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The Relationship between COVID-19 and Retinal Vascular Occlusive Diseases: A Systemic Review

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Abstract: This systematic examines research into patients diagnosed with retinal vascular occlusive diseases (RVODs) secondary to coronavirus disease 2019 (COVID-19) infection or vaccination. RVODs include central retinal vein occlusion, branch retinal vein occlusion, central retinal artery occlusion, and branch retinal artery occlusion. Previous studies have posited a possible link between RVODs and COVID-19. RVODs are of two types: retinal vein occlusion and retinal artery occlusion. These disorders develop when retinal blood vessels become clogged by thrombi or fat deposition. The retina is an important component of the visual apparatus. Its photoreceptors are stimulated by the light hitting the eye and record its pattern. The retina then relays this visual information to the brain. When retinal blood vessels become clogged, the damage can range from slightly reduced vision to complete blindness. COVID-19 causes endothelial dysfunction and increased levels of von Willebrand factor antigens in the blood. Elevation of von Willebrand factor activates the coagulation process and platelet aggregation. The treatment methods and visual prognosis in COVID-19-related RVODs do not differ from conventional RVODs. However, ophthalmologists need to be aware of the possible relationship and should consider RVODs when they encounter patients with vision loss following COVID-19 infection or vaccination.

Keywords: branch retinal artery occlusion; branch retinal vein occlusion; central retinal artery occlusion; central retinal vein occlusion; COVID-19; retinal vascular occlusive disease

1. Introduction

The coronavirus disease 2019 (COVID-19) has had huge global health implication and continues to ravage healthcare systems around the world [1]. COVID-19 infection can be followed by multi-organ pathology and vascular damage [2] that, in turn, increases the risk of fatal vascular occlusive diseases such as thrombosis, myocardial infarction, arrhythmia, and cerebral apoplexy [3–6]. Elevation of thrombotic tendencies and increased risk of thrombosis have been found to persist for several months after COVID-19 infection [7].

Fundus photography (which is fast and noninvasive) and fundoscopic examination of the ocular fundus give ophthalmologists direct access to the retina and its vasculature. The retinal arteries and veins are believed to be representative of the state of the body's entire microvascular system [8]. Therefore, it is advisable for ophthalmologists to check for any vascular abnormalities caused by COVID-19 following infection. It has been posited that the increased risk of thrombosis caused by COVID-19 may be associated with the development of retinal vascular occlusive diseases (RVODs).

RVODs include retinal vein occlusion (RVO) and retinal artery occlusion (RAO). Both of these are subdivided into central and branch occlusions, i.e., central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), branch retinal vein occlusion (BRVO), and branch retinal artery occlusion (BRAO). After diabetic retinopathy, RVO is the most common retinal vascular disease [9].

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The prevalence of RVOs in the developed world is 5.2 per 1,000, while that of CRVOs is 0.8 per 1,000 [10].

In CRVO, sudden visual impairment is common; while in BRVO, visual field defects and shape distortion are typical symptoms. RVOs affect visual function and are characterized by retinal hemorrhage, soft exudate, and macula edema. CRVO can be classified as ischemic or nonischemic. The ischemic type of CRVO can cause neovascular glaucoma and blindness. The primary treatment methods are anti-vascular endothelial growth factor (VEGF) antibodies and retinal photocoagulation [11–13]. Since the introduction of anti-VEGF antibodies, there has been a significant improvement in the prognoses for these conditions [13].

RAO is an acute disease in which the occlusion usually causes sudden visual reduction. If retinal blood flow does not return promptly, at least some visual reduction and visual field defects will be permanent. Although many treatment methods are reported [14,15], there is not yet an established standardized treatment and RAO remain difficult to treat. Yet, RAO carries a risk of cardiovascular events [16], such as cerebral stroke and may also be a symptom of a systemic condition. The visual prognosis for CRAO is poor and decimal visual acuity (VA) usually falls below 0.05 [17].

RVODs are relatively common disorders that can cause severe visual impairment. Risk factors for RVODs include hypercoagulability and thrombotic disorders. In this review, we investigate the relationship between COVID-19 and RVODs.

2. Mechanism of Vascular Occlusion of COVID-19

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, invades cells by attaching to angiotensin-converting enzyme 2 (ACE2) proteins [18,19]. COVID-19-associated coagulopathy increases the generation of the coagulation factor, thrombin, in the veins and arteries. This phenomenon is strongly correlated with vascular endothelial damage [20,21]. Vascular endothelial cells infected with SARS-CoV-2 release through ACE 2 release von Willebrand factor and angiopoietin 2. Von Willebrand factor causes platelets to adhere to the connective tissue under vascular endothelial cells and this becomes a foothold for thrombin [22]. ACE2 increases inflammation and exacerbates apoptosis and the permeability of vascular endothelial cells [22]. Infection of these cells also decreases antithrombogenicity. Inflammatory macrophages secrete inflammatory cytokines as a defense against viral infection. Then, crosstalk between the inflammatory and coagulation factors further reinforces both processes. SARS-CoV-2 can also directly infect macrophages. Infected macrophage then expresses tissue factor, another coagulation factor, activating the exogenous blood coagulation system. Crosstalk between inflammatory and coagulation processes cause platelet and neutrophil activation. Neutrophil extracellular traps are released from the activated neutrophils and a coagulation cascade proceeds. This reduces the levels of ACE2 on cell surfaces, creating an ideal microenvironment for thrombin production.

3. CRVO after COVID-19 Infection

Reported cases of CRVO development after COVID-19 infection are summarized in Tables 1A and 1B [23–38]. The average age across the studies listed was 36.4 ± 11.0 years. This is significantly younger than the average age of 71.2 ± 12.0 years obtained from our unpublished data ($p < 0.001$, unpaired t-test), which was gathered before the COVID-19 pandemic. This difference seems to suggest that COVID-19 infection can lead to CRVO at an earlier age than it might usually occur. The total number of cases reported in the listed studies was 27, comprising 16 males and 11 females. Our unpublished data included 148 CRVO cases, comprising 74 males and 74 females. There were no significant differences in incidence between this study and our unpublished data ($p = 0.38$, unpaired t-test). In a study conducted before the pandemic, Li et al. reported that CRVO presents more frequently in men (50.3%) before COVID-19 pandemic [39]. The time between COVID-19 diagnosis and CRVO symptom onset ranged between 0–6 months. The authors point out the difficulties in defining the point at which symptoms should no longer be considered COVID-19-related, and judging when CRVO was not a complication of COVID-19 infection. There was no fixed period within which blood test results due to COVID-19 infection returned to normal. The average

