




# Retinal vascular occlusions in COVID-19 infection and vaccination: a literature review

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## Abstract

**Purpose** Abnormal hypercoagulability and increased thromboembolic risk are common in patients with coronavirus disease (COVID-19). COVID-19 has been suggested to cause retinal vascular damage, with several studies on COVID-19 patients with retinal vascular occlusions. We reviewed and investigated studies on retinal vascular occlusions in patients diagnosed with COVID-19 and in those vaccinated for COVID-19.

**Methods** Studies that reported retinal vascular occlusion in COVID-19 patients or in vaccinated people were identified using the terms “retinal occlusion,” together with “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2,” “COVID-19,” “coronavirus,” and “vaccine,” through systematic searches of PubMed and Google Scholar databases until January 7, 2022.

**Results** Thirteen cases of retinal artery occlusion (RAO) and 14 cases of retinal vein occlusion (RVO) were identified among patients diagnosed with COVID-19. Half of the patients with RAO or RVO revealed no systemic disorders except current or past COVID-19, and ocular symptoms were the initial presentation in five cases. Among patients with RAO, most presented with central RAO at 1–14 days of COVID-19 diagnosis, with abnormal coagulation and inflammatory markers. Among those with RVO, two-thirds presented with central RVO and one-third with RVO. Eleven cases with acute macular neuroretinopathy (AMN) and/or paracentral acute middle maculopathy (PAMM) were reported among patients with COVID-19, presenting scotoma resolved spontaneously in most cases. Among the 26 cases vaccinated with either mRNA or adenoviral vector vaccines for COVID-19 and presenting retinal vascular occlusions, there were more RVO cases than RAO cases, and ocular symptoms mostly occurred within 3 weeks after vaccination. One case presented bilateral AMN and PAMM after COVID-19 vaccination.

**Conclusion** Retinal vascular occlusions might be a manifestation of COVID-19, although rare, especially in patients at risk of systemic hypercoagulability and thromboembolism. For COVID-19 vaccines, the causal relationship is controversial because there are few case reports of retinal vascular occlusions after COVID-19 vaccination.

**Keywords** Coronavirus · COVID-19 · Retinal artery occlusion · Retinal vein occlusion · Vaccine

## Key messages

- Central retinal artery/vein occlusions are a frequent type of retinal vascular occlusion in patients with COVID-19.
- Retinal vascular occlusions might be one of the clinical manifestations of COVID-19, especially in patients at risk of systemic hypercoagulability and thromboembolism.
- There are only few case reports of retinal vascular occlusions associated with COVID-19 vaccination; therefore, the causality remains unknown.

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## Introduction

A novel coronavirus was detected during an outbreak of pneumonia of unknown etiology in late 2019 in Wuhan, Hubei Province, China [1]. It is now officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is responsible for the ongoing global pandemic [2]. Patients with coronavirus disease (COVID-19) caused by SARS-CoV-2 present with various systemic symptoms, including fever, cough, fatigue, breathing difficulties, and loss of smell and taste [2]. Besides respiratory symptoms, patients may also present with cardiovascular disorders including ischemic/inflammatory heart disease, arrhythmia, and thrombotic events [3]. Although relatively less involved, the nervous and gastrointestinal systems are also affected in COVID-19 [4, 5].

Meanwhile, important procoagulant mechanisms appear to be upregulated in COVID-19, leading to significant thrombotic complications [6, 7]. SARS-CoV-2 has distinctive spike proteins that show a higher affinity for the angiotensin-converting enzyme 2 (ACE2) receptor of host target cells [8]. This augments angiotensin II signaling and triggers the release of proinflammatory cytokines in the neighboring endothelia [8]. The prothrombotic pathway is also stimulated to lead to thrombotic angiopathy in multiple organs, including the lungs, legs, heart, and brain [6]. The most common thromboembolic complications are pulmonary thromboembolism and deep vein thrombosis, while the risk of venous thromboembolism remains high despite anticoagulation prophylaxis in COVID-19 [6]. Furthermore, vaccine-related side effects are of significant concern when associated with thromboembolism or thrombocytopenia [9].

Ocular manifestations have also been reported in patients admitted for treatment of COVID-19 [10, 11]. The prevalence of ocular manifestations is estimated to be 11%, with symptoms such as dry eye or foreign body sensation, redness, tearing, ocular pain, and discharge [11]. The involvement of the external eye is more common, presenting as follicular or pseudomembranous conjunctivitis, keratoconjunctivitis, and episcleritis [10]. There have also been reports of visual disturbances and ocular inflammation after COVID-19 vaccination [12]. Similar to the ocular manifestations reported with COVID-19 infection, most descriptions with COVID-19 vaccines are case reports with symptoms such as photophobia and blurred vision [12].

The retina, a highly vascularized tissue, is prone to thromboembolic disorders. Although less than external eye involvement, there have also been reports of manifestations in the posterior segment of the eyes of COVID-19 patients, especially in the retina. A report based on 12

patients diagnosed with COVID-19 revealed cotton wool spots and retinal hemorrhages on fundus examination and hyperreflective bands on optical coherence tomography (OCT) [13], although controversy remains as these findings can be identified in various disorders [14]. Retinal vascular occlusions have also been reported following COVID-19 vaccination, but their causality remains unclear [15, 16].

