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Hemi- and Central Retinal Vein Occlusion Associated with COVID-19 Infection in Young Patients without Known Risk Factors

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Purpose: Venous thromboembolic complications have been reported in association with coronavirus disease 2019 (COVID-19) infection. We raised awareness regarding a potential temporal association between COVID-19 infection and retinal vein occlusion (RVO).

Design: Multicenter, retrospective, nonconsecutive case series.

Subjects: Patients presenting with hemi-RVO (HRVO) or central RVO (CRVO) between March 2020 and March 2021, with confirmed COVID-19 infection, were included. The exclusion criteria were as follows: age >50 years, hypertension, diabetes, glaucoma, obesity, underlying hypercoagulable states, and those requiring intubation during hospitalization.

Methods: This was a multicenter, retrospective, nonconsecutive case series including patients presenting with hemi-RVO (HRVO) or central RVO (CRVO) between March 2020 and March 2021, with confirmed COVID-19 infection. The exclusion criteria were as follows: age >50 years, hypertension, diabetes, glaucoma, obesity, underlying hypercoagulable states, and those requiring intubation during hospitalization.

Main Outcome Measures: Ophthalmic findings, including presenting and final visual acuity (VA), imaging findings, and clinical course.

Results: Twelve eyes of 12 patients with CRVO (9 of 12) or HRVO (3 of 12) after COVID-19 infection were included. The median age was 32 years (range, 18–50 years). Three patients were hospitalized, but none were intubated. The median time from COVID-19 diagnosis to ophthalmic symptoms was 6.9 weeks. The presenting VA ranged from 20/20 to counting fingers, with over half (7 of 12) having a VA of $\geq 20/40$. OCT revealed macular edema in 42% of the eyes; of these, 80% (4 of 5) were treated with anti-VEGF injections. Ninety-two percent (11 of 12) had partial or complete resolution of ocular findings at final follow-up. Four eyes (33%) had retinal thinning, as determined using OCT, by the end of the study interval. The final VA ranged from 20/20 to 20/60, with 11 of the 12 (92%) eyes achieving a VA of $\geq 20/40$ at a median final follow-up period of 13 weeks (range, 4–52 weeks).

Conclusions: Although we acknowledge the high seroprevalence of COVID-19 and that a causal relationship cannot be established, we reported this series to raise awareness regarding the potential risk of retinal vascular events due to a heightened thromboinflammatory state associated with COVID-19 infection. *Ophthalmology Retina* 2022;6:520-530 © 2022 by the American Academy of Ophthalmology

Coronavirus disease 2019 (COVID-19), an illness caused by severe acute respiratory syndrome coronavirus 2, is characterized by a spectrum of multiorgan clinical manifestations.¹ The virus enters the host immune cells by fusing with the angiotensin-converting enzyme 2 receptor concentrated in the lungs, heart, intestines, arteries, and veins.² The common symptoms of COVID-19 infection include fever, myalgias, dry cough, pharyngitis, dyspnea, and anosmia, but severe disease can progress to acute respiratory distress syndrome, sepsis, multiorgan failure, and death.³

Although COVID-19 is primarily a respiratory illness, there has been emerging data indicating that coagulation

dysfunction associated with the virus predisposes the patients to arterial and venous thromboembolic events.³⁻⁶ A meta-analysis of 425 studies showed an overall venous thromboembolic rate of 21% in patients with COVID-19, and this rate was even higher in patients in the intensive care unit.⁷ The hypercoagulable state associated with COVID-19 is thought to be multifactorial and associated with the activation of the fibrinolytic pathway, a “cytokine” storm, and viral-mediated endothelial damage.^{3,8} These coagulation abnormalities associated with COVID-19 are distinct from those associated with severe infections such as disseminated intravascular coagulopathy or thrombotic

microangiopathy. Specifically, thrombocytopenia is not as profound as that associated with disseminated intravascular coagulopathy, and the D-dimer level is markedly higher with COVID-19.^{3,8} Given this, it is plausible that this so-called “COVID-19–associated coagulopathy”⁹ increases the risk of diagnosing retinal vascular abnormalities.

Moreover, recent literature has expanded the potential clinical spectrum of COVID-19 infection. The ocular manifestations reported in the literature to date include conjunctivitis,¹⁰ retinal microangiopathy,^{11–17} paracentral acute middle maculopathy, acute macular neuroretinopathy,¹⁸ uveitis,^{19,20} and optic neuropathy.^{19–21} Additionally, multiple reports describing retinal vascular events, such as central retinal artery occlusions,^{22–25} branch retinal vein occlusions (BRVOs),^{26,27} hemiretinal vein occlusion (HRVO), central retinal vein occlusion (CRVO),^{28–36} and papillophlebitis,³⁷ after the diagnosis of COVID-19 have been published. The series presented herein expands on the literature and aims to highlight a potential temporal association between COVID-19 infection and the development of retinal vein occlusions (RVOs) in otherwise young, healthy patients without other risk factors for RVO.