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logarithmic VA at the initial visit as 0.73 ± 0.75 referring to previous report [40]. This was not significantly different from that found in our unpublished data (0.77 ± 0.57; $p = 0.71$, unpaired t-test). The most common treatment for CRVO was intravitreal injection of anti-VEGF antibodies; however, systemic corticosteroids were administered to those patients whose CRVO symptoms were within a few days of COVID-19 infection. Although photocoagulation is sometimes performed in the treatment of CRVO, none of the cases reported underwent this procedure. The final mean logarithmic VA was 0.22 ± 0.49, whereas that in our unpublished CRVO data, gathered before the COVID-19 pandemic, was 0.58 ± 0.75. Our unpublished final logarithmic VA was taken 12 ± 2 months after treatment. The final mean logarithmic VA in the present study is significantly better than that from our unpublished data ($p < 0.01$, unpaired t-test). Sen et al. have reported that younger age affected visual outcomes in CRVO treated with intravitreal injection of anti-VEGF antibodies [41]. Furthermore, in a sample comprised of 85 patients with CRVOs and 26 with BRVOs, Dărăbuș et al. found that the most important nonimaging predictors of best-corrected visual acuity (BCVA) after RVOs were age and baseline BCVA [42]. Thus, it should be borne in mind that the younger average age in this study is likely to have affected the visual outcomes.

Table 1. A.

No.	Authors	Age	Sex	Laterality	Time between COVID-19 diagnosis and symptom onset (days)	Abnormal blood test findings
1	Invernizzi A et al.	54	F	R	5	CRP (31.1 mg/L) Erythrocyte sedimentation rate (78) lactate dehydrogenase (269 U/L) PT 13.8 sec aPTT 36.6 sec fibrinogen (6.82 g/l) d-dimer (426 μg/L)
2	Gaba WH et al.	40	M	R, L	1	ferritin (1518 μg/L) lactate dehydrogenase (402 U/L) d-dimer (>20 μg/L) CRP (68 mg/L) interlekin-6 (87.1 pg/mL)
3	Riazi-Esfahani H et al.	35	M	L	120	CRP borderline homocysteine level borderline
4	Sheth JU, et al.	52	M	L	10	unremarkable
5	Walinjkar JA, et al.	17	F	R	23	not listed
6	Kılıçarslan O, et al.	50	M	R	0	PTT (20.3 s)
7	Raval et al.	39	M	R	7	lactate dehydrogenase (222 U/L) unremarkable
8	Finn AP et al.	32	M	R	30	not listed
9	Lin CH et al.	48	M	R, L	30	d-dimer (1050 μg/L) CRP (86.89 mg/L)

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10	Yahalomi T et al.	33	M	L	20	unremarkable
11	Venkatesh R, et al.	56	F	L	0	d-dimer (707 µg/L) ESR (52 mm)
12	Shroff D et al.	41	F	R	21	d-dimer (0.9 µg/L)
13	Staropoli PC et al.	15	M	L	0	no particular
15	Ashkenazy N et al.	33	M		42	not listed
		29	M		84	not listed
		24	F		28	not listed
		36	F		98	not listed
		22	M		63	not listed
		18	F		21	not listed
		50	F		126	not listed
		41	F		105	not listed
		34	M		98	not listed
		30	M		42	not listed
		31	F		7	not listed
		38	F		28	not listed
16	Płatkowska-Adamska B et al.	38	M	R	180	cholesterol (243 mg/dL)
17	Quigley C, et al.	42	M	R	240	d-dimer (543 ug/L) WBC (3.5 x 10^9/L) total cholesterol (5.4 mmol/L) neutrophils (1.4 x 109/L)

aPTT, activated partial thromboplastin time; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; L, left; M, male; PT, prothrombin time; PPT, partial prothrombin time; R, right; WBC, white blood cells.

Table 1. B.

No.	Authors	BCVA at initial visit	Treatment	Final BCVA
1	Invernizzi A et al.	20/40	oral prednisolone 60 mg/day	20/20 (1 week)
2	Gaba WH et al.	6/9 in the right eye 6/18 in the left eye	rivaroxaban 15 mg twice daily	
3	Riazi-Esfahani H et al.	CF	IV anti-VEGF (3 times)	not listed
4	Sheth JU, et al.	6/60	oral methylprednisolone (40 mg/day) IV Ranibizumab BS	6/9 (1 month)
5	Walinjkar JA, et al.	6/24	IVR	6/12 (2 month)
6	Kılıçarslan O, et al.	CF	IVA Systemic steroid therapy	CF (3 months)
7	Raval et al.	20/150	IVB	20/30
8	Finn AP et al.	20/20	not listed	not listed
9	Lin CH et al.	CF (both eyes)	IV anti-VEGF	not listed

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10	Yahalomi T et al.	20/25	not listed	not listed
11	Venkatesh R, et al.	6/18	oral aspirin	6/6 (1 month)
12	Shroff D et al.	3/60	IV anti-VEGF	not listed
13	Staropoli PC et al.	E" at 2 feet	Doxycycline 100mg twice daily prednisolone eye drops IVB	20/200
15	Ashkenazy N et al.	20/20		20/15
		20/80	IVB	20/20
		20/60		20/30
		20/70	IVB	20/20
		20/20		20/20
		20/25		20/20
		20/30	plavix	20/25
		20/50		20/30
		20/20		20/20
		CF	oral prednisolone oral aspirin IVB	20/20
		20/20		20/20
		20/20	IVB	20/60
16	Płatkowska-Adamska B et al.	5/25	IVR	20/20
17	Quigley C, et al.	6/18	IVB	not listed

BCVA, best-corrected visual acuity; BS, biosimilar; CF, counting fingers; IV, intravitreal; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; VEGF, vascular endothelial growth factor.

4. CRVO after COVID-19 Vaccination

Reported cases of CRVO that developed after COVID-19 vaccination are shown in Tables 2A–2D [43–54]. The average age in this subject was 39.4 ± 13.3 years a, which was not significantly different to the age of those who developed CRVO after COVID-19 infection (summarized in Tables 1A and 1B) (p = 0.45, unpaired t-test). There were 13 cases of postvaccine CRVO, comprised of nine males and four females. The sex ratio of those with CRVO after vaccination did not differ significantly from that of the CRVO after infection subset (p = 0.79, unpaired t-test). The time between receipt of the COVID-19 vaccine and CRVO symptom onset ranged from was 0 to 25 days, with an average of 9.1 ± 7.3 days.