Retinal vascular occlusion is a common disorder that causes severe visual impairment and is associated with risk factors such as hypercoagulability and thrombotic disorders. In this review, we focus on retinal occlusive disorders, including retinal artery occlusions (RAO) and retinal vein occlusions (RVO), reported with COVID-19 infection and vaccines, and discuss the associated pathophysiologic mechanisms.

## Methods

PubMed, Google Scholar, and Cochrane databases were last searched on January 7, 2022, using keywords such as “retinal occlusion,” “SARS-CoV-2,” “COVID-19,” “coronavirus,” and/or “vaccine.” There were no restrictions on study design, but duplicate articles were removed. After a systematic search of databases, the searched articles were initially screened for relevance, and the results reporting retinal vascular occlusions associated with either COVID-19 infection or vaccination were included in this review. Articles published in English were included.

We reviewed the ocular manifestations and diagnoses associated with retinal vascular occlusions to interpret their relationship with COVID infection or vaccination. Demographic features, including age, sex, systemic history, initial symptoms associated with COVID-19 infection or vaccination, and clinical course of the disease, were collected. Laboratory findings, including inflammatory markers, coagulation workup, and brain or cardiovascular imaging, were also investigated.

## Results

There were no randomized controlled trials, while two cross-sectional studies on retinal vascular occlusion in COVID-19 patients were identified through a literature search. Twenty-seven case reports were identified, including 13 cases of RAO and 14 cases of RVO. Twenty-five cases of retinal vascular occlusion have been reported, suggesting an association with the COVID-19 vaccination.

## Abnormal retinal findings associated with SARS-CoV-2 infection

Abnormal retinal findings were first reported in 12 patients with COVID-19 without visual symptoms and presented as hyperreflective bands in the inner retinal layers on OCT [13]. However, questions were raised, as reported hyperreflective OCT lesions might not be pathological findings associated with COVID-19 [14], and there were no comparable data taken prior to COVID-19. The authors also reported that some of the patients showed subtle cotton wool spots and microhemorrhage [13]; however, controversies remain as cotton wool spots can be identified in various retinal diseases, and myelinated nerve fibers might be misconceived as subtle cotton wool spots [14].

Similar reports of retinal hemorrhage and cotton wool spots in patients with COVID-19 have been reported. An observational case series of hospitalized COVID-19 patients revealed that retinal changes were observed in 12% of the patients [17]. These retinal changes were suggested to occur secondary to clinical comorbidities or intercurrents [17].

## Retinal vascular occlusions associated with SARS-CoV-2 infection

### Retinal artery occlusions

Briefly, 13 cases of RAO in COVID-19 patients were found in the literature search (Table 1). The age ranged from 29 to 68 years, and 70% of the patients were male. Most cases presented ocular symptoms within 1–2 weeks of COVID-19 diagnosis; ocular symptoms preceded in two cases, and one case was diagnosed 3 months after COVID-19 diagnosis [18–20]. About half of the patients reported no systemic illness, while hypertension was noted in four cases [18, 19, 21, 22]. Those who presented with pneumonia and/or respiratory failure mostly presented abnormal coagulation parameters, including D-dimer, C-reactive protein (CRP), ferritin, and fibrinogen [18, 21–23], although increased D-dimer levels were also noted in patients with mild disease [24, 25]. Three patients had normal coagulation parameters [26, 27]

Echocardiography, brain imaging including magnetic resonance (MR) and computed tomography (CT), or carotid artery evaluation via Doppler sonography was performed in most patients to evaluate any associated systemic thromboembolism. Imaging results were unremarkable in over 75% of patients with RAO, but two cases showed carotid artery occlusion [18, 19]. One patient showed cavernous sinus thrombosis identified on CT venography [28], whereas two patients had concomitant stroke identified on brain MR [18, 29].

Most patients presented with central retinal artery occlusion (CRAO), while there were two cases of branch retinal artery occlusion (BRAO) and one case with cilioretinal

artery occlusion [20, 24, 30]. One patient presented with bilateral CRAO and profound visual impairment [27]. Patients presenting with BRAO or cilioretinal artery occlusions revealed no concomitant systemic thromboembolism.

In particular, sudden visual loss associated with orbital infarction syndrome has been reported secondary to rhino-orbital mucormycosis in patients with COVID-19. Ophthalmic artery occlusion was presented, along with total ophthalmoplegia and diffuse retinal ischemia [31]. History of diabetes and corticosteroid use was predisposing factor for the rhino-orbital mucormycosis, and one-fifth of patients with irreversible severe vision loss [32, 33].