Methods

This was a multicenter, retrospective, nonconsecutive case series. Individual case contributors across the United States provided relevant information about eligible cases based on diagnostic criteria. Cases from each respective institution were identified using a local survey of known RVO cases occurring after confirmed COVID-19 infection. Information about each case was obtained from a review of medical records at each participation site. The participating sites included the following: Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida; Massachusetts Eye and Ear Infirmary, Harvard University, Boston, Massachusetts; VitreoRetinal Surgery, PLLC, Minneapolis, Minnesota; Connecticut Retina Consultants, Fairfield, Connecticut; Texas Retina Associates, Dallas, Texas; Eastern Retina Consultants of Puerto Rico Psc, Humacao, Puerto Rico; Department of Ophthalmology, Sunnybrook Health Sciences Center; Toronto, Canada; Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada; South Coast Retina Center, Long Beach, California; New York Eye and Ear Infirmary of Mount Sinai, New York, New York; Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, Minnesota; Mid Atlantic Retina, Wills Eye Hospital Retina Service, Philadelphia, Pennsylvania; Northern California Retina Vitreous Associates, Mountain View, California; and Department of Ophthalmology, University of California, San Francisco, California. This study received approval from the institutional review board at University of Miami Miller School of Medicine and was conducted after the approval of the Human Subjects Committee. Our research methods adhered to the tenets of the Declaration of Helsinki and were compliant with the Health Insurance Portability and Accountability Act. All participants provided informed consent.

We included patients aged >5 years diagnosed with HRVO or CRVO between March 2020 and March 2021 and presenting within 18 weeks of COVID-19 infection. Only patients who underwent a hypercoagulable workup to exclude any pre-existing thrombophilia (e.g., including prothrombin time, partial thromboplastin time, anticardiolipin antibody, lupus anticoagulant antibody, factor V Leiden, protein C, protein S, antithrombin III, and

homocysteine) were included. Patients aged >50 years and those with comorbidities, including hypertension, diabetes, cardiovascular disease, glaucoma, obesity, and underlying hypercoagulability, determined based on a laboratory evaluation, were excluded. Patients with other types of pathology, such as arterial occlusions, BRVOs, and optic neuropathy, and patients requiring intubation or positive-pressure ventilation (i.e., continuous positive airway pressure or intubation) during hospitalization for COVID-19 infection, were excluded.

After reviewing 22 collected cases, 12 eyes of 12 patients were included in the series. One case that was previously published by 2 coauthors of the present series (R.N.K. and A.P.F.), was included.³² We excluded 3 patients with BRVOs, 1 with a central retinal artery occlusion, and 4 who were aged >50 years and had confounding comorbidities. Two others were excluded because their laboratory evaluation result was positive for inherent hypercoagulability (1 with a *MTHFR* homozygous mutation and another positive for anticardiolipin and borderline lupus anticoagulant antibodies).

Only patients with CRVO and HRVO were included in this study because the pathophysiology is thought to be strongly related to hypercoagulability and venous injury, with occlusion occurring at the level of the lamina cribrosa.³⁸ In contrast, the authors excluded patients with BRVO because it is thought to result from mechanical venous compression of an adjacent thick-walled artery, more likely in the setting of chronic vascular risk factors.³⁹ Patients with arterial occlusions and those with underlying coagulopathies were excluded because of complex mechanisms that do not directly correspond with the concepts of the Virchow triad.^{40,41}

Patient charts were reviewed by individual case contributors for information regarding patient demographics, ophthalmic findings, imaging studies, diagnoses, treatments, clinical course, and medical history. Statistical analyses were performed using the SPSS 25.0 (SPSS Inc) software package. Mean, median, mode, and range were used to present descriptive statistics.

Results

The clinical characteristics of the 12 eyes of 12 patients in our study are summarized in [Table 1](#). All the patients tested positive for COVID-19 infection (91.7%, 11 of 12 confirmed using reverse transcriptase polymerase chain reaction and 1 of 12 confirmed using an unknown method), none were intubated, and none were known to have an underlying coagulopathy. Of the 12 cases, 75% (9 of 12) had CRVO and 25% (3 of 12) had HRVO. The median age at presentation was 32 years (range, 18–50 years). Twenty-five percent (3 of 12) were hospitalized for COVID-19 management. The median time from COVID-19 diagnosis to ocular symptoms was 6.9 weeks (range, 1–13 weeks), with a median of 10.5 days (range, 1–42 days) of reported symptoms before ophthalmic diagnosis. Six (50%) patients had ocular symptoms within 1 month of the viral infection. The median follow-up duration in our cohort was 13 weeks (range, 4–52 weeks).

Most eyes did not develop macular edema at any point throughout follow-up. Macular edema developed in 42% (5 of 12) of the eyes; in 80% (4 of 5) of these cases, macular edema was noted at presentation, and 1 developed macular edema at 6 weeks of follow-up and 9 weeks after the diagnosis of COVID-19 infection ([Fig 1](#)).