Table 2. A.

No.	Authors	Age	Sex	Laterality	Time between vaccination and symptom onset (days)
1	Sonawane NJ et al.	50	M	R	4
		43	F	R	3
2	Ishiguro K et al.	47	M	R	0 (8 hours)
3	Lee S et al	34	M	L	10-12
4	Wu D et al	54	M	L	9
5	Romano D et al.	54	F	R	2
6	Endo B et al	52	M	L	15
7	Sung SY et al.	25	F	L	10
8	Dutta Majumder P et al.	28	M	R	25
9	Shah PP et al.	27	F	L	10
10	Takacs A et al.	35	M	R	14
11	Nangia P et al.	13	M	L	15

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12	Bialasiewicz AA et al.	50	M	L	0

F, female; L, left; M, male; R, right.

Table 2B shows which vaccine type each patient received. However, the relatively small number of reported cases prevent us from determining whether the risk of CRVO differs between the different vaccines. The number of COVID-19 vaccination that patients had received prior to CRVO onset ranged between 1–3 and averaged 1.8 ± 0.7.

Table 2. B.

No.	Authors	Vaccine type	Vaccine number
1	Sonawane NJ et al.	Oxford-AstraZeneca (ChAdOx1 nCoV-19/ AZD1222)	second
		Oxford-AstraZeneca (ChAdOx1 nCoV-19/ AZD1222)	second
2	Ishiguro K et al.	Pfizer/BioNTech (BNT162b2)	first
3	Lee S et al	Pfizer/BioNTech (BNT162b2)	second
4	Wu D et al	Pfizer/BioNTech (BNT162b2)	second
5	Romano D et al.	Oxford-AstraZeneca (ChAdOx1 nCoV-19/ AZD1222)	second
6	Endo B et al	Pfizer/BioNTech (BNT162b2)	first
7	Sung SY et al.	Pfizer/BioNTech (BNT162b2)	third
8	Dutta Majumder P et al.	Oxford-AstraZeneca (ChAdOx1 nCoV-19/ AZD1222)	third
9	Shah PP et al.	Pfizer/BioNTech (BNT162b2)	first
10	Takacs A et al.	mRNA vaccine	first
11	Nangia P et al.	Corbevax COVID-19 vaccine	first
12	Bialasiewicz AA et al.	Pfizer/BioNTech (BNT162b2)	second

There was no fixed tendency in blood correction. Logarithmic VA at the initial visit was 0.81 ± 0.73 referring to previous report [40] and there was not significant difference from CRVO after COVID-19 infection shown in Table 1B (p = 0.78, unpaired t-test).

Table 2. C.

No	Authors	Abnormal blood test findings	BCVA at initial visit
1	Sonawane NJ et al.	HbA1c 13.2% Cre 1.9 mg/dL	6/60
		ESR 49 CRP 14.6 RF 11 d-dimer 6,077.4 ng/mL	5/60
2	Ishiguro K et al.	triglyceride 256 mg/dL aPTT 30.6 s CRP 177%	20/200
3	Lee S et al	total cholesterol 227 LDL 159 ESR 26	CF
4	Wu D et al	not listed	6/30
5	Romano D et al.	normal	20/400
6	Endo B et al	normal	20/20
7	Sung SY et al.	HbA1c 9.2%	20/100
8	Dutta Majumder P et al.	normal	2/60
9	Shah PP et al.	not listed	20/20
10	Takacs A et al.	serum prothrombin time 9.1 s anti-prothrombin 123% serum homocysteine 16.4 μmol/l	0.5
11	Nangia P et al.	normal	6/7.5

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12	Bialasiewicz AA et al.	normal	0.5

aPTT, activated partial thromboplastin time; BCVA, best-corrected visual acuity; CF, counting fingers; Cre, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBA1c, hemoglobin A1c; LDL, low density lipoprotein; PT, prothrombin time; RF, rheumatoid factor.

Although intravitreal injection of anti-VEGF antibody was the main treatment, whole body administration of corticosteroid was performed in some instances. Only one case was treated with retinal photocoagulation. The mean final logarithmic VA was 0.18 ± 0.31 and there was no significant difference between this and the mean final logarithmic VA of those with CRVO after COVID-19 infection shown in Table 1B (p = 0.78, unpaired t-test).

Table 2. D.

No.	Authors	Treatment	Final BCVA
1	Sonawane NJ et al.	IV anti-VEGF	not listed
		none	not listed
2	Ishiguro K et al.	IVA (5 treatments)	20/20 (10 months)
3	Lee S et al	oral methylprednisolone	20/30 (3 weeks)
		IV methylprednisolone	
4	Wu D et al	IVB	6/12
5	Romano D et al.	intravitreal dexamethasone implant	20/200
		PRP	
6	Endo B et al	IV dexamethasone	20/20
		IVB, oral apixaban	
7	Sung SY et al.	IVR, IVA (3 treatments)	20/30
8	Dutta Majumder P et al.	pulse corticosteroid	6/9
		oral corticosteroid	
9	Shah PP et al.	IVR (3 treatments)	not listed
		Acetazolamide	
		intravenous iron infusions	
10	Takacs A et al.	IVA	1.0 (2 months)
		oral ASA protect	
11	Nangia P et al.	pulse corticosteroid	6/6
12	Bialasiewicz AA et al.	aspirin	1.0 (3 days)
		IVA	

BCVA, best-corrected visual acuity; BS, biosimilar; CF, counting fingers; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; PRP, pan-retinal photocoagulation; VEGF, vascular endothelial growth factor.

5. BRVO after COVID-19 Infection

The subset who developed BRVO after COVID-19 infection are summarized in Table 3A and 3B [55–60]. Their average age was 56.8 ± 11.7 years. In a study conducted before the COVID-19 pandemic, Lee et al. reported an average age of 58.2 years in a sample of 354 BRVO patients [61]. This is very close to the average age found in this review. Li et al. and Lee et al. have both reported a slightly higher incidence of BRVO among women (54.5% and 58.8%, respectively) [39,61]. The ratio of males to females was 5: 3. The ocular laterality in those with BRVO after COVID-19 infection was one right eye and six left eyes. Li et al. reported a right eye onset preference in BRVO (51.0%) [39]. The mean time, in days, between COVID-19 diagnosis and initial BRVO symptoms was 50.6 ± 41.2 days. There were no patterns observed in the return to normal of blood test abnormalities

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Table 3. A.

