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## MYTHS AND TRUTHS OF THE ASSOCIATION OF RETINAL VASCULAR OCCLUSION WITH COVID-19

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### Abstract

**Purpose:** To critically review data published in the recent past to scrutinize a causal relationship between retinal vascular occlusion and COVID-19.

**Method:** A comprehensive literature search was performed on Pubmed with the key words retinal vascular occlusion, retinal vein occlusion, retinal artery occlusion, and COVID-19.

**Results:** A total of 17 case reports were published during this period, and 10 were on retinal vein occlusion and 7 on retinal artery occlusion. Most of the published reports lacked convincing evidences in one or the other aspects, such as insufficient laboratory workup or presence of multiple confounding risk factors.

**Conclusion:** In this index article, strength of the data is insufficient to establish a definitive cause-and-effect relationship of retinal vascular occlusive disorders with COVID-19. Hence, clinicians can continue to manage these cases according to the standard guidelines until there are more robust evidences to support this association to alter the diagnostic and treatment modalities.

### Keywords

COVID-19; retinal vein occlusion; retinal artery occlusion

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The surge in coronavirus disease of 2019 (COVID-19) cases had initially created a frenzy among the medical community with its unpredictable nature and course. As the pandemic progressed, a better understanding of its manifestations and treatment protocol has brought down the morbidity and mortality. Coronavirus disease of 2019–associated retinal vascular occlusions (arterial and venous) has been debated extensively during multiple virtual scientific meetings, based on the assumption of causal relationship. There are very few published case reports based on such similar assumptions. However, the data are too scattered in the form of case reports to allow clinicians to decide on diagnosis and treatment algorithm. The aim of the index article is to critically analyze the strength of this association and understand if ophthalmologists need to alter their management strategy.

## Method of Literature Search

We performed a Pubmed literature search on July 01, 2021, with the keywords: retinal vein occlusion (RVO), retinal artery occlusion (RAO), retinal vascular occlusion, and COVID-19. We found 31 articles that were published during the period of October 2020 to May 2021. We have included only 17 articles that were claimed by the authors to have a causal association with COVID-19. Among these reports, 10 were RVOs (7 central RVO [CRVO], one hemi-RVO [HRVO], one probable HRVO and one branch RVO [BRVO]), 6 central retinal artery occlusions (CRAO), and 1 cilioretinal artery occlusion (see Supplementary table 1, Supplemental Digital Content 1 <http://links.lww.com/IAE/B582>).

Based on the current understanding of the pathophysiology of COVID-19, coagulation and inflammatory parameters were considered as major determinants to assess the causality of this association. Furthermore, confounding factors were analyzed in each case. Only patients with deranged coagulation and inflammatory parameters at the time of retinal vascular occlusion with no confounding factors were considered as possible true association.

## Results

The following are the key cumulative clinical information extracted from the published data (see Supplementary table 1, Supplemental Digital Content 1 <http://links.lww.com/IAE/B582>).

### Age Group

The age range was between 17 and 74 years. Patients with RAO were in the age group of 26 to 61 years as compared with RVOs between 17 and 74 years.

### Sex

Eleven men and six women.

### Bilateral Involvement

Four cases had bilateral involvement. Among these cases, two were CRVO and two were CRAO.

### **Onset of Vascular Occlusion**

The onset was between 3 and 60 days from the start of clinical symptoms of COVID-19 or a positive real-time polymerase chain reaction (RT-PCR). Three cases had IgG positivity at the time of onset of vascular occlusion. In one case, RT-PCR was negative at the time of ocular complaints.

### **Best-Corrected Visual Acuity**

It was 20/20 to 20/200 in vein occlusion cases and no light perception to counting fingers in cases of artery occlusion. All the retinal vein occlusion cases improved to near normal visual acuity. However, none of the cases caused by artery occlusion showed any significant improvement.

### **Imaging Evidences**

Most of the patients underwent either fundus photography or bedside ophthalmoscopic examination. In addition, majority of them underwent fundus fluorescein angiography and/or optical coherence tomography. Five of the cases revealed cystoid macular edema on optical coherence tomography in the RVO group, and two patients revealed paracentral acute middle maculopathy in the RAO group.

### **Prothrombotic Parameters**

Special emphasis was given to D-dimer because it was considered a key parameter in the COVID-19 pathogenesis. The coagulation profile was deranged in 9 cases, normal in 6 cases, and not done in 2 cases.

### **Inflammatory Markers**

Information about inflammatory markers was not available for three patients, normal in six patients, and deranged in eight patients.

### **Management**

Among the five RVO cases that had cystoid macular edema, three were treated with anti-vascular endothelial growth factor injections, one was treated with intravitreal dexamethasone implant and one was treated only with an antiplatelet drug (aspirin 150 mg/day). Among these cases, one patient was also treated with oral steroids along with anti-vascular endothelial growth factor. One patient with impending CRVO was treated with intravenous methyl prednisolone and oral steroids. The remaining of the RVO cases were not given any specific ocular therapy. Among the RAO cases, two were given routine CRAO treatment, which included ocular massage, intraocular pressure-lowering drugs, and hyperbaric oxygen. One patient with bilateral CRAO was treated with 6 mg of dexamethasone and 75 mg of aspirin. Apart from these two patients who received aspirin, none of the patients received anticoagulation therapy specifically for the management of retinal vascular occlusion.