The presenting visual acuity (VA) ranged from 20/20 to counting fingers, with 58% of the eyes (7 of 12) having an initial

Table 1. Demographics and Clinical Characteristics of Patients Diagnosed with hemi- or central- Retinal Vein Occlusion after Confirmed COVID-19 Infection

Case #	Age (yrs)	Gender (M/F)	Race/Ethnicity	Diagnosis	COVID-19 Test	Hospitalized	Duration of Symptoms Prior to Exam (days)	Time from Systemic to Ocular Diagnosis (weeks)	Macular Edema at Presentation	Treatment after RVO	VA Initial	VA Final	Final OCT Status	Follow Up (weeks)
1	33	M	White	HRVO	RT-PCR	No	21	6	No	None	20/20	20/15	Thin	24
2	29	M	Hispanic	CRVO	RT-PCR	Yes	7	12	Yes - massive CME	Bevacizumab (1)	20/80	20/20	Normal [10]	11
3	24	F	White	CRVO	RT-PCR	No	2	4	No	None	20/60	20/30	Thin	22
4	36	F	White	CRVO	RT-PCR	No	21	14	Yes- massive CME	Bevacizumab (3)	20/70	20/20	Normal [4]	9
5	22	M	White	CRVO	Unknown method	No	7	9	Yes- mild CME	None	20/20	20/20	Normal [4]	4
6	18	F	Black	HRVO	RT-PCR	No	14	3	No	None	20/25	20/20	Normal	15
7	50	F	Hispanic	CRVO	RT-PCR	Yes	32	18	No	Plavix	20/30	20/25	Normal	21
8	41	F	Black	HRVO	RT-PCR	Yes	14	15	No	None	20/50	20/30	Thin	10
9	34	M	White	CRVO	RT-PCR	No	42	14	No	None	20/20	20/20	Normal	6
10	30	M	White	CRVO	RT-PCR	No	1	6	Yes - massive CME	Prednisone PO Aspirin 81mg Bevacizumab (1)	CF	20/20	Thin [6]	52
11	31	F	Hispanic	CRVO	RT-PCR	No	1	1	No	None	20/20	20/20	Normal	33
12	38	F	White	CRVO	RT-PCR	No	7	4	No – delayed CME	Bevacizumab (2)	20/20	20/60	CME	11

Key: CME = cystoid macular edema; COVID-19 = coronavirus disease 2019; CRVO = central retinal vein occlusion; F = female; HRVO = hemiretinal vein occlusion; M = male; PO = oral administration; RVO = retinal vein occlusion; RT-PCR = real-time polymerase chain reaction; VA = visual acuity (Snellen).

() indicates number of intravitreal injections throughout follow up course; [] indicates time to resolution of macular edema.

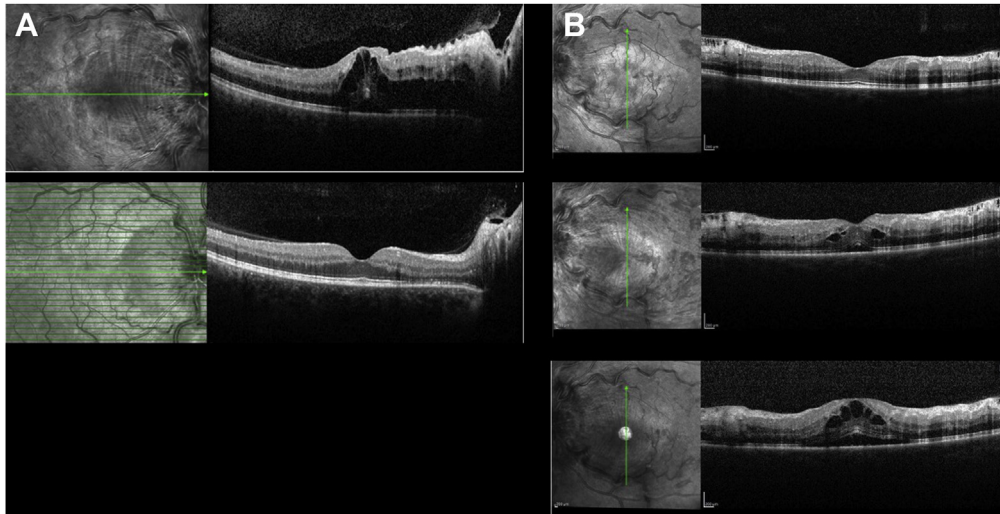


Figure 1. Clinical response to intravitreal anti-VEGF therapy for the treatment of macular edema associated with central retinal vein occlusion after coronavirus disease 2019 infection. **A**, OCT (Heidelberg Spectralis) of the right eye in case 4 showed macular edema (top), which resolved (bottom) following treatment with 3-monthly intravitreal bevacizumab (Avastin, Genentech) injections. **B**, OCT of the left eye in case 12 lacked macular edema at presentation (top) but developed macular edema at week 6. Macular edema was persistent despite the administration of 2 intravitreal bevacizumab injections at weeks 6 (middle) and 11 (bottom).

VA of $\geq 20/40$. Macular edema was associated with a poorer presenting VA, as illustrated in [Figure 2](#). Four cases were treated with anti-VEGF injections (range, 1–3 total injections) for macular edema, identified using OCT, and the remaining case was observed. The standard dosage of the intravitreal bevacizumab injections was 1.25 mg/0.05 mL.

