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Retrobulbar ocular blood flow and choroidal vascular changes in patients recovering from COVID-19 infection

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ABSTRACT

Background: To evaluate the effects of COVID-19 infection on the ocular vascular structure including choroidal thickness and retrobulbar blood flow values in comparison with healthy subjects.
Methods: Ninety eyes of 90 patients were included in this study. Participants were divided into Group 1 ($n = 30$) with mild COVID-19 infection, Group 2 ($n = 31$) with moderate disease, and Group 3 with age- and sex-matched healthy subjects ($n = 29$). Choroidal thickness was measured at the subfoveal area and at 500-μm intervals nasal and temporal to the fovea up to a distance of 1500 μm, using the enhanced depth imaging (EDI) technique of spectral coherence tomography (SD-OCT). The peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), and pulsatility index (PI) values of the central retinal artery (CRA) and ophthalmic artery (OA) were evaluated with color Doppler ultrasonography (CDU).
Results: The choroidal thickness was significantly thinner in Group 1 and Group 2 than in Group 3 at all measurement points ($p < 0.001$). This difference was not present between Group 1 and Group 2 who had COVID-19 disease of different severity ($p > 0.05$).Among the retrobulbar blood flow parameters, OA PSV value was significantly lower in Group 1 and Group 2 compared to Group 3 ($p = 0.025$, $p = 0.016$, respectively). However, the CRA PSV and EDV and OA EDV values, and the CRA and OA PI and RI values were not statistically different between the groups ($p > 0.05$).
Conclusion: COVID-19 infection may predispose patients to ocular vascular pathologies by affecting both choroidal and retrobulbar blood flow.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2), which emerged in Wuhan, China, and then spread to more than 200 countries worldwide to affect millions of people [1]. SARS-CoV-2 infection may be asymptomatic and the course of the disease can range from mild flu-like symptoms to life-threatening complications [2]. SARS-CoV-2 not only affects the respiratory system, but also causes gastrointestinal, cardiovascular, neurological, ocular, olfactory, cardiac, renal, hepatic, and hematological system involvement, gustatory dysfunction, and skin lesions such as Kawasaki-like disease [3–5].

Immune dysregulation, hyperinflammation, endothelial cell damage and the vascular system damage that occurs as a result of increased thrombosis play a role in SARS-CoV-2 infection and its long-term effects [6]. In addition to the fact that the choroid is one of the highly vascular structures of the body, changes in choroidal thickness have been detected in inflammatory diseases [7]. Choroidal thickness is measured by using the Enhanced Depth Imaging (EDI) mode of the spectral domain optic coherence tomography (SD-OCT) device.

Inflammation and thrombotic processes can also affect retrobulbar hemodynamic structures. Color Doppler Ultrasonography (CDU) is a non-invasive method that enables the evaluation of ocular and orbital hemodynamics. With CDU, blood flow in the ophthalmic artery (OA), central retinal artery (CRA) and vein, and short posterior ciliary artery is quantitatively evaluated [8]. Although the choroidal and retinal changes in patients with COVID-19 infection have previously been studied [9–12], there is no study yet where both the choroidal and

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retrobulbar vascular structures have been evaluated in association with the severity of the disease. The aim in our study was to evaluate the choroid, with abundant vascular supply, and the retrobulbar ocular perfusion in patients with COVID-19 infection, and to investigate their relationship with the severity of the disease.

2. Material and method

This prospective, observational, case control study included the 61 eyes of 61 patients who were suffering from COVID-19 infection at the Sabuncuoğlu Şerefeddin Training and Research Hospital between August 2021 and March 2022 and the 29 eyes of 29 healthy individuals matched for age and gender. The study was approved by the Amasya University Ethics Committee (approval number 09.07.2021-23,469). All procedures were conducted in accordance with the Declaration of Helsinki. An informed consent form was completed by all the subjects.

Routine confirmation of COVID-19 infection was performed by detecting specific sequences of the virus RNA with the real-time reverse transcription polymerase chain reaction (rRT-PCR) test conducted on a nasopharyngeal swab sample. The participants were divided into three groups. Group 1 included asymptomatic or mildly symptomatic COVID-19 cases with a positive PCR test, no need for oxygen support and hospitalization, Group 2 included more severe COVID-19 cases with a positive PCR test who were hospitalized for pneumonia, needed oxygen support, but did not develop acute respiratory distress, Group 3 included healthy individuals with a negative PCR test and without any systemic disease. The patients' ocular examinations, SD-OCT and CDU were performed within 2 weeks to 3 months following the PCR test positivity. The PCR tests of the patients were negative during imaging, and they did not have any symptoms at that time.