### Retinal vein occlusions

We summarized the 14 cases of RVO associated with COVID-19 (Table 2). Compared to RAO cases, the onset of ocular symptoms varied from a few days to several months. Three patients who presented with ocular symptoms first due to RVO were confirmed to have a past COVID-19 infection [34–36]. In contrast, there was a case of branch retinal vein occlusion (BRVO) 3 months after COVID-19 diagnosis [37].

About 50% of RVO patients reported no systemic symptoms associated with COVID-19 or only presented with mild disease [34–40]. RVO patients with pneumonia due to COVID-19 presented abnormal coagulation parameters, such as D-dimer, CRP, and fibrinogen levels [39, 41–43].

Fluorescein angiography, fundus photography, and OCT were performed in most of the patients. About two-thirds presented with central retinal vein occlusion (CRVO); two cases had bilateral CRVO, and most cases of CRVO were non-ischemic [35, 39, 41, 43, 44]. Five cases presented with BRVO, with one case presenting bilateral BRVO [37, 38, 42, 45, 46]. Interestingly, the degree and distribution of retinal hemorrhage tended to be mild compared to the typical flame-shaped retinal hemorrhages of RVO. Macular edema was observed in most cases, which were mostly improved by intravitreal injections of corticosteroids or anti-vascular endothelial growth factor (VEGF) agents, along with improved vision [36–38, 40, 47].

### Retinal capillary occlusions

Recent discovery and investigations of acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM) suggest the localization of ischemic lesions at the capillary plexus [48], and cases have been reported in patients with COVID-19 (Table 3). Ocular symptom preceded COVID-19 diagnosis in one case [49], while other cases presented unilateral or bilateral scotoma from 2 weeks to 2 months after COVID-19 diagnosis. Notably, one patient was in 14 weeks of uncomplicated pregnancy

**Table 1** Cases of retinal artery occlusion associated with COVID-19

Number	Age/sex	Systemic history	COVID manifestation	Onset of ocular symptoms	Ocular diagnosis	Abnormal lab	Imaging	Ocular Exams	COVID Treatment	Source
1	68/M	A-fib, HTN, liver cirrhosis	Respiratory failure, ARF	2nd day of hosp. Eye symptom 16 h earlier	CRAO (OD) CN VI palsy	Lactate, D-dimer, ESR, CRP	Right int carotid occlusion on CTA Stroke on brain MR	FP (indirect)	Intravenous steroid Heparin for A-fib	Larochelle et al. [18]
2	Fifth decade/M	HTN, Occasional marijuana use	Mild pharyngitis, diarrhea	Eye symptom first	CRAO (OD)	D-dimer, PT, INR, fibrinogen, LDH, CRP	Unilateral carotid obstruction	FP	LMWH	Murchison et al. [19]
3	34/F	None	Pneumonia	3 months after COVID Dx	BRAO (OD)	CRP, fibrinogen, D-dimer, ferritin, lupus anticoagulant	Unremarkable – Brain MR	FP, FA	Levofloxacin, Dexamethasone, Enoxaparin, HCQ, Favipiravir	Ateş et al. [20]
4	60/M	HTN Dyslipidemia Stable angina COPD	Pneumonia	12th day of hosp.	CRAO (OD)	IL-6, CRP, ferritin, fibrinogen, D-dimer	Unremarkable – Brain CTA	Fundoscopy	HCQ, Azithromycin, Tocilizumab	Acharya et al. [21]
5	59/F	HTN Hyperuricemia	Pneumonia, ARF	10th day of ICU (Dx at OPD)	CRAO (OS)	D-dimer, fibrinogen, IL-6, IL-7	Unremarkable – Brain CTA, MR	OCT, FP, FA	HCQ, Lopinavir/Ritonavir, Tocilizumab	Montesel et al. [22]
6	48/M	Obesity, Sleep disorder	Pneumonia → septic shock, dCMP, ARF, Fungemia	6th week of hosp. (24 h after apixaban change)	OAO (OD)	Pro-calcitonin, ferritin, fibrinogen, D-dimer	Unremarkable – Brain MR, Orbit MR, Head and neck CT, Echo	Fundoscopy	HCQ, Tocilizumab, Enoxaparin to Apixaban	Dumitrascu et al. [23]
7	65/F	None but obese	Mild disease → no admission	5 weeks after COVID-19 Dx	BRAO (OS)	D-dimer	Unremarkable – Echo	Fundoscopy	Favipiravir	Uzun et al. [24]
8	54/M	None	Fever, anosmia, cough → no admission	3 weeks after COVID-19 Dx	CRAO (OD)	D-dimer, CRP, ferritin, platelet, fibrinogen	Unremarkable – Brain MR, Carotid US	FP, OCT, FA	HCQ, Azithromycin, Favipiravir, Enoxaparin	Ucar et al. [25]
9	54/M	None	Mild myalgia, fever	14 days after COVID-19 Dx	CRAO (OD)	Unremarkable	Unremarkable – Brain MR	OCT, FP, FA	HCQ, Enoxaparin, Pantoprazole	Turedi et al. [26]
10	42/M	None	Fever, cough	2 weeks after COVID-19 Dx	CRAO (OU)	Unremarkable	Unremarkable – Echo, Brain MR	OCT, FP, FA	Dexamethasone, Aspirin	Bapaye et al. [27]