There was partial or complete resolution of RVO in 92% (11 of 12) of the eyes of patients with confirmed COVID-19 infection at final follow-up, as illustrated in [Figure 3](#). Although most patients did not require systemic treatment with anticoagulation, 17% (2 of 12) were treated with antiplatelet therapy at the time of CRVO, 1 of whom was also treated with high-dose oral prednisone ([Table 1](#)).

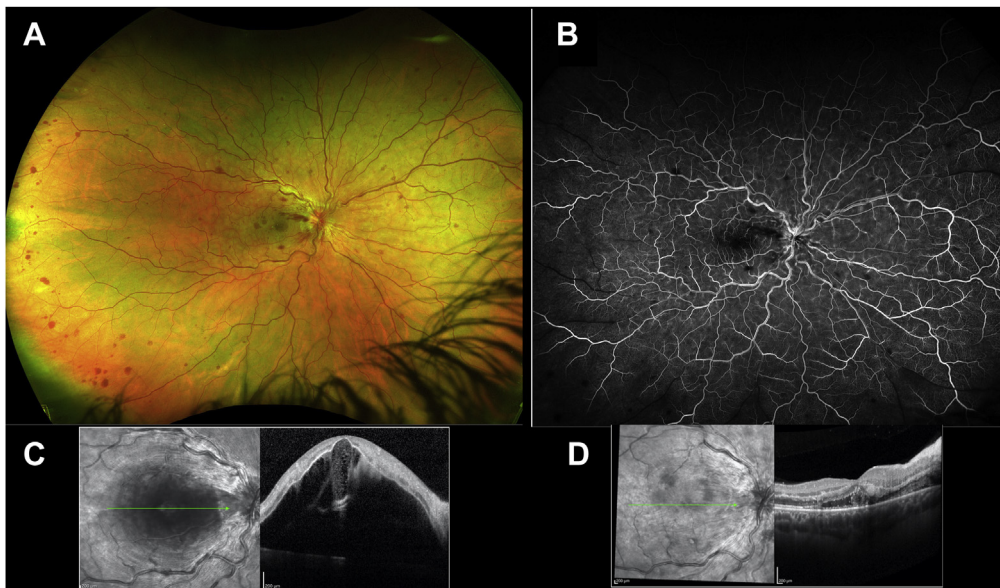


Figure 2. Right eye in case 10 presenting with central retinal vein occlusion (CRVO) following coronavirus disease 2019 infection. **A**, A fundus photograph (Optos) shows intraretinal hemorrhages in all quadrants, a flame hemorrhage off the disc, and tortuous vessels, consistent with CRVO. **B**, Fluorescein angiography (Optos) shows delayed peripheral perfusion and diffuse small-vessel leakage. **C**, **D**, The presenting OCT (Heidelberg Spectralis) (**C**) showed massive cystoid macular edema, which improved (**D**) just 1 week after treatment with a single intravitreal bevacizumab (Avastin, Genentech) injection. There was complete resolution of macular edema and the development of residual retinal thinning, as determined using OCT (not shown), by 52 weeks of follow-up.