No.	Authors	Age	Sex	Laterality	Time between COVID-19 diagnosis and symptom onset (days)	Abnormal blood test findings
1	Nourinia R, et al.	60	F	L	10	slightly prolonged PT and PTT high ESR level high CRP level high d-dimer level high ferritin level elevated WBC
2	Duff S, et al.	74	F	L	90	not listed
3	Karasu B, et al.	48	M	L	60	not listed
				R	90	not listed
4	Kapsis P, et al.	65	M	L	not listed	normal
5	Shiroma HF, et al.	54	F	not listed	7	not listed
		36	M	not listed	90	not listed
		64	M	not listed	7	not listed
6	Güven YZ, et al.	53	M	L	not listed	ESR 74 mm/h CRP 29.8 mg/L d-dimer 404 μg/L

aPTT, activated partial thromboplastin time; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; L, left; M, male; PT, prothrombin time; PPT, partial prothrombin time; R, right; WBC, white blood cells.

Logarithmic visual acuity at initial visit was 0.67 ± 0.66 referring to previous report [40]. For those with BRVO after COVID-19 infection, intravitreal injection of anti-VEGF antibodies was the main treatment. The final logarithmic VA of this subset was 0.38 ± 0.42.

Table 3. B.

No.	Authors	BCVA at Initial visit	Treatment	Final BCVA
1	Nourinia R, et al.	20/200	IVB	not listed
2	Duff S, et al.	20/50	intravitreal dexamethasone implant	not listed
3	Karasu B, et al.	20/100	heparin	30/100
		10/100	pantoprazole favipiravir	40/100
4	Kapsis P, et al.	6/36	IVA	6/9
5	Shiroma HF, et al.	20/25	ketorolacid	20/20
		20/30	IV anti VEGF	20/20
		CF	IV anti VEGF	20/200
6	Güven YZ, et al.	20/20	not listed	not listed

BCVA, best-corrected visual acuity; CF, counting fingers; IV, intravitreal; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; VEGF, vascular endothelial growth factor.

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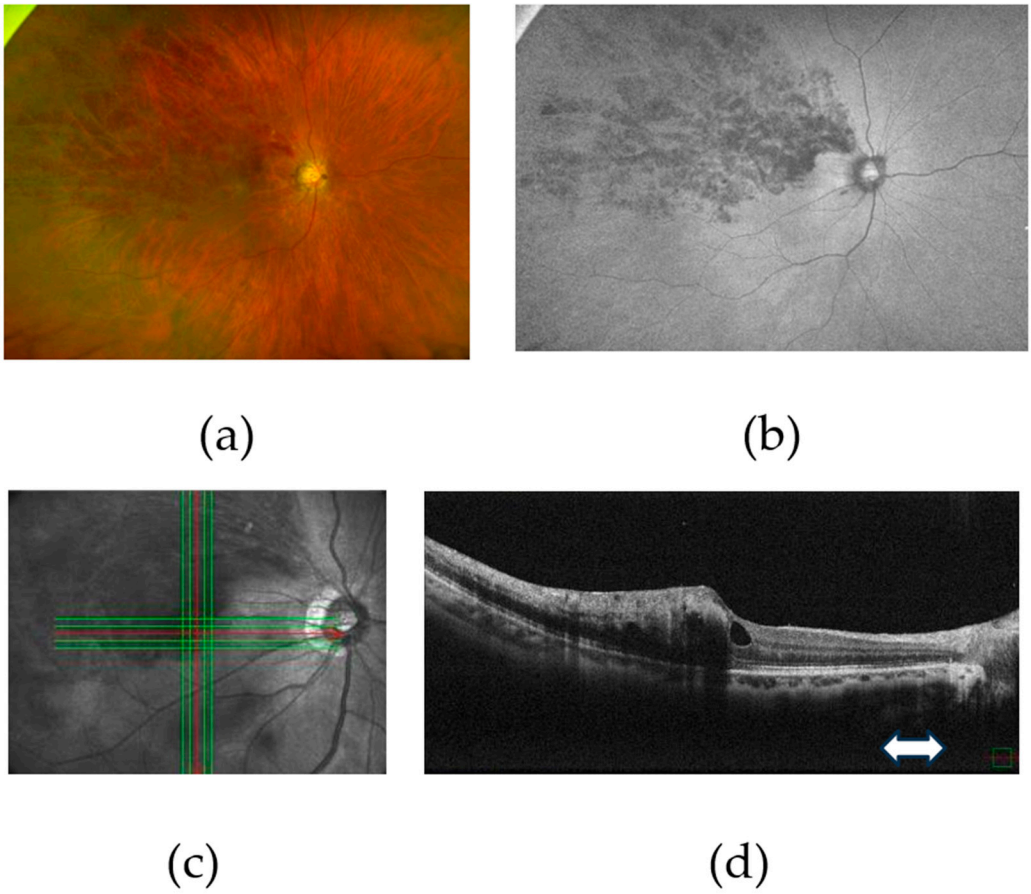

Figure 1. Images from a 47-year-old female who developed branch retinal vein occlusion 3 weeks after receiving a COVID-19 diagnosis. (**a**) A retinal hemorrhage caused by the failure of the supratemporal vein in the patient's right eye; (**b**) The retinal hemorrhage is visualized more clearly using autofluorescence mode; (**c**) Optical coherence tomography was used to focus in on the retinal foveola; (**d**) Retinal edema and an intraretinal cyst that have developed alongside the retinal hemorrhage.

6. BRVO after COVID-19 Vaccination

The cases who developed BRVO after COVID-19 vaccine are shown in Table 4A and 4B [62–71]. Their average age was 55.5 ± 13.2 years and there was no significant difference between this and the average age of those who developed BRVO after COVID-19 infection (p = 0.82, unpaired t-test). The ratio of males to females was 6: 7. The mean time between COVID-19 vaccination and BRVO symptom onset was 5.1 ± 5.8 days. This was not significantly different from the mean time of those with CRVO after COVID-19 vaccination (p = 0.10, unpaired t-test).

Table 4. A.

No.	Authors	Age	Sex	Laterality	Time between vaccine and symptom onset (days)
1	Pur DR, et al.	34	M	R	2
2	Sugihara K, et al.	38	M	L	2
3	Gironi M, et al.	50	M	R	1
				L	
4	Tanaka H, et al.	50	F	R	3
		56	F	R	3
5	Karageorgiou G, et al.	60	M	R	7
6	Lee J, et al.	41	F	R	2

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7	Silva LSCD, et al.	66	F	R	16
8	Peters MC, et al.	71	M	not listed	2
		73	F	not listed	3
		47	F	not listed	5
9	Choi M, et al.	66	M	L	7
		69	F	L	3
10	Bolletta E, et al.	not listed	not listed	L	23
		not listed	not listed	L	2
		not listed	not listed	L	2
		not listed	not listed	L	3

F, female; L, left; M, male; R, right.