## Comorbidities and Risk Factors

Of the 17 patients, 9 had comorbid conditions with hypertension being the most common (4 cases). Two cases had no mention of comorbid conditions, and six cases were supposedly healthy patients with no comorbid conditions. Other than hypertension, noninsulin-dependent diabetes mellitus, hyperlipidemia, sickle cell disease, marijuana use, chronic smoking, hyperuricemia, polycystic ovarian disease, and arsenic intake were the risk factors.

## Discussion

### Scrutinizing the Association

**Central Retinal Vein Occlusions.**—The strongest association of COVID-19 and RVO is probably from the case reports by Invernizzi et al and Gaba et al, as both the reports had abnormal coagulation and inflammatory profiles consistent with the pathogenic cascade of CRVO.<sup>1,2</sup> Furthermore, the case report by Gaba et al had significant systemic thrombosis at multiple sites because of COVID-19 (no history of coagulation disorders), strengthening the possibility of a COVID-induced thrombotic RVO. However, rest reports lacked the strength of association based on the scientific evidences mentioned.

The case report by Lorca et al had no venous tortuosity, which is a major characteristic of CRVO. Furthermore, the eye had vitreous hemorrhage, and HBA1c was 13%, which points more toward diabetic retinopathy.<sup>3</sup> The youngest patient, 17 years of age described by Walinjikar et al, had polycystic ovarian disease and history of arsenic intake in the form of a homeopathic medication as risk factors.<sup>4</sup> Arsenic has been known to induce platelet aggregation and venous thrombosis.<sup>5</sup> Furthermore, polycystic ovarian disease by itself is a cause of venous thrombosis.<sup>6</sup> The case by Yahalomi et al<sup>7</sup> showed the typical nonischemic CRVO picture but lacked evidence to consider it as a COVID-associated vein occlusion because the coagulation profile was normal, and inflammatory markers were not reported. The case described by Sheth et al spared the superotemporal sector of the retina (a possible HCRVO<sup>8</sup>), and fundus fluorescein angiography showed vasculitic changes; the author too did mention it as a vasculitic RVO. But, COVID-19 inflammatory markers were normal, which weakened the possibility of a COVID-induced vasculitic RVO. Furthermore, the study lacked D-dimer values.<sup>9</sup> The case described by Finn et al<sup>10</sup> had normal coagulation and inflammatory profile, and the authors themselves mentioned that a causal relationship cannot be established. Although the case report by Venkatesh et al<sup>11</sup> had deranged D-Dimer values, which could be an aggravating factor, the patient had preexisting mild nonproliferative diabetic retinopathy, which weakens the direct causal relationship with COVID –19 because patient already had microangiopathy in the form of diabetic retinopathy, which per se can lead to venous occlusion. The report by Raval et al<sup>12</sup> had no derangement of coagulation and inflammatory parameters. The case described by Duff et al lacked reports on coagulation and inflammatory profiles. Furthermore, the patient had history of hyperlipidemia.<sup>13</sup>

**Central Retinal Artery Occlusions.**—The case reported by Turedi et al lacked the classic CRAO finding. The findings were significantly more of paracentral acute middle maculopathy. Despite the COVID-19 anticoagulation therapy for 14 days, the fact that

the patient developed CRAO makes it less likely to be COVID induced. There was no mention of systemic comorbidities by the authors.<sup>14</sup> The case report by Murchison et al had history of cannabis usage and hypertension, both of which are risk factors of CRAO.<sup>15,16</sup> The strongest association of COVID-19 and RAO is probably from the case reports by Ozsaygili et al because the report had deranged coagulation and inflammatory profiles with no systemic comorbidity.<sup>17</sup> Bilateral CRAO described by Maneesh et al had normal coagulation and inflammatory profiles. Furthermore, at the time of presentation, patient showed negative results for RT-PCR test.<sup>18</sup> All other cases had deranged coagulation and inflammatory profiles, but they also had systemic risk factors that could cause retinal artery occlusion independently, which weakens the COVID-19 association.<sup>19–21</sup>

Until the date, this article was being prepared, 182 million people have been affected with COVID-19 worldwide,<sup>22</sup> and we have only 17 case reports of retinal vascular occlusion in the published literature with possible association of COVID-19. The estimated prevalence of CRVO is 0.8/1,000 in the non-COVID era.<sup>23</sup> Similarly, the incidence of CRAO is 1 in 100,000,<sup>24</sup> which makes it difficult to attribute retinal vascular occlusion to COVID-19 when the disease has been much more common in the non-COVID-19 era. Recently, Sunny also analyzed 66 patients with CRVO who presented to their center and concluded that the occurrence of CRVO could be a coincidence in these at-risk COVID-19–positive patients.<sup>25</sup> However, we need to agree on the fact that thromboembolic phenomenon post cytokine storm is seen most often in moderate-to-severe COVID-19 cases where ophthalmological examination may not be practical and patients in such critical conditions may also not be able to detect decreased vision. Complete spectrum of laboratory investigations, ophthalmic examination, and clinical documentation would be able to shed some light on this association in the future.<sup>26</sup>

## Conclusion

To summarize, the incidence of COVID-19–related retinal vascular occlusion is extremely low, and the strength of association is weak based on the current published data. COVID-19–induced prothrombosis and inflammation were considered as background hypothesis to explain the causal relationship, but prothrombotic and inflammatory markers were normal or missing in half of the reports along with systemic confounding factors in majority of the cases. We agree that we are still in the process of understanding COVID-19 and its microvascular complications.<sup>26</sup> This review should be considered as an index article based on the scrutiny of available evidences till date. Clinicians can continue to manage these patients according to the standard guidelines until there are more robust evidences to support this association to alter the diagnostic and treatment approach.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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