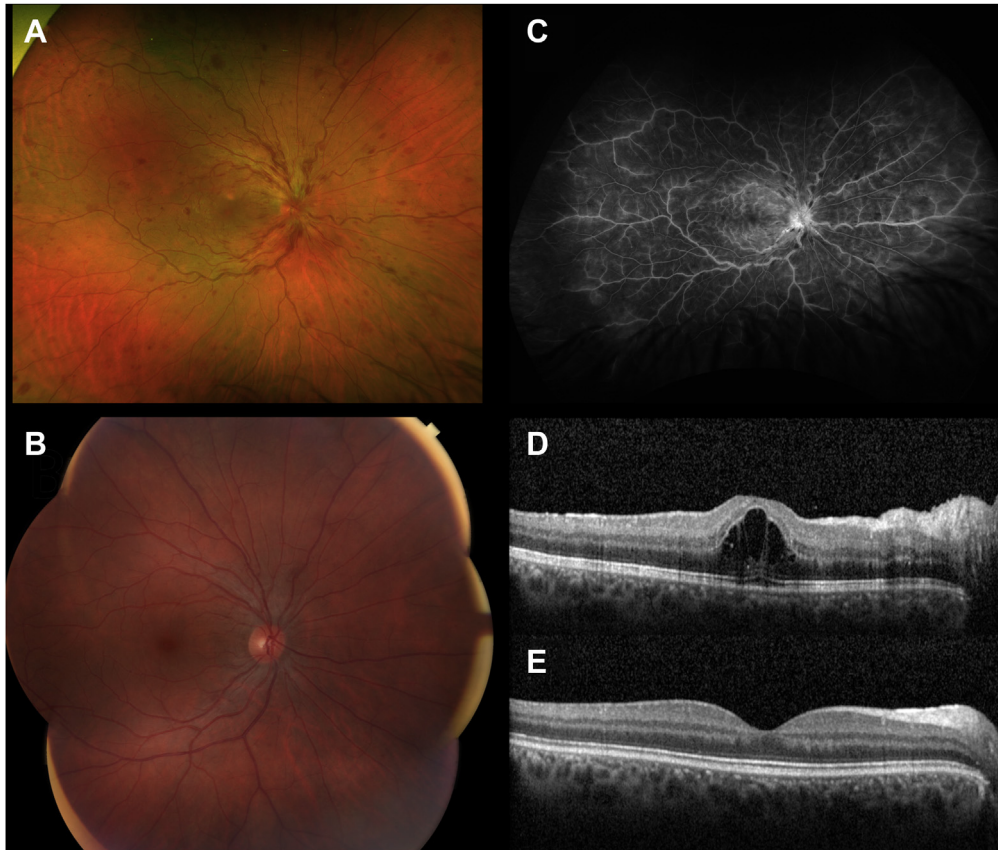


Figure 3. Right eye in case 2 presenting with central retinal vein occlusion following coronavirus disease 2019 infection. **A**, A fundus photograph (Optos) shows diffuse intraretinal hemorrhages and dilated, tortuous venules at presentation. **B**, Fluorescein angiography (Optos, UK) shows diffuse vascular leakage in late phases. **C**, Fundus abnormalities (Topcon) resolved 10 weeks later. **D and E**, Initial OCT (Heidelberg Spectralis) showed cystoid macular edema (**D**), which resolved by 10 weeks of follow-up (**E**) after treatment with 1 intravitreal bevacizumab (Avastin, Genentech) injection.

Most eyes maintained good VA throughout the follow-up interval. The final VA ranged from 20/20 to 20/60. Ninety-two percent (11 of 12) of the eyes achieved a final vision of 20/30 or better. The vision in some eyes that lacked macular edema improved as the vascular occlusive event resolved (Fig 4). Four eyes had retinal thinning, determined using OCT, at final follow-up (Table 1).

Discussion

Coagulopathy in the setting of COVID-19 infection has been well reported in the general medical literature. COVID-19 causes the activation of the fibrinolytic pathway, leading to increased fibrinogen, D-dimer, and prothrombin time; decreased platelets; and, in some cases, rebound thrombocytosis.^{3,5} Proinflammatory cytokines are also released, and these contribute to a generalized prothrombotic milieu.⁴²

The pathogenesis of CRVO or HRVO is believed to be secondary to the Virchow triad as well as compression in the shared venous and arterial adventitial sheath at the level of the lamina cribrosa.³⁸ Similarly, the pathophysiology of venous thromboembolism following COVID-19 infection is suspected to be related to a combination of inflammation, endothelial injury, vascular stasis, and coagulopathic risk

factors.³⁷ The interplay of tissue hypoperfusion as well as vascular injury, thrombosis, and dysfunction explains the thromboembolic state in patients with COVID-19.^{43,44} This may be a result of direct viral damage to the endothelium as well as the activation of endothelial and immune cells by a cytokine storm. Direct viral-mediated endothelial injury in the setting of RVO following COVID-19 infection was supported by studies that isolated severe acute respiratory syndrome coronavirus 2 from ocular tissues. Viral RNA was sequestered from the tears of infected patients in up to 7% of cases.^{45,46} Casagrande et al⁴⁶ reported that severe acute respiratory syndrome coronavirus 2 RNA was detected in the retina of 3 of 14 deceased patients with COVID-19 using polymerase chain reaction at the time of autopsy. Furthermore, Araujo-Silva et al⁴⁷ illustrated the findings of presumed viral particles within the retina of 3 deceased patients with COVID-19.

Multiple studies have described retinal microangiopathy, commonly, cotton wool spots and small intraretinal hemorrhages, in patients with COVID-19.^{11–17} Sim et al,¹² in their prospective, cross-sectional analysis of 216 eyes of 108 patients who tested positive for COVID-19, showed that 1 in 9 (11.6%) patients had signs of retinal microvascular disease. The authors observed that there was no significant

