SARS-CoV-2 antibodies. The fundus examinations showed cotton wool spots and micro hemorrhages along the retinal arcade in 4/12 patients (33.3%). In addition, SD-OCT exams also showed hyperreflective lesions at the GCL and IPL.

Invernizzi *et al*.[25] reported a cross-sectional study of retina abnormalities in 54 patients tested positive for SARS-CoV-2 infection. A total of 15/54 patients (27.7%) experienced ocular symptoms including near vision difficulties, redness, burning sensation, and photophobia. In addition, the funduscopic examinations also demonstrated retinal hemorrhages in 5/54 patients (9.3%), cotton wool spots in 4/54 patients (7.4%), drusen in 6/54 patients (11.1%), dilated veins in 15/54 patients (27.7%), and tortuous vessels in 7/54 patients (12.9%).

A cross-sectional study by Pereira *et al*.[28] also supported these findings. In total, 18 patients with positive RT-PCR result from nasopharyngeal swabs for SARS-CoV-2 were included in this study. A total of 10/18 patients (55.6%) had abnormalities on their funduscopic examinations. The main findings were flame-shaped hemorrhages in 4/18 patients (22.2%) and cotton wool spots in 3/18 patients (16.7%). The other findings were peripheral retinal hemorrhages in 2/18 patients (11.1%), retinal sectorial pallor in 1/18 patient (5.6%), retinal pigment epithelium hyperplasia in 1/18 patient (5.6%), and macular hemorrhages.

Retinal abnormalities were also shown to be relevant in patients with a previous history of COVID-19 infection and current negative SARS-CoV-2 RT-PCR result of the nasopharyngeal swab. A study by Landecho *et al*.[26] reported a total of 6/27 patients (22.2%) presented with cotton wool spots indicating retinal microangiopathy in the funduscopic examination. The examinations were done 14 days following hospital discharge.

Discussion

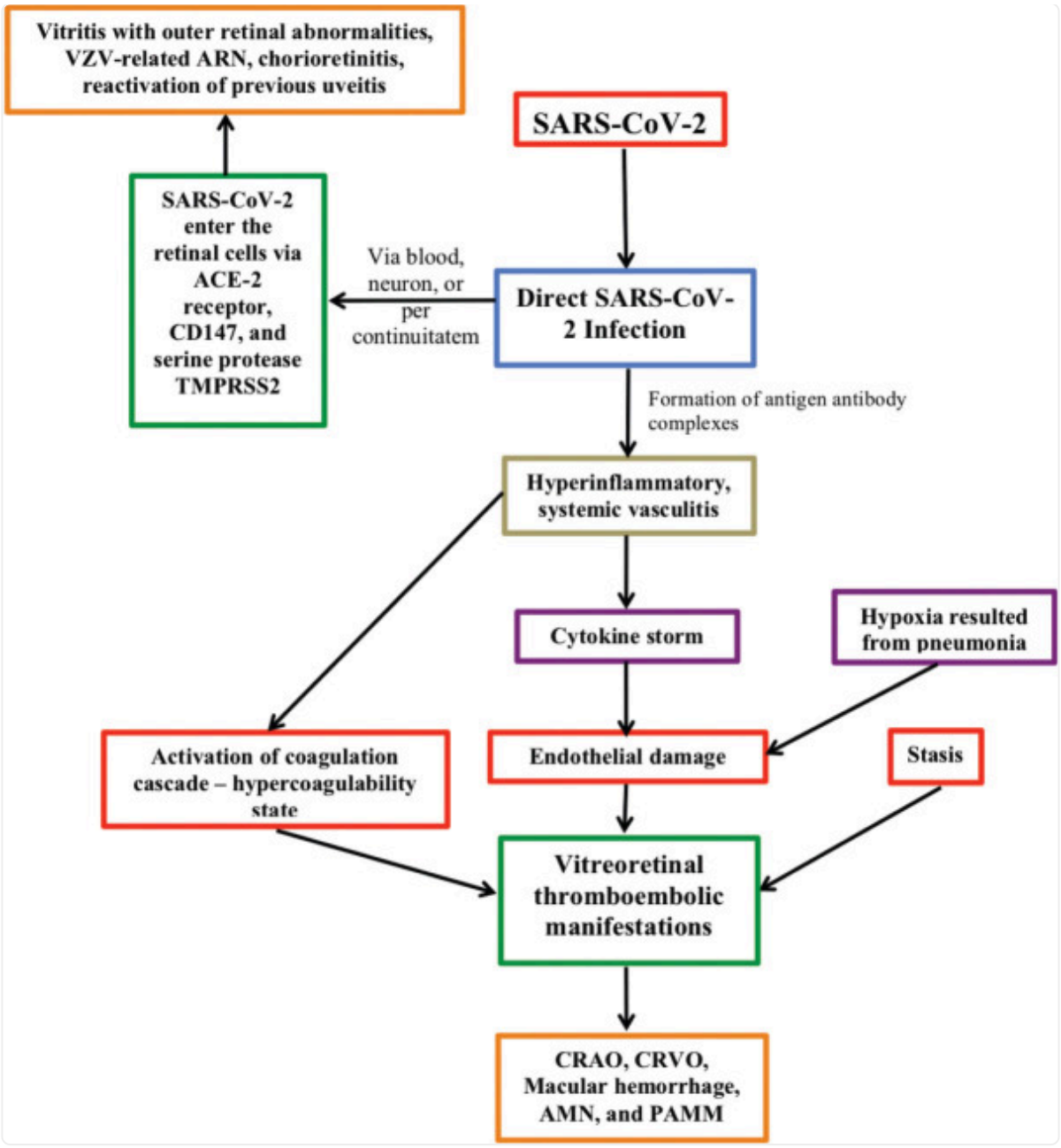
COVID-19 has been highly associated with major systemic inflammatory response and hypercoagulation state. Numerous literatures have demonstrated these phenomena in various organs including kidney, lungs, brain, and skin.[34,35]

