



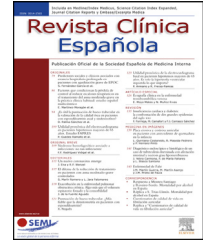
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## BRIEF ORIGINAL

# Effects of the COVID-19 pandemic on a cohort of patients with vein occlusion\*



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COVID-19;  
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### Abstract

**Background and objectives:** A new coronavirus disease in humans, COVID-19, caused by SARS-CoV-2, emerged in December 2019. It has been associated with the development of thrombotic phenomena. Retinal vein occlusion (RVO) is mainly a consequence of vascular risk factors (VRF). This study aimed to analyze cases of COVID-19 in a cohort of patients with RVO (Valdecilla cohort).

**Patients and methods:** Between December 2008 and December 2020, 429 patients with RVO were attended to in our clinic. Ten patients had COVID-19, one of which did not have VRF or thrombophilia. The remaining nine patients had RVO prior to the infection and VRF, six had carotid atherosclerosis, and four had antiphospholipid syndrome. The infection did not cause thrombotic phenomena in any of them.

**Conclusions:** RVO is a rare manifestation of COVID-19. In our cohort of patients with RVO, COVID-19 disease did not lead to thrombotic events.

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### PALABRAS CLAVE

COVID-19;  
Obstrucción venosa  
retiniana;  
Factores de riesgo  
vascular;  
Trombofilia

### Efectos de la pandemia por SARS-CoV-2 en una cohorte de pacientes con obstrucción venosa retiniana

### Resumen

**Antecedentes y objetivos:** En diciembre de 2019 surgió una nueva enfermedad por coronavirus en humanos causada por el virus SARS-CoV-2, la COVID-19, que se ha asociado con fenómenos tromboticos. La obstrucción venosa retiniana (OVR) es principalmente una consecuencia de

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los factores de riesgo vascular (FRV). El objetivo de este estudio ha sido analizar los casos de infección por SARS-CoV-2 en una cohorte de pacientes con OVR (cohorte Valdecilla).

*Pacientes y métodos:* Entre diciembre de 2008 y 2020 hemos atendido 429 pacientes con OVR. Diez han padecido COVID-19, de los que uno no presentaba FRV ni trombofilia. Los otros 9 fueron diagnosticados de OVR antes de la infección: todos tenían FRV; 6 ateromatosis carotídea y 4 presentaban un síndrome antifosfolípido. La infección no causó en ellos fenómenos trombóticos.

*Conclusiones:* La OVR es una manifestación infrecuente de la COVID-19. En nuestra cohorte de pacientes con OVR la COVID-19 no indujo eventos trombóticos.

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## Introduction

Retinal vein occlusion (RVO) is a consequence of vascular risk factors (VRF) and, to a lesser extent, thrombophilia<sup>1,2</sup>. Locally, glaucoma is a factor that favors onset of RVO in a central localization<sup>3</sup>.

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, a pandemic in March 2020. The disease's spectrum varies widely, from asymptomatic patients to others with severe pneumonia and respiratory distress syndrome<sup>4,5</sup>. As a result of the hyperinflammatory response which develops in severe cases, COVID-19 has also been associated with thromboinflammation and thrombosis, causing artery and vein occlusion, microinfarcts, and multiple organ failure<sup>6</sup>. Retinal vascular involvement due to COVID-19 is rare, with five cases described in the literature<sup>7-10</sup>; one of these cases was in Spain<sup>11</sup>.

## Aim

This work aims to analyze cases of SARS-CoV-2 infection in a cohort of patients with RVO during the first and second waves of the pandemic (March to December 2020).

## Patients and methods

All patients in our healthcare area who were diagnosed with RVO were referred to the internal medicine clinic for study (Valdecilla cohort), where diagnosis, optimization, treatment, and follow-up on VRF and thrombophilia were conducted.

The Valdecilla cohort study was conducted in the Marqués de Valdecilla University Hospital in Santander, Spain, a tertiary hospital with a reference population of 350,000 inhabitants. The Ethics Committee of Cantabria (2019.340) approved the study and subjects signed informed consent forms in order to participate.

From December 2008 to December 2020, 429 patients with RVO were treated. Forty of them died before the start of the pandemic (March 2020). From the first cases of SARS-CoV-2 infection to the end of the second wave, ten patients from the Valdecilla cohort had COVID-19.

## Clinical variables

The clinical variables recorded were differentiation between central or branch RVO (temporal or nasal); presence of hypertension (blood pressure  $\geq 140$  and/or 90 mmHg or receiving antihypertensive drug treatment); diabetes mellitus (according to the American Diabetes Association criteria)<sup>12</sup>; dyslipidemia (total cholesterol or triglycerides  $>230$  and  $>150$  mg/dL, respectively, in at least two measurements after a 24 h fasting period or receiving lipid-lowering treatment); and presence of genetic or acquired thrombophilia.