**Table 1** (continued)

Number	Age/sex	Systemic history	COVID manifestation	Onset of ocular symptoms	Ocular diagnosis	Abnormal lab	Imaging	Ocular Exams	COVID Treatment	Source
11	37/M	None	Pneumonia	14 days after COVID Dx	CRAO (OS), Proptosis, Eyelid drooping	ESR, CRP, D-dimer, ferritin, IL-6	Cavernous sinus thrombosis in CT venography	OCT, FP	Remdesivir, Azithromycin, Tocilizumab	Raj et al. [28]
12	38/M	Diabetes	Fever, cough, dyspnea	7th day of hosp.	CRAO(OS)	ESR, CRP, ferritin, LDH, D-dimer, aPTT	Acute infarct in Lt parieto-occipital region on Brain MR Unremarkable – Echo	Fundoscopy FP	Anticoagulant, Dexamethasone, Remdesivir	Been Sayeed et al. [29]
13	29/F	None	Mild disease → no admission	2 weeks after COVID Dx	Cilioretinal artery occlusion, PAMM	Unremarkable	Unremarkable – Echo, neck Doppler	OCT, FP, FA, VF		Ozsaygili et al. [30]

*A-fib* atrial fibrillation, *aPTT* activated partial thromboplastin time, *ARF* acute renal failure, *BRAO* branch retinal artery occlusion, *CN* cranial nerve, *COPD* chronic obstructive pulmonary disease, *CRAO* central retinal artery occlusion, *CRP* C-reactive protein, *CT* computed tomography angiography, *dCMP* dilated cardiomyopathy, *Dx* diagnosis, *ESR* erythrocyte sedimentation rate, *FA* fluorescein angiography, *FP* fundus photography, *HCCQ* hydroxychloroquine, *HTN* hypertension, *IL* interleukin, *INR* international normalized ratio, *LDH* lactate dehydrogenase, *LMWH* low molecular weight heparin, *MR* magnetic resonance, *OAO* ophthalmic artery occlusion, *OCT* optical coherence tomography, *OD* oculus dexter, *OS* oculus sinister *OU* oculi uterque, *PAMM* paracentral acute middle maculopathy, *US* ultrasound Sonography

**Table 2** Cases of retinal vein occlusion associated with COVID-19

Number	Age/sex	Systemic history	COVID manifestation	Onset of ocular symptoms	Ocular diagnosis	Abnormal lab	Ocular Exams	Ocular treatment	Source
1	17/F	None	No symptom	Eye symptom first (Confirmed past infection)	CRVO, ME (OS)	Unremarkable	FP OCT FA	IVT-ranibizumab×3 (V/A 6/24 improved 6/12, 1 month after 2nd IVTA)	Walinjkar et al. [34]
2	56/F	Diabetes	No symptom	Eye symptom first (Confirmed past infection)	Non-ischemic CRVO, ME (OS)	D-dimer, ESR	FP OCT FA	Refused IVT-bevacizumab (Initial V/A 6/6 and resolved ME after 1 month)	Venkatesh et al. [35]
3	46/M	HTN, Dyslipidemia	No symptom	Eye symptom first (Confirmed past infection)	CRVO, ME (OD)	Unremarkable	FP OCT FA	IVT aflibercept (V/A 20/80+improved 20/20, 6 weeks after 1st IVT-A)	Miller et al. [36]
4	74/F	Dyslipidemia	Symptom free (COVID Dx 3 months ago)	3 months after COVID Dx	BRVO, ME (OS)	Not done	FP OCT FA	IVT-dexamethasone implant (initial V/A 20/50 but unknown improved V/A)	Duff et al. [37]
5	52/M	None	Mild disease	10 days after COVID Dx	BRVO, ME (OS)	Unremarkable	FP OCT FA	Oral methyl-prednisolone, IVT-ranibizumab biosimilar (V/A 6/60 improved 6/9)	Sheth et al. [38]
6	54/F	None	Mild pneumonia	5 days after COVID Dx	Non-ischemic CRVO (OD)	CRP, ESR, LDH, INR, Fibrinogen, D-dimer	OCT FA		Invernizzi et al. [39]
7	32/M	None	Mild disease → no admission	2 months after COVID Dx	CRVO, ME (OD)	Lupus anticoagulant	FP OCT FA	IVT-dexamethasone implant (V/A 20/32 improved 20/20)	Cuadros Sanchez et al. [40]
8	40/M	HTN, obesity	Pneumonia DVT	2 days after COVID Dx	CRVO (OU)	Ferritin, LDH, D-dimer, CRP, IL-6	FP OCT		Gaba et al. [41]
9	60/F	Unknown	Pneumonia, fever	10 days after COVID Dx	BRVO (OU), ME (OS)	ESR CRP D-dimer Ferritin	FP OCT FA	IVT-bevacizumab (OS) (Initial V/A 20/200 but unknown improved V/A)	Nourinia et al. [42]