The vaccines used were by Pfizer, Moderna, and AstraZeneca. The average number of vaccines received was 1.4 ± 0.5. This was not significantly different from the average number received by those with CRVO after COVID-19 vaccination ($p = 0.14$).

Table 4. B.

No.	Authors	type of vaccines	Numbers of times of vaccines
1	Pur DR, et al.	BNT162b2 (Pfizer-BioNTech)	first
2	Sugihara K, et al.	BNT162b2 (Pfizer-BioNTech)	second
3	Gironi M, et al.	mRNA-1237 vaccine (Moderna).	booster dose
4	Tanaka H, et al.	BNT162b2 (Pfizer-BioNTech)	first
		BNT162b2 (Pfizer-BioNTech)	first
5	Karageorgiou G, et al.	ChAdOxl nCoV-19 (Oxford-AstraZeneca)	not listed
6	Lee J, et al.	not listed	second
7	Silva LSCD, et al.	ChAdOxl nCoV-19 (Oxford-AstraZeneca)	not listed
8	Peters MC, et al.	ChAdOxl nCoV-19 (Oxford-AstraZeneca)	first
		ChAdOxl nCoV-19 (Oxford-AstraZeneca)	first
		BNT162b2 (Pfizer-BioNTech)	first
9	Choi M, et al.	ChAdOxl nCoV-19 (Oxford-AstraZeneca)	second
		ChAdOxl nCoV-19 (Oxford-AstraZeneca)	first
10	Bolletta E, et al.	not listed	second
		not listed	first
		not listed	second
		not listed	second

There are no specific findings in blood correction. Logarithmic visual acuity at the initial visit was 0.27 ± 0.34 and there was no significant difference compared to logarithmic visual acuity at the initial visit BRVO after COVID-19 infection ($P = 0.14$).

Table 4. C.

No.	Authors	Abnormal blood test findings	BCVA at initial visit
1	Pur DR, et al.	normal	20/20
2	Sugihara K, et al.	normal	0.9
3	Gironi M, et al.	mild alteration in liver function	20/200
			20/28
4	Tanaka H, et al.	not listed	20/25
		not listed	13/20
5	Karageorgiou G, et al.	normal	20/20
6	Lee J, et al.	ESR 46 mm/h	6/18
7	Silva LSCD, et al.	CRP 1.0 mg/dL	not listed

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8	Peters MC, et al.	not listed	not listed
		not listed	6/60
		not listed	6/19
9	Choi M, et al.	not listed	6/9.6
		not listed	20/20
10	Bolletta E, et al.	not listed	20/20
		not listed	20/20
		not listed	20/100
		not listed	20/32
		not listed	20/22

BCVA, best-corrected visual acuity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

The main treatment was intravitreal anti-VEGF antibody injection. The final logarithmic VA was 0.0.35 ± 0.11 and there was no significant difference between this final VA and that reported in those with BRVO after COVID-19 infection (p = 0.14).

Table 4. D.

No.	Authors	Treatment	Final BCVA
1	Pur DR, et al.	observation	20/20
2	Sugihara K, et al.	second dose of IVA	1.2
3	Gironi M, et al.	IVR PC	not listed
		IVR PC	not listed
4	Tanaka H, et al.	three doses of IVR	20/20
		three doses of IVR	20/20
5	Karageorgiou G, et al.	not listed	not listed
6	Lee J, et al.	three doses of IVR	6/6
7	Silva LSCD, et al.	not listed	not listed
8	Peters MC, et al.	not listed	not listed
		IVB	not listed
		IVA	not listed
9	Choi M, et al.	IVB	not listed
		observation	not listed
10	Bolletta E, et al.	oral aspirin	not listed
		IV anti-VEGF	20/20
		IV anti-VEGF	20/40
		IV anti-VEGF	20/25
		IV anti-VEGF	20/20

BCVA, best-corrected visual acuity; IV, intravitreal; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; PC, photocoagulation; VEGF, vascular endothelial growth factor.

7. CRAO after COVID-19 Infection

Cases of CRAO after COVID-19 infection are shown in Table 5A and 5B [72–82]. The average age was 50.0 ± 17.3 years and the ratio of males to females was 9: 3. Four of the cases were in the right eye, six in the left, and one in both eyes. Lee found that, in 91 patients with acute nonarteritic CRAO, 62.6% were male and the average age was 66.4 years [83]. In this instance, the average age was reduced considerably by the inclusion of a 6-year-old boy [74]. Consistent with the findings of Li et al. [39], Lee reported a higher incidence of CRAO after COVID-19 infection in men. The mean time from COVID-19 diagnosis to symptom onset was 12.6 ± 9.5 days.

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Table 5. A.

No.	Authors	Age	Sex	Laterality	Time between COVID-19 diagnosis and symptom onset (days)	Abnormal blood test findings
1	Bapaye MM, et al.	42	M	B	13	normal
2	Heidarzadeh HR, et al.	44	M	L	21	normal
3	Abbati G, et al.	6	F	L R	0 0	CRP 1.12 mg/L
4	Montesel A, et al.	59	M	L	10	normal
5	de Oliveira MR, et al.	68	F	L	23	d-dimer 1,386 µg/L
6	Ucar F, et al.	54	M	L	not listed	CRP 22.9 mg/L fibrinogen 587 mg/dL fibrinogen 405.1 mg/dL CRP 128.29 mg/L d-dimer 1041 µg/L ferritin 458.53 platelets 486x10^9
7	Yalçınbayır Ö, et al	48	F	R	14	elevated d-dimer levels elevated fibrinogen levels elevated factor VIII levels elevated von Willebrand factor levels decreased antithrombin levels
		66	M	L	22	elevated d-dimer levels elevated fibrinogen levels elevated factor VIII levels elevated von Willebrand factor levels
8	Lekha T, et al.	47	M	R	unknown	not listed
9	Acharya S, et al.	60	M	R	12	not listed
10	Larochelle RD, et al.	68	M	R	0	not listed
11	Been Sayeed SKJ, et al.	38	M	L	unknown	not listed

CRP, C-reactive protein; F, female; L, left; M, male; R, right.