Patients with systemic diseases such as blood disorders, diabetes, and hypertension; a history of retinal disease, optic nerve pathology, glaucoma, intraocular surgery, ocular trauma, ocular inflammatory disease, or laser treatment; those with significant corneal or lens opacities that would prevent OCT imaging; those with refractive errors above ±2 Diopter (D); and patients <18 years of age were not included. Demographic characteristics of the patients, the clinical course of the disease, treatment process and type, hospitalization duration, and history of steroid treatment and smoking were recorded. All patients underwent a detailed ophthalmological examination including best-corrected visual acuity (BCVA) with the Snellen chart, intraocular pressure (IOP) by Goldmann applanation tonometry, and anterior segment and dilated fundus examination with slit-lamp biomicroscopy. The central corneal thickness (CCT) measurement was done by using ultrasonic pachymetry (Nidek UP-1000; Nidek Co., Ltd., Aichi, Japan), and the axial eye length measurement by using the Echoscan US 800 system (Nidek Co. Ltd, Aichi, Japan).

The subfoveal macular thickness (CMT) was measured following OCT imaging in all subjects. According to the Early Treatment Diabetic Retinopathy Study (ETDRS) map obtained as a result of the automatic measurement of the macular thickness, the value in the central circle at a diameter of 1 mm among the values from 9 different areas was accepted as the CMT. Choroidal thickness measurements were performed by using the EDI mode of the SD-OCT device (3D OCT-2000, Topcon, Japan) after pupil dilation. All measurements were performed at the same time of the day (09.00–11.00 am) to avoid the effect of circadian variation. Sections with a signal strength index below 6/10 were not included in the evaluation. Choroidal thickness was measured subfoveally and at points 500 μm, 1000 μm and 1500 μm nasal and temporal to the subfoveal area, with vertical lines manually lowered by using the measuring tool of the device from the hyperreflective outer band of the retinal pigment epithelium and the area where the inner surface of the sclera begins. Choroidal thickness measurements were performed by two experienced physicians (MT, NA) at different times and with the groups masked. The mean value of three measurements was taken.

Retrobulbar blood flow was measured by the same radiologist (ATK) with the CDU device (Toshiba Aplio 500, Tokyo, Japan) by using the 7.5–10-MHz linear probe . The patients were in the supine position with their eyes closed and looking straight ahead during the color Doppler examination. The evaluation was performed after applying methylcellulose gel to the eyelids. In order to prevent an artifact, the patient was instructed to keep the eyes still and care was taken not to apply pressure to the eye with the probe. For optimal imaging of orbital vessels, the study was started in the transverse plane, and the probe was then angled according to the longest axis of the vessel that could be found for spectral analysis. The spectral waveform of each vessel was determined three times, and the most ideal one was chosen as the correct spectral sample. In order to evaluate the OA, the sampling interval was applied to the immediate nasal side of the optic nerve where the OA crossed the optic nerve. For CRA, the optic nerve was first found on B-mode and the optic disc localized. Color Doppler was then used to scan the retinal artery in the optic nerve. Peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), and pulsatile index (PI) values of the CRA and OA were recorded. The RI (PSV-EDV)/PSV value was calculated automatically by the device. All the measurements of the same patient were taken on the same day.Time-velocity waveforms of the OA and CRA are shown in Fig. 1A and 1B, respectively.

2.1. Statistical analysis

Statistical analysis was performed using the SPSS software for Windows, version 22 (SPSS Inc., Chicago, IL, USA). The continuous variables were reported as mean ± standard deviation while the categorical variables were summarized with the use of frequencies. The normality of all data samples was checked with the Kolmogorov–Smirnov test. Only the right eye values were used for statistical purposes. The chi-square test was used in the analysis of categorical variables. Comparisons of the parametric values among the groups were performed with one-Way ANOVA and comparisons of the nonparametric values among the groups were performed with the Kruskal-Wallis test. Subsequently, Dunn's post hoc multiple comparison tests or the Bonferroni post hoc test was used for pairwise comparisons for the determination of the differences between each group. A two-tailed p value <0.05 was considered significant.