Table 2 (continued)

Number	Age/sex	Systemic history	COVID manifestation	Onset of ocular symptoms	Ocular diagnosis	Abnormal lab	Ocular Exams	Ocular treatment	Source
10	30/F	Diabetes	Pneumonia	Symptom after discharge	CRVO (OU)	CRP, Fibrinogen, Ferritin, D-dimer HbA1c 13%	FP OCT FA		Rego Lorca et al. [43]
11	33/M	None	Fatigue, dry cough	2 weeks after general symptom	Non-ischemic CRVO (OS)	Unremarkable	FP OCT FA		Yahalomi et al. [44]
12	32/M	None	Fever, cough, fatigue, anosmia	1 month later COVID Dx	BRVO (OD)	Unremarkable	FP OCT FA		Finn et al. [45]
13	Unknown /F	HTN, diabetes, CKD	Lethargy, nasal congestion, diarrhea	7 days after general symptom (COVID-19 confirmed in 4 weeks)	BRVO, ME (OS)	Not done	FP OCT FA	Refused IVT anti-VEGF (self-report of improved vision after 3 weeks)	Russe-Russe et al. [46]
14	39/M	None	Fever	1 week after COVID Dx	CRVO, ME (OD)	Unremarkable	FP OCT FA	IVT-bevacizumab — multiple (V/A 20/150 improved 20/30)	Raval et al. [47]

*BRVO* branch retinal vein occlusion, *CKD* chronic kidney disease, *CRVO* central retinal vein occlusion, *CRP* C-reactive protein, *Dx* diagnosis, *ESR* erythrocyte sedimentation rate, *FA* fluorescein angiography, *FP* fundus photography, *HTN* hypertension, *IL* interleukin, *IVT* intravitreal injection, *LDH* lactate dehydrogenase, *ME* macular edema, *OCT* optical coherence tomography, *OD* oculus dexter, *OS* oculus sinister, *OU* oculi uterque, *V/A* visual acuity, *VEGF* vascular endothelial growth factor

**Table 3** Cases of retinal capillary occlusion associated with COVID-19

Number	Age/sex	Systemic history	COVID manifestation	Onset of ocular symptoms	Chief complain	Ocular diagnosis	Abnormal lab	Ocular exams	Source
1	53/M	None	No symptom	Eye symptom first	Scotoma, dyschromatopsia (OS)	AMN, PAMM (OS)	CRP, ferritin, platelet	FP OCT FA ICGA	Gascon et al. [49]
2	37/F	Pregnancy	Fever, cough, anosmia	1 month after COVID Dx	Paracentral scotoma (OS)	PAMM (OS)	Unremarkable	OCT	Virgo et al. [50]
3	32/M	None	No symptom	16 days after COVID Dx	Paracentral scotoma (OD)	AMN (OD)	Not done	OCT IR	Virgo et al. [50]
4	32/M	None	Symptom free	4 months after COVID Dx	Paracentral scotoma (OD)	AMN, PAMM (OU)	Unremarkable	FP OCT	Goyal et al. [51]
5	19/F	None	Symptom free	2 weeks after COVID Dx	Bilateral scotoma	PAMM (OU)	D-dimer	FP OCT	Padhy et al. [52]
6	41/F	None	Symptom free	1 month after COVID Dx	Visual impairment, paracentral scotoma (OD)	PAMM (OD)	D-dimer	OCT FA OCTA mfERG VF	Sonmez et al. [53]
7	47/M	None	Symptom free	2 months after COVID Dx	Paracentral scotoma (OD)	PAMM (OD)	Not done	FP OCT FA FAF	Jonathan et al. [54]
8	4 cases (25 y)	None	Systemic symptoms of COVID			AMN (2 OD, 2 OU)		OCTA	Azar et al. [77]

ANM acute macular neuroretinopathy, CRP C-reactive protein, Dx diagnosis, FA fluorescein angiography, FAF fundus autofluorescence, FP fundus photography, ICGA indocyanine green angiography, IR infrared reflectance, mfERG multifocal electroretinogram, OCT optical coherence tomography, OCTA optical coherence tomography angiography, OD oculus dexter, OS oculus sinister, OU oculi uterque, PAMM paracentral acute middle maculopathy, VF visual field

[50], and other patients revealed no systemic illness. There was one case presenting unilateral AMN [50], two cases of combined AMN and PAMM [49, 51], and others with PAMM [50, 52–54]. Visual acuity was generally preserved, and scotomas were spontaneously resolved without treatment in most patients.

Most patients did not reveal any systemic symptoms associated with COVID-19 at the time of presentation for ocular symptoms, while two patients showed abnormal coagulation parameters, including D-dimer, ferritin, and D-dimer [49, 52, 53].

### Retinal vascular occlusions associated with COVID-19 vaccination

Among the reports of retinal vascular occlusions associated with COVID-19 vaccines, one report was a case series from Korea [9], and the others were individual case reports

summarized in Table 4. There were more RVO cases than RAO cases, and ocular symptoms mostly occurred within 3 weeks after vaccination.