In the eye itself, the pooled prevalence of ocular manifestations in COVID-19 ranged from 1% to 32% (7%, 95% confidence interval: 0.00–0.03). Overall, conjunctivitis is the most commonly occurring ocular problems in COVID-19 patients. The main signs and symptoms experienced by these patients were conjunctival hyperemia, chemosis, foreign-body sensation, epiphora, increased secretion, itching, ocular pain, and photophobia. Other

anterior segment abnormalities including eyelid dermatitis, episcleritis, and keratitis were reported in low number of cases. To add, isolated case reports on neuro-ophthalmic signs of COVID-19 patients are also available.[9,10,11,12,13,14,15,34]

Small but growing numbers of reports are now focused on retinal circulation. Therefore, this review aims to demonstrate the ocular manifestations associated with COVID-19, particularly in the posterior segment. This review also highlighted the risks of developing vision-threatening complications in patients with COVID-19. There are two major possible pathophysiologies of vitreoretinal manifestations associated with COVID-19, first systemic vasculitis due to direct viral infection and second a thromboinflammatory cascade following hyperinflammatory response as seen in Figure 2.[23,31]

Figure 2.



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Proposed mechanism of vitreoretinal manifestations in COVID-19 patients

Direct SARS-CoV-2 Infection

In COVID-19 patients, it was hypothesized that there are three possible mechanisms of entry for SARS-CoV-2 to reach the retina, either through the blood, neuron, or per continuitatem. [36] So far, the most detailed explanation regarding the mechanism of SARS-CoV-2 direct infection suggested that SARS-CoV-2 binds to host cells through the angiotensin-converting enzyme 2 (ACE2) receptor. In addition, together with ACE 2 receptor, CD147 and serine

protease TMPRSS2 expressed in retinal cells were proposed to mediate the entry of SARS-CoV-2 into the retinal cells.[35,36,37]

There are several examples of vitreoretinal disorders originated from direct viral infection in COVID-19 patients including reactivation of previously diagnosed serpiginous choroiditis[29] and AMN.[21] To add, white dot syndromes, a group of inflammatory chorioretinal diseases, including APMPPE[15] and AZOOR,[19] were also documented to occur in COVID-19 patients. SARS-CoV-2 infection is thought to trigger the choroidal inflammation, similar to the other infectious agent such as *Mycobacterium tuberculosis*.[29] In addition, there is evidence to suggest that SARS-CoV-2 has the ability to compromise blood retinal barrier, allowing greater immune response to be involved. It is also worth noting that SARS-CoV-2 is a zoonotic pathogen and gross intraocular inflammation such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis were observed in feline and murine studies.[21,37,45]