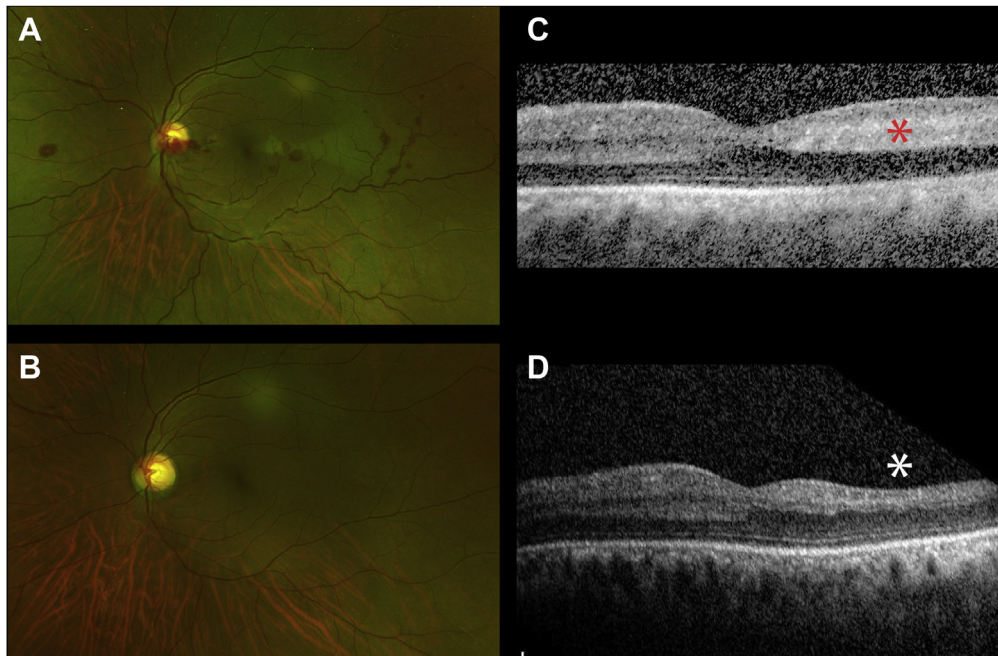


Figure 4. Right eye in case 8 presenting with an inferior hemiretinal vein occlusion (HRVO) after coronavirus disease 2019 infection. **A**, A fundus photograph (Optos) shows inferior intraretinal hemorrhages, a hemorrhage off the disc, and inferior venous dilation and tortuosity, consistent with the diagnosis of HRVO. **B**, OCT (Heidelberg Spectralis) showed that macular edema was lacking but revealed an area of focal hyperreflectivity, consistent with paracentral acute middle maculopathy (red asterisk). **C**, A fundus photograph (Optos, UK) at 10 weeks of follow-up showed normalization of the retinal anatomy. **D**, Final OCT at the 10-week follow-up visit demonstrated macular thinning in the area of the prior paracentral acute middle maculopathy (white asterisk).

difference in the presence of microangiopathy between the groups of patients with symptomatic and asymptomatic COVID-19. The retinal vascular changes were attributed to cardiovascular and thrombotic alterations related to the viral infection. Abrishami et al¹⁴ reported that patients who had recovered from COVID-19 had alterations in their retinal microvasculature, as seen using OCT angiography, compared with healthy controls. They reported an increased retinal vessel diameter and decreased vascular density in the superficial and deep capillary plexuses in these patients. Furthermore, a meta-analysis by Sen et al¹³ concluded that in 15 included articles, both sick and healthy patients with COVID-19 developed retinal vascular disease.

Our study identified that most patients with CRVO occurring after COVID-19 infection presented for their eye examination within weeks of a positive viral test result. The most delayed case in this series was the patient in case 9, who presented with CRVO at 18 weeks after the infection after a 4-week delay in ophthalmic evaluation from symptom onset. Consistent with the findings in our study, Von Meijenfeld et al⁴⁴ showed that the prothrombotic state may last up to 4 months after COVID-19 infection. Because of the subjective nature of ocular symptoms, it is difficult to determine when a CRVO event truly occurs in relation to the onset of systemic infection. Our study findings highlight the importance of having a high clinical suspicion for a vascular event at the onset of ocular symptoms to minimize delay in care.

To date, retinal vascular occlusions occurring after COVID-19 infection have been limited to case reports and

are, likely, very rare. Various authors have described retinal vascular occlusions, including central retinal artery occlusion, BRVOs, and CRVOs, in association with COVID-19 (Table 2).^{22–37} The present report is the largest case series of CRVO and HRVO occurring after COVID-19 infection. It nearly doubles the currently published cases in the literature and is the only 1 to exclude predisposing risk factors. Furthermore, we performed a complete literature review of all previously published cases.

Of 12 previously published reports (13 eyes) of CRVOs or HRVOs after COVID-19 infection in the literature, half lacked predisposing conditions.³⁷ Similar to our cohort, the VA outcomes were favorable, with most patients achieving a Snellen acuity of 20/40 or better. Macular edema was identified and treated with intravitreal injections in the 46% (6 of 13) of the eyes in the published cases of HRVO or CRVO after COVID-19 infection. Similarly, our study showed that 42% (5 of 12) of the eyes developed macular edema. Based on the Central Vein Occlusion Study, in which the angiographic evidence of macular edema occurred in 84% of eyes with CRVO,⁴⁸ it is possible that macular edema occurs at a lesser frequency in patients with CRVO after COVID-19 infection. Alternatively, young patients have previously been reported to have better visual outcomes and lower rates of macular edema.^{49,50} As such, age may simply be a driver of these prognostic factors in our series. Although a statistical analysis of a larger cohort would be necessary to draw this conclusion, we hypothesize that this is related to the transient nature of the prothrombotic state following the

Table 2. A Summary of the Literature Describing Retinal Vascular Occlusions Associated with COVID-19 Infection