The characteristics differed at several points between those reported by Park et al. [9] and the other cases. The case series of Korean patients included 11 patients, consisting of 5 patients vaccinated with adenoviral vector vaccines (ChAdOx1 nCoV-10, AstraZeneca) and 6 patients with mRNA vaccines (BNT162b2, Pfizer-BioNTech) [9]. All cases were identified as RVO cases, and ocular manifestations occurred after the first vaccination dose in 76% of the patients.

Besides the abovementioned case series, other cases were reported as separate case reports with either adenoviral vector vaccine (three cases with AstraZeneca vaccines and one case with Sputnik V vaccine of Gamaleya Institute) [55–57] or mRNA vaccine (eight cases with Pfizer/BioNTech vaccines and two cases with Moderna vaccines) [15, 16, 58–64]. Among those who were vaccinated with mRNA vaccines,



**Table 4** Cases of retinal vascular occlusion associated with COVID-19 vaccination

Number	Age/sex	Systemic history	COVID vaccination	Onset of ocular symptom	Ocular diagnosis	Abnormal lab	Ocular exam	Ocular treatment	Source
1	11 cases (68 y)	27% Diabetes 73% HTN	5 AstraZeneca, 6 Pfizer	1–21 days (mean 2 days)	RVO	6 not done 4 neg results 1 low Hb, Hct	FP OCT FA VF	ASA, IVT-affibercept (V/A 0.5 improved to 1.0, 3 days after 1st IVT-A)	Park et al. [9]
2	50/M	Atopic dermatitis	BioNTech/Pfizer, 2nd dose	Immediate after vaccination	CRVO, ME (OS)	Unremarkable	FP OCT FA	ASA, IVT-affibercept (V/A 0.5 improved to 1.0, 3 days after 1st IVT-A)	Bialasiewicz et al. [15]
3	74/F	A-fib	Moderna, 2nd dose	48 h	BRVO (OD)	Mild thrombocytopenia	FP OCT FA	IVT-bevacizumab after ME development (V/A 20/40 improved 20/32)	Sacconi et al. [16]
4	76/F	Hypothyroidism	AstraZeneca, 1st dose	48 h	CRAO (OS)	Mild thrombocytopenia	FP OCT FA	Aspirin, pentoxifylline (initial V/A hand movement)	Abdin et al. [55]
5	50/M	Diabetes	AstraZeneca, 1st dose	4 days	CRVO, ME (OD)	Unremarkable except HbA1C	FP OCT	IVT-anti-VEGF (initial V/A 6/60 but unknown improved V/A)	Sonawane et al. [56]
6	43/F	None	AstraZeneca, 2nd dose	3 days	CRVO (OD)	ESR, CRP, RF, D-dimer	FP, OCT		Sonawane et al. [56]
7	28/M	None	Sputnik V/ Gamaleya, 2nd dose	11 days	BRVO, ME (OD)	Unremarkable	FP OCT	Prednisolone p.o., apixaban p.o. (V/A 6/9 improved to 6/6, 3 days after treatment)	Goyal et al. [57]
8	52/M	None	BioNTech/Pfizer, 1st dose	15 days	Non-ischemic CRVO (OD)	Unremarkable	FP OCT FA	IVT-dexamethasone, later Apixaban and IVT-bevacizumab (initial V/A 20/20)	Endo et al. [58]
9	38/M	AS—no therapy required	BioNTech/Pfizer, 2nd dose	3 days	BRAO (OD)	Unremarkable	FP OCTA	ASA p.o. (initial V/A 1.0)	Girbardt et al. [59]
10	81/F	HTN	BioNTech/Pfizer, 2nd dose	12 days	Combined RAO & RVO (OD)	Not done	FP OCT FA		Girbardt et al. [59]
11	54/F	Hypothyroidism	Moderna, 2nd dose	2 days	Combined CRAO & CRVO (OD)	Reduced platelets at 2 days, but normal at re-exam	FP OCT FA		Ikegami et al. [60]

Table 4 (continued)

Number	Age/sex	Systemic history	COVID vaccination	Onset of ocular symptom	Ocular diagnosis	Abnormal lab	Ocular exam	Ocular treatment	Source
12	38/M	None	BioNTech/Pfizer, 2nd dose	15 days	BRVO, ME (OS)	Unremarkable	FP OCT FA	IVT-affibercept (V/A 0.9 improved to 1.2, 2 months after 1st IVT-A)	Sugihara et al. [61]
13	34/M	None	BioNTech/Pfizer, 1st dose	2 days	BRVO (OD)	Unremarkable	FP OCT FA		Pur et al. [62]
14	27/F	None	BioNTech/Pfizer, 1st dose	10 days	CRVO, ME (OS)	Unremarkable	FP OCT FA VF	IVT-ranibizumab (Initial V/A 20/20)	Shah et al. [63]
15	34/M	None	BioNTech/Pfizer, 2nd dose	10–12 days	Combined CRAO, CRVO & NAION (OS)	ESR	FP OCT FA VF	IVT-affibercept, apixaban p.o., pentoxifylline p.o., methylprednisolone i.v. (V/A F:C improved to 20/30, 3 weeks after initial presentation)	Lee et al. [64]
16	35/M	None	AstraZeneca, 2nd dose	4 weeks	AMN, PAMM (OU)	Unremarkable	FP OCT FAF		Vinzamuri et al. [65]