The logarithmic visual acuity at the initial visit was 2.29 ± 0.95 referring to previous report [40]. Treatment was irregular and the final logarithmic visual acuity was 2.44±0.90. Some cases had no light perception (NLP) at the initial visit, while others had NLP by the final visit. The visual outcomes among this subset were very severe. Shah et al. reported that 447 of the 484 patients who presented within 30 days and had comprehensive documentation showed VA ≤20/200 [84]. They further reported that, of the 441 patients with documented follow-up, 380 (86.2%) remained at that VA level long-term. It has previously been inferred that the shorter the duration between CRAO symptom onset and treatment, the better the prognosis. However, Shah et al. found this to have no effect on final VA outcomes [84]. St Peter et al. found that hyperbaric oxygen may be an effective treatment for nonarteritic CRAO, especially with early treatment and salvageable vision [85]. They emphasize the importance of the earliest treatment possible in patients with CRAO [85]. Currently, patients may receive one of various treatments for CRAO because no individual treatment has been established as particularly effective. Visual outcomes are very poor among those who suffer CRAO.

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Table 5. B.

No.	Authors	BCVA at initial visit	Treatment	Final BCVA
1	Bapaye MM, et al.	LP	not listed	LP
2	Heidarzadeh HR, et al.	LP	oral prednisolone, PRP	NLP
3	Abbati G,et al	HM NLP	heparin intravenous steroid oral prednisolone	CF NLP
4	Montesel A, et al.	LP	not listed	CF
5	de Oliveira MR, et al.	20/400	ocular massage	CF
6	Ucar F, et al.	CF	hypotensive eyedrops 20% mannitol anterior chamber paracentesis topical brimonidine dorzolamide/timolol moxifloxacin/dexamethasone combination drops oral acetazolamide oral aspirin	not listed
7	Yalçınbayır Ö, et al	HM LP	anterior chamber paracentesis amoxicillin clavulanic acid prednisolone	HM LP
8	Lekha T, et al.	6/36	not listed	not listed
9	Acharya S, et al.	NLP	not listed	not listed
10	Larochelle RD, et al.	LP	not listed	not listed
11	Been Sayeed SKJ, et al.	CF	not listed	not listed
11	Been Sayeed SKJ, et al.	CF	not listed	not listed

BCVA, best-corrected visual acuity; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; PRP, pan-retinal photocoagulation.

8. CRAO after Vaccination

CRAO cases after COVID-19 vaccination are shown in Table 6A-6D [86–91]. The average age was 55.5 ± 18.5 years and the male to female ratio was 3: 3. Of the 91 patients with acute nonarteritic CRAO reported by Lee, 62.6% were male and the average age was 66.4 years [83]. Thus, the average age among the cases shown in Tables 6A to 6D is younger than that previously reported in CRAO unassociated with COVID-19 [83]. Also among patients with CRAO unrelated to COVID-19, Kido et al. have reported an incidence rate 1.4 times higher in males than females [92]. The time from COVID-19 vaccination to CRAO symptom onset ranged from 1 to 21 days, with a mean of 7.3 ± 7.4 days. The time between receipt of the COVID-19 vaccine and CRVO symptom onset was 9.1 ± 7.3 days. There was no significant difference between these times for CRVO and CRAO after vaccination (p = 0.63, unpaired t-test).

Table 6. A.

No.	Authors	Age	Sex	Laterality	Time between vaccine and symptom onset (days)
1	Abdin AD, et al.	76	F	L	2
2	Chow SY, et al.	70	M	R	5
3	Chen J, et al.	40	F	L	21
4	Yamagishi A, et al.	33	F	L	1

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5	Thakar M, et al.	44	M	L	10
6	Wang LU, et al.	70	M	R	5

F, female; L, left; M, male; R, right.

The COVID-19 vaccines used were by Pfizer, Moderna, AstraZeneca, and Bharat Biotech.

Table 6. B.

No.	Authors	Vaccine type	Vaccine number
1	Abdin AD, et al.	ChAdOxl nCoV-19 (Oxford-AstraZeneca)	first
2	Chow SY, et al.	mRNA-1237 vaccine (Moderna).	first
3	Chen J, et al.	BNT162b2 (Pfizer-BioNTech)	first
4	Yamagishi A, et al.	BNT162b2 (Pfizer-BioNTech)	second
5	Thakar M, et al.	Covaxin (Bharat Biotech, BBV152)	second
6	Wang LU, et al.	mRNA-1237 vaccine (Moderna).	not listed

Although there were some slightly abnormal blood test results, they were not a characteristic feature of the patients in this subset. VA at the initial visit was poor in most cases, but 20/40 in one case.

Table 6. C.

No.	Authors	Abnormal blood test findings	BCVA at initial visit
1	Abdin AD, et al.	normal	HM
2	Chow SY, et al.	unremarkable	CF
3	Chen J, et al.	LDL 125 mg/dL	20/40
4	Yamagishi A, et al.	not listed	not listed
5	Thakar M, et al.	ESR 28 mm/h	LP
6	Wang LU, et al.	anti-PF 4 73.34 ng/mL	CF

BCVA, best-corrected visual acuity; CF, counting fingers; ESR, erythrocyte sedimentation rate; HM, hand motion; LDL, low density lipoprotein; LP, light perception; PF, platelet factor.

Some cases had NLP by their final visit and only one case recovered some of their visual function, which increased to 1.2 in decimal VA.

Table 6. D.

No.	Authors	Treatment	Final BCVA
1	Abdin AD, et al.	ocular massage 500 ml pentoxifylline IV dorzolamide eye drop aspirin 100 mg	not listed
2	Chow SY, et al.	clopidogrel and hyperbaric oxygen therapy	CF
3	Chen J, et al.	heparin	NLP
4	Yamagishi A, et al.	intravenous D-mannitol acetazolamide 10-minute ocular massage	1.2
5	Thakar M, et al.	not listed	not listed
6	Wang LU, et al.	hyperbaric oxygen therapy topical antiglaucoma drops	CF

BCVA, best-corrected visual acuity; CF, counting fingers; NLP, no light perception.

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9. BRAO after COVID-19 Infection

Published cases of BRAO after COVID-19 infection are summarized in Tables 7A and 7B [93–96]. The average age of this subset was 41.3 ± 17.8 years and all patients were male. The average time between COVID-19 diagnosis and BRAO symptom onset was 48.3 ± 39.6 days. There were no identifiable patterns in the return of blood test results to normal levels.

Table 7. A.