3. Results

The 90 eyes of 90 patients were included in the study. There were 30 patients (17 female, 13 male) in Group 1, 31 patients (16 female, 15 male) in Group 2, and 29 patients (16 female, 13 male) in Group 3. The mean age was 44 ± 13.2 in Group 1, 46.2 ± 13,1 in Group 2, and 48.6 ± 12.6 years in Group 3. No significant difference was present between the groups in terms of age, gender, CCT, axial length, refractive error, IOP, and smoking status ($p = 0.405$, $p = 0.920$, $p = 0.238$, $p = 0.908$, $p = 0.783$, $p = 0.228$, $p = 0.743$, respectively) (Table 1). The mean duration from the time of diagnosis of the COVID-19 infection to the ophthalmologic and radiological examination was 46.9 ± 22.4 (range: 15–90) days in Group 1, and 45.5 ± 18.9 (range: 15–81) days in Group 2. The mean hospitalization duration for Group 2 was 20.8 ± 19 days. While 43.7% of the patients in Group 1 had received steroid treatment, all patients in Group 2 had been treated with steroids (100%) ($p<0.001$).

There was no statistically significant difference in CMT between the three groups ($p = 0.645$). When the choroidal thickness was compared between the groups, the Group 1 and Group 2 values were significantly lower than in Group 3 at all measurement points ($p <0.001$). Choroidal thickness was lower in Group 2 than in Group 1 at all measurement points but this difference was not statistically significant ($p>0.05$) (Table 2).

Comparison of the OA parameters revealed the OA PSV value to be significantly lower in Group 1 and Group 2 compared to Group 3 ($p = 0.025$, $p = 0.016$, respectively). There was no statistically significant difference between the groups in terms of the OA EDV value but it was

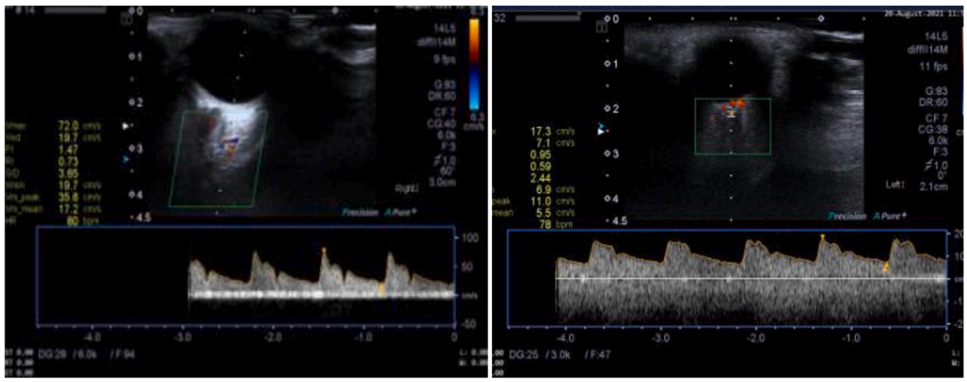

Fig. 1. A) Time-velacIty waveforms of the ophtalmlc artery. B) Time-velocity waveforms of the central retinal artery.

Table 1
The demographic and clinical characteristics of all subjects.

Parameters mean± SD	Group 1 (n = 30)	Group 2 (n = 31)	Group 3 (n = 29)	p value
Age, years	44±13.2 (18 to 77)	46.2 ± 13.1 (25 to 75)	48.6 ± 12.6 (18 to 58)	0.405*
Sex (%)				
▒Female	17(56.7%)	16(51.6%)	16(55.2%)	0.920**
▒Male	13(43.3%)	15(48.4%)	13(44.8%)	
IOP (mmHg)	15.1 ± 3.2 (9 to 21)	14.8 ± 2.7 (10 to 22)	16±2.5 (10 to 20)	0.228*
Refractive Error(D)	−0.2 ± 0.8 (−2 to 1.5)	0 ± 0.7 (−2 to 1.5)	0 ± 0.7 (−2 to 1)	0.783***
CCT (μm)	527.2 ± 24.6 (485 to 585)	532.6 ± 25.4 (491 to 592)	538.6 ± 26.4 (490 to 588)	0.238*
Visual acuity	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.000**
Axial length (mm)	21.8 ± 1.5 (19.23 to 24.13)	21.9 ± 1.2 (19.16 to 24.35)	21.9 ± 1.2 (19.69 to 24.15)	0.908*
Smoking				
▒No	23 (76.7%)	22 (71%)	23 (79.3%)	0.743**
▒Yes	7 (23.3%)	9 (29%)	6 (20.7%)	
Steroid treatment				
▒No	17 (56.7%)	0	–	<0.001**
▒Yes	13 (43.7%)	31 (100%)	–	
Duration after COVID-19(days)	46.9 ± 22.4	45.5 ± 18.9	–	—
Length of stay in hospital(days)	–	20.8 ± 19 (6 to 90)	–	–

IOP:Intraocular pressure, D: Dioptri, CCT: Central corneal thickness.
* :One Way-ANOVA test.
** : Chi-square test.
*** : Kruskal Wallis test.