## Laboratory determinations

A routine biochemistry profile, including a lipid panel, was conducted with an Advia<sup>®</sup> 2400 (Siemens) autoanalyzer. Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and  $\beta 2$ -glycoprotein I) were measured in all patients. A diagnosis of antiphospholipid syndrome was established according to the guidelines of the International Society on Thrombosis and Haemostasis<sup>13</sup>. Whenever there was a positive antibodies result, a second measurement was performed at 12 weeks; if the lupus anticoagulant was positive and/or the anticardiolipin antibody and/or  $\beta 2$ -glycoprotein I titers were in intermediate or high ranges on the second measurement, it was considered positive. In those whose results were not conclusive, a third measurement was conducted 12 weeks later.

A genetic thrombophilia study (prothrombin gene, factor V Leiden, protein C, protein S, antithrombin) was conducted in all patients from December 2008 to December 2015. Later, given that this thrombophilia only plays an important role in subjects younger than 50 years of age or without VRF, it was only measured in this group of patients<sup>1</sup>.

## Imaging tests

A Doppler ultrasound of the supra-aortic trunks was used to evaluate the presence of atheroma plaques and quantify the degree of vascular stenosis. The study was conducted with a B-mode, color Doppler, and spectral Doppler ultrasound

**Table 1** Principal epidemiological characteristics of patients with RVO and COVID-19.

Patient	Age (years)	Sex	Type of RVO (involvement)	Date of diagnosis	VRF	Thrombophilia - APLA - Genetic thrombophilia - Negative	Carotid atheromatosis (Doppler SAT)	Associated diseases	Treatment
1	55	Woman	Temporal	May 2020	No	- Negative	No	Ankylosing spondylitis	Secukinumab
2	62	Woman	Central	October 2019	HT	- LA positive	Yes	SAHS	ASA, atorvastatin, LMWH
3	74	Man	Central	June 2013	DLP HT	- Negative - LA positive	Yes	Liver Disease	ASA, valsartan, amlodipine, atorvastatin, ezetimibe, LMWH
4	82	Man	Temporal	April 2014	No	- Negative - Negative	Yes	Peripheral artery disease	ASA
5	83	Woman	Temporal	December 2018	HT	- Negative	Yes	No	ASA, olmesartan, amlodipine, gliclazide, atorvastatin/ezetimibe
6	62	Man	Central	April 2017	DM DLP HT	- NP - Negative	No	AF	Enalapril, atorvastatin, apixaban
7	77	Woman	Temporal	July 2018	DLP HT	- NP - Negative	Yes	Glaucoma RA	Olmesartan, atorvastatin
8	90	Woman	Temporal	October 2018	HT	- LA positive	Yes	Advanced renal neoplasm Hypothyroidism	Valsartan, ASA, atorvastatin, metformin, LMWH
9	62	Woman	Central	March 2015	DLP DM DLP	- NP - LA positive	No	Severe adjustment disorder	Rosuvastatin, LMWH
10	59	Woman	Central	December 2019	HT	- Negative - Negative	No	Osteopenia	Atorvastatin, ASA

AF: atrial fibrillation; APLA: antiphospholipid antibodies; ASA: acetylsalicylic acid; DLP: dyslipidemia; DM: diabetes mellitus; HT: hypertension; LA: lupus anticoagulant; LMWH: low-molecular-weight heparin (in prolonged bedrest); NP: not performed; RA: rheumatoid arthritis; RVO: retinal vein occlusion; SAHS: sleep apnea-hypopnea syndrome; SAT: supra-aortic trunks; VRF: vascular risk factors.

**Table 2** Characteristics of COVID-19 in patients with RVO.

Patient	Date of diagnosis	Diagnostic method	Manifestations	Hospital admission/reason	COVID-19 treatment	<i>de novo</i> RVO
1	04/15/2020	CRP	Fever, headache, dysgeusia, anosmia	No	No	Yes
2	04/16/2020	CRP	Fever, dyspnea	Yes/left basal pneumonia	Lopinavir/ritonavir, hydroxychloroquine, ceftriaxone, enoxaparin	No
3	03/20/2020	CRP	Fever	Yes/comorbidities	Hydroxychloroquine, enoxaparin.	No
4	12/09/2020	CRP	Fever	No	Levofloxacin	No
5	03/16/2020	CRP	Fever, dysgeusia, changes in smell	No	No	No
6	05/10/2020	Antibodies (IgG <sup>+</sup> )	Asymptomatic	No	No	No
7	09/17/2020	CRP	Asymptomatic	Yes/neoplasm	No	No
8	10/06/2020	CRP	Asymptomatic	No	No	No
9	03/27/2020	CRP	Asymptomatic	No	No	No
10	09/18/2020	CRP	Fever, headache	No	No	No

RVO: retinal vein occlusion; PCR: polymerase chain reaction.

of the carotid and vertebral systems with a high-frequency linear probe (General Electric, Logiq® model).

## Results

A total of 429 patients with RVO were treated in our clinic as of December 2020. Of them, 290 had peripheral RVO (284 temporal and six nasal) and 139 had central RVO. Of the 429, 40 had died before the start of the pandemic. Therefore, the study group comprised 389 patients.