No.	Authors	Age	Sex	Laterality	Time between COVID-19 diagnosis and symptom onset (days)	Abnormal blood test findings
1	Ateş O, et al.	34	F	R	107	CRP levels slightly abnormal lupus anticoagulant levels slightly abnormal fibrinogen levels slightly abnormal d-dimer levels slightly abnormal ferritin levels slightly abnormal
2	Panigrahi PK, et al.	23	F	R	21	PT 16 s d-dimer 732 ng/ml serum ferritin 411 μg/L
3	Hirosawa K, et al.	43	F	R	30	WBC 11.7 x 10^9/L
4	Uzun A, et al.	65	F	L	5 w	d-dimer 1.76 mg/L

CRP, C-reactive protein; F, female; L, left; M, male; PT, prothrombin time; R, right; w, week; WBC, white blood cells.

VA at the initial visit was 0.092 ± 0.071 and this value is significantly better than VA at the initial visit of CRAO after COVID-19 infection ($p < 0.001$). Because excellent treatment is not established today, many treatments methods were irregular. The final VA value was not reported in all cases, which prevented a detailed examination of treatment effects on visual outcomes.

Table 7. B.

No.	Authors	BCVA at initial visit	Treatment	Final BCVA
1	Ateş O, et al.	10/10	hyperbaric oxygen therapy	not listed
2	Panigrahi PK, et al.	6/9	systemic anticoagulants	not listed
3	Hirosawa K, et al.	20/25	alprostadil	not listed
4	Uzun A, et al.	20/25	aspirin	not listed

BCVA, best-corrected visual acuity.

10. BRAO after COVID-19 Vaccination

Reported cases of BRAO after COVID-19 vaccination are summarized in Tables 8A–8D [97–99]. The average age of this subset was 62.3 ± 21.2 years and the average number of days between vaccination and BRAO symptom onset was 21.0 ± 24.9. As stated above, the average age of patients with CRAO after COVID-19 vaccination was 55.5 ± 18.5 years, which was not significantly different from that of the patients with BRAO after COVID-19 vaccination ($p = 0.57$). The time between vaccination and symptom onset was 21.0 ± 24.9 days. This was not significantly different from the time between vaccination and CRAO symptom onset ($p = 0.25$).

Table 8. A.

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No.	Authors	Age	Sex	Laterality	Time between vaccine and symptom onset (days)
1	Ishibashi, et al.	38	F	R	15
		80	M	R	42
		86	M	L	4
		57	F	R	61
2	Girbardt, et al.	38	M	R	3
3	Murata, et al.	75	M	R	1

F, female; L, left; M, male; R, right.

Although all of the vaccines were made by the multinational corporation, Pfizer-BioNTech, there have been few reports on their relationship with RVODs.

Table 8. B.

No.	Authors	Vaccine type	Number of the vaccine received
1	Ishibashi, et al.	BNT162b2 (Pfizer-BioNTech)	first
		BNT162b2 (Pfizer-BioNTech)	second
		BNT162b2 (Pfizer-BioNTech)	second
		BNT162b2 (Pfizer-BioNTech)	second
2	Girbardt, et al.	Comirnaty (Pfizer-BioNTech)	second
3	Murata, et al.	BNT162b2 (Pfizer-BioNTech)	fourth

VA at the initial visit averaged −0.025 ± 0.16, which was significantly better than that found among patients with CRAO after COVID-19 vaccination ($p < 0.001$). No significant difference was observed between BRAO after COVID-19 infection and BRAO after COVID-19 vaccination ($p = 0.19$).

Table 8. C.

No.	Authors	Abnormal blood test findings	BCVA at initial visit
1	Ishibashi, et al.	not listed	20/13
		not listed	20/20
		not listed	20/25
		not listed	20/13
2	Girbardt, et al.	normal	not listed
3	Murata, et al.	normal except those affected by diabetes	0.7

BCVA, best-corrected visual acuity.

Because treatment methods and final VA values were not provided in most reports, it was difficult to conduct a comprehensive investigation.

Table 8. D.

No.	Authors	Treatment	Final BCVA
1	Ishibashi, et al.	not listed	not listed
		not listed	not listed
		not listed	not listed
		not listed	not listed
2	Girbardt, et al.	aspirin	not listed
		simvastatin	
3	Murata, et al.	no treatment	0.7

BCVA, best-corrected visual acuity.

We will now consider the mechanisms involved in the pathogenesis of RVODs. Retinal veins can be occluded by arteriosclerosis. This causes components of the plasma to leak out of the vessel,

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which results in retinal hemorrhage and retinal edema. If the lesion does not reach the arcade area, no symptoms occur. However, once this region is reached, VA begins to decline rapidly. Risk factors for RVODs are older age, hypertension, diabetes, hyperlipidemia, smoking, and glaucoma [13]. RAO is frequently a symptom of an underlying disease, such as atrial fibrillation; heart valve diseases; stenosis or plaque formation in the internal carotid artery; or arteriosclerosis in older adults due to hypertension, diabetes, or hyperlipidemia [17]. However, RAO can also occur in youth among those with antiphospholipid syndrome and, exceptionally, those who take oral contraceptives. RVODs require medical scans and imaging and systemic treatments with internal medicine.

When the COVID-19 pandemic began, the resultant abnormalities of the blood coagulation system were greatly remarked upon. Tang et al. proposed that elevated d-dimer levels were predictive of a poor prognosis in infected patients. In fatal cases, the rate of disseminated intravascular coagulation (DIC) was 71.4% [100]. Tang et al. indicated that the patient was very unlikely to survive if DIC occurred [100]. COVID-19-associated coagulopathy is strongly correlated with vascular endothelial cell damage [20,21] and increased thrombin production in the veins and arteries. Several previous studies have verified that d-dimer elevation is an independent risk factor for thrombosis and death in COVID-19 patients [101–103]. However, the present study found that coagulative abnormalities are an infrequent occurrence in COVID-19 patients. Wang et al. posited that mild or focal coagulation activation could cause retinal vessel occlusions without a significant change in the patient's d-dimer level [104].

The COVID-19 vaccine approved for clinical use at the end of 2020, is the primary infection control strategy. The vaccine is a combination of an adenovirus vector vaccine and a messenger RNA vaccine. While adenovirus vector vaccines rarely cause thrombosis or thrombocytopenia syndrome [105], messenger RNA vaccine can cause venous thrombosis and thrombocytopenia and is likely to be the element of the COVID-19 vaccine responsible for vaccine-related thrombi [106]. It is apparent that ophthalmologists need to monitor patients closely for thrombosis after COVID-19 infection and COVID-19 vaccination.