*A-fib* atrial fibrillation, *ANM* acute macular neuroretinopathy, *AS* ankylosing spondylitis, *ASA* acetylsalicylic acid, *BRAO* branch retinal artery occlusion, *BRVO* branch retinal vein occlusion, *CRAO* central retinal artery occlusion, *CRVO* central retinal vein occlusion, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FA* fluorescein angiography, *FAF* fundus autofluorescence, *FP* fundus photography, *HTN* hypertension, *IVT* intravitreal injection, *ME* macular edema, *NAION* non-arteritic anterior ischemic optic neuropathy, *OCT* optical coherence tomography, *OCTA* optical coherence tomography angiography, *OD* oculus dexter, *OS* oculus sinister, *OU* oculi uterque, *PAMM* paracentral acute middle maculopathy, *RF* rheumatoid factor, *RVO* retinal vein occlusion, *V/A* visual acuity, *VF* visual field

70% presented ocular symptoms after the second dose [15, 16, 59–61, 64]. In contrast, two-thirds of patients vaccinated with adenoviral vector vaccines presented ocular symptoms at the first dose [55]. There was also a case of bilateral AMN and PAMM, reported after the second dose of adenoviral vector vaccine (CoviShield, formerly ChAdOx1 nCoV-10, AstraZeneca) [65].

One patient who presented with severe unilateral visual loss was a case of CRAO that was vaccinated with the first dose of adenoviral vector vaccine (AstraZeneca) [55]. One patient with BRAO presented with a normal visual acuity of 20/20 [59]. Other case reports consisted of RVO, including three cases that presented with combined RAO and RVO [59, 60, 64]. CRVO cases were mostly non-ischemic with preserved visual acuity [15, 58, 63]. Three patients presented with mild thrombocytopenia [16, 55, 60], while other patients did not present any systemic complications associated with COVID-19 vaccines.

## Discussion

Several pathogeneses have been suggested to influence the effects of SARS-CoV-2 on retinal involvement. Direct virus localization in the retina has been suggested based on viral RNA detection in the postmortem retina [66]. However, no significant levels of viral RNA in the retina and vitreous fluid of deceased COVID-19 patients have also been reported [67]. Retinal hemorrhages and cotton-wool spots are non-specific findings that can be considered as primary insults via viral localization. Accordingly, endothelial involvement is more likely the explanation to the retinal findings in COVID-19. SARS-CoV-2 affects the vascular endothelium via the ACE2 receptor, leading to loss of ACE2 activity [68]. This in turn increases the level of angiotensin II, which induces vasoconstriction and thrombogenicity [68]. As a result, vascular endothelial injury leads to a pro-inflammatory pathway in COVID-19 [68].

Thrombosis is a hallmark of COVID-19. It is now known that COVID-19 causes multi-systemic thromboembolic complications via severe endothelial injury and inflammatory reactions [6, 69]. Hypercoagulability, platelet activation, and endothelial dysfunction are associated with thrombosis in COVID-19 [70], and approximately one-third of COVID-19 patients experience thrombosis despite thromboprophylaxis [6]. Abnormal coagulation markers such as increased levels of fibrinogen and D-dimer are common in COVID-19 and are probably associated with endothelial damage [6].

### Retinal vascular occlusion and COVID-19

As described above, most reports regarding retinal vascular occlusions are cases; therefore, their association with

COVID-19 remains unclear. Two cohort studies concerning the incidence of retinal vascular occlusions in the COVID-19 period reported different trends [71, 72]. One cohort study recently investigated the prevalence of retinal vascular occlusions before and during the COVID-19 pandemic period [71]. This study performed in the US showed that the number of new patients was dramatic during the first few months of the COVID-19 pandemic, while the percentages of new CRAO, CRVO, and BRAO cases slightly increased during the COVID-19 period [71]. We can assume that CRAO, CRVO, and BRAO were more frequently present in the COVID-19 period, although the overall number of new patients with retinal vascular occlusions did not differ between the pre-COVID-19 and COVID-19 period [71]. In contrast, another cohort study performed in the US revealed that the incidence of new RVO was higher in COVID-19 patients, while that of new RAO was not significantly different compared to the pre-COVID-19 period [72]. Thus, the association between BRVO and COVID-19 requires further investigation.

For RAO, its relationship with COVID-19 should be discussed cautiously despite the abovementioned cases due to the low incidence of RAO itself. As presented in this review, CRAO and CRVO were also more frequently reported among COVID-19 patients than BRAO and BRVO, although we should consider the higher prevalence of BRVO compared to other types of retinal vascular occlusions. Accordingly, the frequent presentation of CRAO among RAO cases in COVID-19 patients can be significant, as CRAO is relatively rare compared to other retinal vascular occlusions. Most cases of RAO present with abnormal coagulation markers along with COVID-19 infection [18–20, 22, 23, 25, 28, 29]. These markers might be elevated due to systemic coagulation rather than RAO itself.