Thromboembolic Events

The second pathogenesis of vitreoretinal disorders in COVID-19 patients is related to the thromboembolic phenomenon. The thromboembolic events have been reported in more than 30% of COVID-19 patients. Initial studies have indicated the higher incidence of vein thrombosis compared to arterial thrombosis.[23,24,38,39,40] It is important to establish patients' comorbidities as it may precipitate thromboembolic complications in COVID-19 patients.[24] Nevertheless, in cases where the patients are healthy, the thromboembolic events are more likely to be cause by the hyperinflammatory, systemic vasculitis effect of COVID-19.[31] Due to its nature, there is a possibility that the retina might be involved. It should be taken into consideration that retina is a metabolically active tissue with end arterial system, which makes it sensible to ischemic events.[33] The initial process started with type three hypersensitivity responses toward the SARS-CoV-2 antigen, which triggers the formation of antigen–antibody complexes. These deposits combined with the apoptotic and ischemic process leads to pro-inflammatory stage, which initiates the cytokine storm and results in complement-mediated thrombotic microangiopathy.[20,31]

While discussing about the thromboembolic risks of COVID-19, we should always remember about the basic mechanism of three pivotal factors also known as Virchow's triad. The Virchow's triad (hypercoagulability, endothelial damage, and stasis) plays important roles in the pathogenesis of coagulopathy. In COVID-19 patients, the combination of hypoxia resulted from the pneumonia and systemic diseases associated with endothelial injury induce the endothelial cells to produce tissue factors, which leads to the endothelial damage. In addition, the whole hyperinflammatory and cytokine storm responses continue the activation of extrinsic coagulation pathways. The presence of possible risk factors for blood stasis should not be neglected.[23,24,25]

Several examples of thromboembolic vitreoretinal manifestations in COVID-19 patients have been documented. CRVO seemed to be the most common vitreoretinal manifestation in COVID-19.[20,23,24,31,33] The other manifestation reported was CRAO, in which the arteritic cause has been excluded due to the low number of inflammatory markers in this patient.[17] The macular hemorrhage was proposed to be initiated by the cold agglutinin hemolytic anemia. Several conditions have been considered to precipitate hemolysis including hypoxia, fever, and viral infection, which in this case seemed to be triggered by the SARS-CoV-2 cross-reactivity phenomenon. The process of hypoxia and deformed erythrocyte leads to an increased blood viscosity and prothrombotic state, resulting in a low perfusion retina. This causes the blood vessels to enlarge, increasing the pressure inside the wall, which in the end generates microtrauma along the walls and leads to hemorrhage.[18] Ultimately, COVID-19-associated retinopathy had also been reported. Numerous cases have associated viral infection such as dengue with cases of maculopathy, retinopathy, and foveolitis. The underlying mechanism was endothelial dysfunction and precapillary arterioles occlusion due to the deposition of immune complex which leads to the retinal ischemia.[22,32]

SARS-CoV-2 Ocular Samples Detection

The limitation of SARS-CoV-2 detection in the ocular tissue should be highlighted. Studies have supported the evidence of low viral detection in the ocular samples of COVID-19 patients, leading to the possibility that SARS-CoV-2 may have less tissue tropism in the ocular tissue, especially the retina. However, we should take into account the reliability of the laboratory tests performed, as it is a relatively new procedure.[21,41] Several literatures have demonstrated contradicting results. A study by Casagrande *et al*.[42] reported the existence of SARS-CoV-2 RNA in the retina of COVID-19 patients. On the contrary, a study by *Bayyoud et al*.[43] concluded that no SARS-CoV-2 RNA was detected in all ocular samples of the COVID-19 patients. A report by *Loon et al*.[44] suggested the presence of RNA in tear samples of COVID-19 patients. However, none has been detected in the ocular tissue. Study in animal models by *Seah et al*.[45] demonstrated the existence of the virus in the aqueous humor, which may lead to the occurrence of conjunctivitis, uveitis, choroiditis, and retinal vasculitis. A pooled meta-analysis from seven studies by Ling *et al*.[35] demonstrated a low positive rate of ocular tissue or secretions in detecting SARS-CoV-2 (1%, 95% CI: 0.00-0.03), suggesting the low possibility of ocular samples to be used as a confirmative diagnostic tool for COVID-19. Further diagnostic investigations are needed to address these discrepancies regarding SARS-CoV-2 ocular tropism