The mean age was  $67.9 \pm 12.8$  years. Nine patients in the cohort had already been diagnosed with RVO before the start of the pandemic and one developed peripheral RVO and glaucoma after COVID-19; the patient received treatment with oral deflazacort and timolol eye drops and progressed favorably. He presented with a fever of  $38.5^\circ\text{C}$  for three days and headache, asthenia, and anosmia for one month. Laboratory tests were not performed. Vision changes appeared at three weeks following onset of fever. There were no changes observed in ophthalmologic follow-up appointments conducted after SARS-CoV-2 infection in the rest of the cases which had previously presented with RVO. In four cases, additional tests were conducted, including measurements of platelets (reference range: 150,000–450,000/ $\mu\text{L}$ ), D-dimer (0–500 ng/mL), and fibrinogen (180–500 mg/dL); case 2: 109,000, 1302, and 541; case 3: 329,000, 2692, and 6000; case 4: 103,000, 487, and 766; and case 7: 279,000, 1327, and 815, respectively.

Table 1 shows the age, sex, RVO type, date of diagnosis, VRF (hypertension, dyslipidemia, diabetes mellitus), thrombophilia, presence of carotid atheromatosis, associated diseases, and prior treatment for each of the ten cases.

Table 2 shows the date of COVID-19 diagnosis, the diagnostic technique (PCR or antibodies), symptoms, need for admission, and treatment.

## Discussion

We found one patient with COVID-19 who developed RVO. In addition, we observed an absence of vascular events (including recurrence of RVO) after COVID-19 infection in nine patients with prior RVO (Valdecilla cohort). Cantabria has been one of the autonomous communities with a lower incidence of COVID-19: it had 17,896 total cases as of December 2020 and a cumulative incidence of around 3%<sup>14,15</sup>.

The patient with RVO, which was probably a consequence of COVID-19, was young. She did not have VRF and the thrombophilia study was negative. Although she had ankylosing spondylitis (AS) in treatment with secukinumab, the real effect of immunomodulators in COVID-19 is unknown; on the one hand, they can increase risk of infection, but on the other hand, they could protect against a hyperinflammatory storm. In a series of patients with AS treated with secukinumab, the majority presented with a mild form of COVID-19<sup>16</sup>.

Three of the five cases of RVO and COVID-19 described in the literature<sup>7–9</sup> are similar to our case. They are young women (age: 33–55 years) without any VRF or thrombophilia who presented with unilateral RVO after COVID-19. The other two cases are bilateral RVO in patients between 30 and 40 years of age with VRF and severe COVID-19 pneumonia<sup>10,11</sup>.

It should be noted that in our cohort of patients with RVO, 90% had some VRF, 10% had antiphospholipid syndrome (APLS), 13% had genetic thrombophilia, and just 2% did not present with VRF or thrombophilia<sup>1,2,11</sup>.

In the nine patients who belong to the Valdecilla cohort, COVID-19 was not associated with the onset of new thrombotic phenomena and no new retinal abnormalities or worsening of RVO was observed on ophthalmologic follow-up appointments after SARS-CoV-2 infection. All had at least one VRF: six presented with carotid atheromatosis

and four met the criteria for APLS. VRF were controlled in all subjects and in addition, six received treatment with acetylsalicylic acid, one with apixaban for atrial fibrillation, and low-molecular-weight heparin (LMWH) was recommended for the four diagnosed with APLS for whom prolonged bedrest was indicated. Although there are no randomized, controlled trials which demonstrate it, thromboembolic prophylaxis with LMWH has been used with COVID-19 and a decrease in thrombi and mortality has been observed.

In regard to the behavior of APLS in patients with RVO, it should be noted that this disease has special characteristics. It is mainly associated with manifestations of arteriosclerosis and not with onset of deep vein thrombosis or pulmonary embolism; antiplatelet therapy is the treatment of choice for it<sup>17</sup>. One of our patients presented with pneumonia and three required hospital admission.

COVID-19 has been associated with the onset of artery and vein occlusion, microinfarcts, and multiple organ failure as a result of the hyperinflammatory state and thrombosis generated by the host as a response to SARS-CoV-2 infection. These manifestations are more frequent in severe forms of the disease<sup>5</sup>. RVO can occur with mild SARS-CoV-2 disease, as in our patient, and it has been recorded in the literature<sup>7,8</sup>.

The main limitations of this work are the small number of cases reported and the fact that the majority are mild forms of COVID-19.

## Conclusions

RVO is a rare manifestation of COVID-19. However, it is advisable to take this entity into account when patients with COVID-19 report ocular symptoms such as a decline in visual acuity. In our prospective cohort of patients with RVO who receive treatment for controlling VRF and thrombophilia, SARS-CoV-2 infection did not seem to worsen RVO or favor the onset of new vascular events.

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## Conflicts of interest

The authors declare that they do not have any conflicts of interest in regard to this work.

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