Study	Patient Age, Gender	Comorbid Dx	Hospitalized, Oxygen, Complication	Ocular Dx	Time to Ocular Dx	Hypercoag. work-up	Treatment	Visual Acuity (initial)	Visual Acuity (final)	Follow Up
Central retinal artery occlusions										
Acharya (2020)	60, F	Y-HTN, HL, CAD, COPD	Y, intubated	CRAO, OD	12 d	IL6, CRP, ferritin, fibrinogen, D-dimer (H)	Hydroxychloroquine Azithromycin Tocilizumab	N/A	N/A	N/A
Montesel (2020)	59, M	Y-HTN, hyperuricemia Sickle cell trait	Y, intubated	CRAO, OS Sickle cell retinopathy (sea fans)	3-4 wks	IL6, IL7, CRP, fibrinogen, D-dimer, PTT (H)	Hydroxychloroquine Azithromycin Tocilizumab 800 mg Lopinavir/Ritonavir (200/50 mg) BID LMWH, Apixaban	LP	CF	1 mo
Murchison (2020)	50s, M	N	Y, for ocular dx only, no O2	CRAO, OD	2-3 d	PT, INR, D-dimer, fibrinogen, lactate, CRP (H)	LMWH	HM	N/A	N/A
Turedi (2021)	54, M	N	Y, no O2	CRAO, OD PAMM	14 d	Negative	Hyperbaric oxygen	CF	CF	5 d
Montesel (2020)	59, M	Y-HTN, hyperuricemia Sickle cell trait	Y, intubated	CRAO, OS Sickle cell retinopathy (sea fans)	3-4 wks	IL6, IL7, CRP, fibrinogen, D-dimer, PTT (H)	Hydroxychloroquine Azithromycin Tocilizumab 800 mg Lopinavir/Ritonavir (200/50 mg) BID LMWH, Apixaban	LP	CF	1 mo
Branched retinal vein occlusions (BRVO)										
Duff (2020)	74, F	Y-HL	N	BRVO, OS CME	<1 wk, worse at 3 mo	Unknown	IVI Dex implant	20/25	N/A	N/A
Nourinia (2021)	60, F	N	Y- ICU, O2 unknown	BRVO, OS CME	10 d	ESR, CRP, ferritin, WBC, PTT, PT (H)	IVI Bevacizumab	20/200	N/A	N/A
Study	Patient Age, Gender	Comorbid Dx	Hospitalized, Oxygen, Complication	Ocular Dx	Time to Ocular Dx	Hypercoagulable work-up	Treatment	Visual Acuity (initial)	Visual Acuity (final)	Follow up
Central retinal vein occlusions										
Gaba (2020)	40, M	Y-HTN, obesity	Y, O2 NC, DVT	CRVO, OU	2 d	IL-6, CRP, ferritin, D-dimer, lactate (H)	Rivaroxaban Observation	6/6 OD, 6/12 OS	N/A	N/A
Invernizzi (2020)	54, F	N/A	Y, for ocular tx only, No O2	iCRVO, OD	10 d	CRP, ESR, lactate, D-dimer, fibrinogen, INR (H)	IV Solmedrol PO Prednisone Observation	20/40	20/20	1 wk
Yahalomi (2020)	33, M	N	N	CRVO, OS	5 wks	Fibrinogen, D-dimer (H)	Observation	20/25	N/A	N/A
Lorca (2020)	30, F	Y-DM (A1c 13%)	Y, N/A	CRVO, OU	N/A	CRP, fibrinogen, ferritin, D-dimer, platelets (H)	Observation	0.7	N/A	N/A
Walinjkar (2020)	17, M	N	N	CRVO CME	3 wk	Negative	Antibx, NSAIDS IVI Ranibizumab(x2)	6/24	6/12	2 mo
Miller (2021)	46, M	Y-HTN, HL	N	CRVO, OD CME	1 mo	Negative	IVI Aflibercept	20/20, then 20/80 (11 d)	20/20	7-8 wks
Raval (2021)	39, M	N	N/A	CRVO, OD CME	1 wk	Negative	IVI Bevacizumab (>1)	20/150	20/30	N/A

Table 2. (Continued.)

Study	Patient Age, Gender	Comorbid Dx	Hospitalized, Oxygen, Complication	Ocular Dx	Time to Ocular Dx	Hypercoagulable work-up	Treatment	Visual Acuity (initial)	Visual Acuity (final)	Follow up
Sanchez (2021)	32, M	N	N	CRVO, OD CME	8 wks	+Lupus anticoagulant, negative at 12 wks	IVI Dex implant (x2)	20/32	20/20	4 mo
Venkatesh (2021)	54, F	DM (controlled)	N- asymptomatic	CRVO, OS CME	>1 mo	D-dimer, ESR (H)	ASA 150 mg/d Observation	6/18	6/6	1 mo
Insusti-Garcia (2020)	40, M	N	N	Papillophlebitis, OS CME	6 wk	D-dimer, fibrinogen, CRP (H)	Salicylic acid Bromfenac grt IVI Dex implant	20/20, then 20/200 (2wk)	20/40	2 wks
Hemi-retinal vein occlusions										
Finn (2020)	32, M	N	N	HRVO, OS	2 wks	N/A	Observation	20/20	20/20	1 mo
Sheth (2020)	52, M	N/A	Y, N/A	HRVO, OS CME	10 d	Negative	PO Solumedrol Ranibizumab biosimilar	6/60	6/9	1 mo