Similarly, the frequent presentation of CRVO in young patients is a point to consider for COVID-19. The pathophysiology of RVO implies not only hypercoagulation but also vascular compression at the arteriovenous crossing, vasospasm, localized thrombosis, and degenerative changes in vessel walls [73]. This indicates that the relationship between RVO and hypercoagulation in COVID-19 patients is more complex. Studies on the incidence of RVO mostly reported that BRVO was about four times more common than CRVO [74], and CRVO is usually uncommon in young individuals, that is, under 40 years of age [73]. It should also be noted that RVO patients with systemic manifestations of COVID-19, such as pneumonia, present with abnormal coagulation parameters. Taken together, those with CRVO at a young age among RVO cases and/or presenting abnormal coagulation parameters are more likely to be associated with COVID-19 hypercoagulability.

To discuss retinal capillary occlusions, PAMM involves the intermediate and deep capillary plexus, presented as

hyperreflective band-like lesions at the outer plexiform layer/inner nuclear layer [75]. AMN is associated with ischemia at deep capillary plexus, characterized by hyperreflective lesions at the outer retinal layers [76]. Among these relatively rare diseases, usually diagnosed by OCT, the incidence of AMN was increased in COVID-19 pandemic period compared to the precedent year, while that of PAMM remained unchanged [77]. This tendency seems to be similar to the report of Al-Moujahed et al. [71] presenting higher incidence of CRAO, CRVO, and BRAO in COVID-19 pandemic period. Accordingly, these findings also suggest a possible link between retinal capillary ischemic lesions such as AMN/PAMM and COVID-19.

### Retinal vascular occlusions and vaccines

However, the relationship between systemic thromboembolisms and COVID-19 vaccines remains controversial. Venous thrombosis or pulmonary thromboembolism was reported as possible complications of COVID-19 vaccines, while there were reports showing that the incidence of these thromboembolic events did not increase with vaccines [78–80]. In most countries, COVID-19 vaccination is recommended for overall benefits over rare thromboembolic risks [81]. Furthermore, the relationship is still not clear for retinal vascular occlusions associated with COVID-19 vaccines.

Severe adverse reactions after vaccination are rare, whereas thrombosis appears to occur more frequently with viral vector vaccines [82, 83]. However, retinal vascular occlusions have been reported in cases vaccinated with viral vectors as well as in mRNA vaccines. Interestingly, considering the cases published so far, retinal vascular occlusions frequently occur after the primary dose in viral vector vaccines and after the second dose in mRNA vaccines. For systemic reactions, adverse effects were more common with the second dose of mRNA vaccines [84]. This may be associated with different vaccine mechanisms. mRNA vaccines present nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2 to elicit both B- and T-cell responses against spike proteins and trigger the immune system in future infections [84]. Viral vector vaccines provide information of the spike proteins of virus via “vector” to deliver genetic materials encoding the spike antigen [84]. This produces antibodies against the spike protein, which provides immune protection against SARS-CoV-2 [84].

However, the risk of venous thrombosis and thrombocytopenia syndrome is extremely low with viral

vector vaccine [84]. For mRNA vaccines, myocarditis has been reported as a severe adverse effect, especially after the second dose [84], while associations with other systemic thromboembolic events with COVID-19 vaccines have not yet been recognized. Despite the possibility for the associations of retinal vascular occlusions and COVID-19 vaccines, it is still difficult to determine the causality considering the low incidence of retinal vascular occlusions.

### Limitations

We focused these retinal vascular diseases altogether as they have thromboembolic disorders as a risk factor in common and as thromboembolic complication is a hallmark of COVID-19. Although RAO, RVO, AMN, and PAMM were grossly grouped as “retinal vascular occlusions” in this review, it should be noted that these vascular disorders still have different pathogenesis respectively.

Another limitation of this review is that the literature reviewed in this study was mostly consisted of case reports. As case reports are considered to have the lowest level of evidence, it is cautious to draw clear conclusions in spite of thorough literature review. Further cohort studies are needed to clarify the association of retinal vascular occlusions and COVID-19 infection or vaccination.

### Conclusions

Retinal vascular occlusions can be associated with COVID-19, especially in patients presenting with abnormal hypercoagulability involving the central retinal artery or vein. However, the incidence is not particularly high, considering the results of cohort studies and case reports so far. For COVID-19 vaccines, the causality of retinal vascular occlusions should be cautiously determined; thus, further cohort studies might be necessary.

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### Declarations

**Ethic approval** This article does not contain any studies with human participants or animals performed by any of the authors. The review process was waived for this study by the Institutional Review Board of Ajou University Hospital, Suwon, Korea.

**Informed consent** This article does not contain any studies with human participants.

**Conflict of interest** The authors declare no competing interests.

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