Treatment Recommendation for Vitreoretinal Disorders in COVID-19 Patients

Limited evidence was available regarding the best treatment option in COVID-19 patients with vitreoretinal disorders. Specific local treatments including the laser treatment and

antivascular endothelial growth factor (anti-VEGF) injection such as ranibizumab might be necessary in certain indications, especially in retinal vein occlusion.[31,33] Several literatures also recommended the use of high-dose glucocorticoids such as dexamethasone and prednisolone in mild-to-moderate cases with systemic inflammation or thromboembolic complications.[24,29,31] The other suggestion is to screen for thrombotic markers and start antithrombolytic therapy such as low molecular weight heparin, rivaroxaban, and enoxaparin in high-risk patients.[20] These regimens were shown to have been able to halt the progression of blockage and restore visual acuity in some patients. Unfortunately, due to the limited number of evidence, future prospective studies are needed to develop an established treatment policy for vitreoretinal cases in COVID-19 patients. [20,31,33]

Study Limitations

There are several limitations of this study. This current topic is still a new area of expertise and the information about vitreoretinal manifestations in COVID-19 patients is still rare. Most of the published studies are case reports and only few cohorts were available, thus making us difficult to draw firm conclusion regarding the causal relationship of these conditions. However, as growing evidence on systemic hyperinflammatory response and thromboembolic events in COVID-19 patients were published, together with the fact that most of the patients in our cases developed new-onset vitreoretinal disorders without prior ophthalmologic problems, we strongly ascertain the correlation between these conditions. Finally, there is still no consensus regarding the best treatment option to be administered to patients with vitreoretinal manifestation associated with COVID-19 due to the limited number of cases

Clinical Practice Recommendations

The above evidence suggested the possibility of vitreoretinal involvement and other sight-threatening complications of COVID-19 patients. We would recommend health-care practitioners not to underestimate posterior segment abnormalities related to SARS-CoV-2 infection while interviewing and examining patients, although some patients might not develop any ocular symptoms. We believe that fundus examination in COVID-19 patients should be indicated as it provides access to a complete evaluation of the retina and its vasculature. The fundus photograph is a feasible and noninvasive procedure that has been used widely in large cohorts as a screening tool for identifying anatomical retinal alterations, especially in patients with endothelial diseases that are prone to sudden vascular events.[26] Changes in the retinal structure are also commonly observed in patients with viral infections such as cytomegalovirus and HIV, either related to the direct infection of the virus or due to the secondary cytopathic effect.[25] This was supported by our findings. Five studies reported the presence of posterior segment abnormalities in COVID-19 patients, with or without any ocular symptoms, ranging from cotton wool spots,

hemorrhages, hyperreflective lesions of retinal layers, and exudates.[24,26,27,28,30] It is also important to always examine complete coagulation panels and inflammatory markers in COVID-19 patients such as D-dimer, prothrombin time, partial thromboplastin time prolongation, fibrin degradation products, and C-reactive protein as they all contribute to an overall prothrombotic and hypercoagulable state. Reports have suggested that elevated D-dimer is associated with more severe and worse prognosis of thrombotic-related complications in COVID-19 patients.[17,24,33]

Given the magnitude of the current pandemic, this also highlighted the importance of protocol for practitioner's protective equipment dealing with droplets from these possible undiagnosed COVID-19 patients. Slit lamps should be installed with protective shields and disinfected regularly after clinic session. Doctors doing slit lamp and posterior segment examination should at least be equipped with surgical mask, gown, surgical cap, glasses, gloves, and face shield. In addition, in patients suspected or confirmed with COVID-19, N95 mask, and protective cover roll should be added. Last but not least, multiple strategies including hospital policy, hand hygiene, and environmental control should be implemented to prevent cross infection between patients and health-care practitioners.[23,33,46,47]

Conclusion

In the clinical setting of the current pandemic, vision-threatening complications including vitreoretinal disorders in COVID-19 patients should not be neglected. When patients present with new onset vitreoretinal abnormalities, COVID-19 should be kept on differential diagnosis. A full and complete ophthalmological examination should be conducted in order to fully establish the causal relationship between these manifestations and COVID-19. There were two possible underlying mechanisms of COVID-19-induced vitreoretinal disorders, including the direct ocular tissue tropism and thromboembolic phenomenon. As it is a relatively new field of study, future prospective studies are needed to better understand the diagnostic tools for SARS-CoV-2 detection in the ocular tissues and the best treatment options for COVID-19 patients with vitreoretinal disorders.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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