Key: Antibx = antibiotics; ASA = aspirin; BID = twice a day; BRVO = branched retinal vein occlusion; CAD = coronary artery disease; CF = counting fingers; CME = cystoid macular edema; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; CRAO = central retinal artery occlusion; CRP = C-reactive protein; CRVO = central retinal vein occlusion; d = day; Dex = dexamethasone; DM = diabetes mellitus; DVT = deep vein thrombosis; Dx = diagnosis; ESR = erythrocyte sedimentation rate; f = female; H = high; HL = hyperlipidemia; HM = hand motion; HTN = hypertension; HRVO = hemiretinal vein occlusion; ICU = intensive care unit; IV = intravenous; IVI = intravitreal; LMWH = low molecular-weight heparin; LP = light perception; M = male; mo = month; N = no; N/A = not applicable; NC = nasal cannula; NSAIDS = non-steroidal anti-inflammatory drugs; OD = right eye; OS = left eye; OU = both eyes; O2 = oxygen; PAMM = paracentral acute middle maculopathy; PO = oral; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell; wk = week; Y = yes.

infection. This information would be important in determining the frequency and duration of follow-up for these cases.

The true prevalence of COVID-19 among patients with RVO is unknown. Sunny and Au⁵¹ reported that in their cohort of 66 patients with CRVO, the dominant risk factors were hypertension, diabetes, and hyperlipidemia, and no patients were positive for COVID-19 infection at presentation through a mean follow-up duration of 5.8 months. There are currently no large-scale studies assessing the rate of RVOs in a population of patients diagnosed with COVID-19.

The present study excluded patients with well-defined risk factors for the development of RVOs (Table 1). Generally, RVOs are much less common in patients aged <65 years, in the absence of systemic risk factors.^{52,53} The Beaver Dam Eye Study identified the following risk factors for RVO formation: older age; retinal focal arteriolar narrowing; glaucoma; barbiturate use; and abnormal serum creatinine, phosphorus, ionized calcium levels.⁵³ In contrast, the risk factors for young adults developing RVOs are multifactorial and less understood. In a series of 95 patients diagnosed with CRVO between 18 and 40 years of age, Chen et al⁵⁴ identified that the statistically significant ($P < 0.001$) risk factors for CRVO in young adults included primary open-angle glaucoma, retinal vasculitis, pseudotumor cerebri, hypercoagulable state, hyperlipidemia, and a prior history of venous thromboembolic disease.⁵⁵ Other studies have identified that CRVO in young adults may be linked to smoking, migraine headaches, collagen vascular disease, medications (oral contraceptives, diuretics, and sympathomimetics), and thrombophilia.^{49,55–60}

Young adults presenting with RVO may need a hypercoagulability workup to exclude systemic coagulopathies requiring anticoagulation, such as protein C and S deficiency, factor V Leiden mutation, hyperhomocysteinemia, antiphospholipid antibody syndrome, prothrombin gene mutation, antithrombin deficiency, and hyperviscosity syndrome, among others.^{59,61} The patients included in the present series were negative for thrombophilia, as determined using extensive laboratory evaluations performed by the contributing ophthalmologists and appropriate medical providers. Additionally, given the known coagulation abnormalities associated with COVID-19, we recommend that the D-dimer, fibrinogen, and platelet levels are measured at the time of diagnosis.

Our study has a number of limitations, including a retrospective, nonconsecutive design; small cohort size; and lack of standardized methods to account for all risk factors and biomarkers known to be associated with COVID-19 infection. The study design and low sample size do not support COVID-19 as being an independent risk factor for RVO development. The retrospective design did not allow us to control for all components of a thrombophilia evaluation, and thus, this was deferred to the expertise of the contributing ophthalmology provider and medical consultants. The study design could not account for confounding variables and other risk factors outside of our defined exclusion criteria. The timing of patients presenting for an ophthalmic examination after COVID-19 infection might

have resulted from heightened personal awareness of symptoms following the illness, resulting in a selection bias in our study. Importantly, large, multicenter, controlled studies are needed to compare the RVO rates among young patients with and without recent COVID-19 infection.

Conclusion

Although we acknowledge that a high seroprevalence of COVID-19 exists and that a causal relationship between COVID-19 and CRVO cannot be established, patients and

physicians should be aware of this association, given the heightened thromboinflammatory state caused by COVID-19 infection. Our series showed that in young, healthy patients with CRVO after COVID-19 infection, there was a possible temporal association with ocular symptoms typically occurring within weeks after the viral infection. Although the relationship remains anecdotal, patients may benefit from the reassurance that, like other RVOs occurring in patients of their age group, their condition is episodic and the prognosis is typically favorable with minimal intervention.

Footnotes and Disclosures

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Abbreviations and Acronyms:

BRVO = branch retinal vein occlusion; **COVID-19** = coronavirus disease 2019; **CRVO** = central retinal vein occlusion; **HRVO** = hemiretinal vein occlusion; **RVO** = retinal vein occlusion; **VA** = visual acuity.

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