The regions vulnerable to arterial thrombosis are arteries of the extremities (39%), cerebral vessels (24%), large vessels (19%), coronary arteries (9%), and the superior mesenteric artery (8%) (the remaining 1% of cases occur in other vessels) [108]. Malas et al. has reported an overall incidence of COVID-19-induced venous thromboembolism (VTE) of 21% [108]. Furthermore, the VTE rate was 5% Among general ward patients, the rate of VTE is 5%, while the rate among ICU patients is 31% [108]. When such thrombosis occurs in the retina, it is classed as an RVOD. It has been shown in this review that the increased risk of RVODs following COVID-19 is unsurprising given their reinforcing effects on each other, particularly in relation to coagulation processes. However, it is very difficult to clarify the connection between COVID-19 infection or vaccine and RVODs. Epidemiological investigations make an important contribution to investigations into comorbid conditions and the triggering of one condition by another.

Modjtahedi et al. have reported an RVO incidence rate of 65 in 43,2515 patients (a crude incidence rate of 12.2 per million) in the 6 months after a COVID-19 diagnosis [109]. This is a clear increase in the rate of RVO compared to that seen in those not recently infected with COVID-19 [109]. A study in Spain by Napal et al. also showed an increased RVO incidence during COVID-19 pandemic [110]. Conversely, Parks et al. reported no increase in RVO after COVID-19 infection [111, 112.] Al-Moujahed reported a diagnosis of CRVO in 7,261 (2.5%) of the 285,759 new patients seen in the pre–COVID-19 period and in 4,098 (2.7%) of the 156,427 new patients seen during the COVID-19 pandemic [113]. The percentage of new diagnoses in retina clinics that were CRVO remained stable during the pandemic [113]. Although the rate of patients with newly-diagnosed CRVO during the COVID-19 pandemic is interesting, these rates have not remained clear. According to our unpublished data, the rate of patients with CRVO remained unchanged after the COVID-19 pandemic compared to before. However, retinal photocoagulation was performed significantly more frequently after the pandemic began ($p < 0.001$). This may say something about the possible pathogenesis of CRVO. Hashimoto et al. found low causality between RVO and COVID-19

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vaccination [114]. Rachman et al. could not ascertain differences in the RVO risks of different types of COVID-19 vaccines due to a lack of detailed data on dosages and patient medical histories [115].

The RAO rate before and after COVID-19 pandemic is fascinating. Park et al. reported the RAO incidence rates per 100,000 people/year for 2018–2019 and 2020–2021 as 11.7 and 12.0, respectively [111]. Despite the increased incidence of RAO during the COVID-19 pandemic, SARS-CoV-2 infection did not significantly increase RAO incidence [111]. Al-Moujahed et al reported an increase in CRAO cases during the first few months of the pandemic [113]. However, RAO diagnosis rates as percentages of all new diagnoses in retina clinics remained stable for the majority of the pandemic [113]. We are now investigating this issue and will release our data when the investigation is complete.

We found an increase in Vogt-Koyanagi-Harada disease associated with COVID-19 [116]. Seventy-three cases per 60 months of Vogt-Koyanagi-Harada disease occurred before pandemic and 53 cases per 33 months occurred after COVID-19 pandemic [116]. Liang et al. observed an overall reduction in eye injuries and substantial differences in the spectrum of ocular trauma during the COVID-19 pandemic [117]. There was also an increase in dry eye-related complaints among students during the pandemic. This may have resulted from increased screen time [118]. Alternatively, Krolo et al. reported that mask-associated dry eye increased during the COVID-19 pandemic [119]. While the incidence of endophthalmitis after intravitreal injections remained unchanged [120], the rate of endophthalmitis after vitrectomy increased, especially the variant caused by oral bacteria [121]. Shi et al. found that the incidence of optic neuritis increased during the COVID-19 pandemic as too did acute primary angle closure, although the reason for the latter was unknown [123].

At this point, we would like to briefly describe three interesting cases that we have encountered [124–126]. The first of these was a male in his early 50s who suffered a recurrence of macular edema (ME) due to BRVO 3 days after administration of the messenger RNA COVID-19 vaccine (Pfizer-BioNTech). He was treated for this with an additional intravitreal aflibercept injection [124]. However, the patient believed the COVID-19 vaccine could have been the cause of his ME recurrence, so refused any further vaccinations after that [124]. In the 29 months since his initial visit, no recurrence has been reported. The second case was a 59-year-old female patient who suffered a recurrence of Vogt-Koyanagi-Harada disease following her third dose of the messenger RNA COVID-19 vaccine (Pfizer-BioNTech). This recurrence was 46 years after initial treatment [125]. The patient's inflammation was reduced by eye drops and oral corticosteroids. However, it seems that the vaccine may have triggered the recurrence [125]. The third case was a 21-year-old female who had been using oral contraceptives for 2 years [126]. Despite having received two doses of an mRNA-based COVID-19 vaccine, she contracted COVID-19 [126]. She then suffered BRVO with ME 40 days after COVID-19 diagnosis. She was treated with an intravitreal aflibercept injection [126]. In the 29 months since the patient's initial visit, there has been no ME recurrence. BRVO with ME does not usually occur in young women but oral contraceptive use, COVID-19 vaccination, and COVID-19 infection are all risk factors for venous thromboembolism. In combination, they could have induced the patients of BRVO with ME [126]. These cases illustrate some of the ways COVID-19 infection and vaccine can lead to various ocular disease.

With the global dissemination of COVID-19 vaccines, the pandemic has now (in 2024) been brought under some degree of control. Still, both COVID-19 and its vaccines have several unknown factors. Both could potentially have unknown complications or side effects. Because of the urgency, the usually lengthy process required for drug approval was hastened and this has led to social doubts about the safety of the vaccinations. Ophthalmologists are among the healthcare workers who may identify these complications and side effects in patients after their infection with or vaccination against COVID-19.

11. Conclusions

This review provides a comprehensive summary of RVOD cases secondary to either COVID-19 infection or COVID-19 vaccine reported to date. While RVOD following COVID-19 infection or vaccination is rare, those few cases reported are sufficient to have caused major concern. Although it

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would be prudent for clinicians to closely monitor any visual disturbances in patients recently infected with or vaccinated against COVID-19. However, we can neither support nor reject a possible association between RVOD and COVID-19 infection or vaccination based on the existing evidence. The patients reported in the reviewed studies constitute a heterogenous sample, among whom other underlying conditions and/or risk factors for RVODs cannot be ruled out. Therefore, further research with more data is warranted.

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