Table 2
Comparision of central macular thickness and choroid thickness measurements between groups.

Parameters mean± SD	Group 1 (n = 30)	Group 2 (n = 31)	Group 3 (n = 29)	p*	Pairwise Comparisons
CMT (μm)	222.3 ± 14.9 (197 to 248)	225.4 ± 16.1 (200 to 259)	226.4 ± 15.3 (193 to 247)	0.645	
FCT (μm)	329 ±26.3 (268 to 375)	321.1 ± 22.4 (274 to 358)	370.1 ± 20.2 (315 to 413)	**<0.001**	0.679[a], **<0.001**[b], **<0.001**[c]
N 500 (μm)	321.2 ± 24.2 (262 to 369)	311.5 ± 18.1 (262 to 346)	356 ±20.4 (292 to 405)	**<0.001**	0.284[a], **<0.001**[b], **<0.001**[c]
N 1000 (μm)	314.7 ± 19.9 (274 to 352)	302.9 ± 21 (262 to 340)	346.8 ± 21.6 (298 to 399)	**<0.001**	0.145[a], **<0.001**[b], **<0.001**[c]
N 1500 (μm)	304.5 ± 21.2 (268 to 340)	292.9 ± 20.2 (258 to 334)	336 ±22.1 (280 to 381)	**<0.001**	0.99[a], **<0.001**[b], **<0.001**[c]
T 500 (μm)	315.6 ± 27.7 (262 to 375)	314.1 ± 20.8 (268 to 352)	360.5 ± 18.1 (316 to 399)	**<0.001**	1.00[a], **<0.001**[b], **<0.001**[c]
T 1000 (μm)	315 ±23.6 (268 to 364)	305.2 ± 21.8 (246 to 340)	353 ±20.1 (310 to 393)	**<0.001**	0.245[a], **<0.001**[b], **<0.001**[c]
T 1500 (μm)	310.7 ± 25.2 (260 to 363)	299.5 ± 21.3 (256 to 345)	342.5 ± 22.3 (298 to 382)	**<0.001**	0.225[a], **<0.001**[b], **<0.001**[c]

CMT: Central macular thickness, FCT: Foveal choroidal thickness, N: Nasal T: Temporal.
[a] : p value between Group 1 and Group 2.
[b] :p value between Group 1 and Group 3.
[c] : p value between Group 2 and Group 3. Boldfaced values are statistically significant.

lower in Group 1 and Group 2 compared to the control group (p = 0.120). No statistically significant difference was present between the groups in terms of the CRA PSV and EDV values (p = 0.181, p = 0.920, respectively). There was also no significant difference between the groups in terms of CRA RI and PI (p = 0.195, p = 0.254, respectively), and OA RI and PI (p = 0.127, p = 0.673, respectively) values (Table 3).

4. Discussion

The aim of our study was to investigate the effect of SARS -CoV-2 infection on microvascular structures by evaluating the choroidal thickness and retrobulbar blood flow. We also wanted to investigate whether the ocular circulation varied according to the severity of the disease. We found lower choroidal thickness and OA PSV values among the retrobulbar blood flow parameters in patients with SARS-CoV-2 infection in this study. These results indicated that ocular vascular structures could become affected, just like other organs.

Evaluation of the choroidal thickness provides important information for the diagnosis and treatment of various ocular and systemic diseases [13]. Systemic disorders such as Familial Mediterranean fever,

Table 3
Comparison of color Doppler ultrasonography parameters between groups.

Parameters mean± SD	Group 1 ($n = 30$)	Group 2 ($n = 31$)	Group 3 ($n = 29$)	p value	Pairwise Comparisons
CRA PSV (cm/s)	15.6 ± 3.5 (10.1 to 27.7)	15.2 ± 3.3 (10.3 to 24.9)	13.9 ± 3 (10.7 to 34.9)	0.181	
CRA EDV (cm/s)	6.8 ± 2.2 (3.5 to 12.6)	7.3 ± 3.5 (1.67 to 17.3)	5.7 ± 1.8 (3.25 to 10.8)	0.920	
CRA RI	0.6 ± 0.1 (0.2 to 0.9)	0.5 ± 0.2 (0.2 to 0.9)	0.6 ± 0.1 (0.4 to 0.8)	0.195	
CRA PI	0.9 ± 0.2 (0.4 to 1.2)	0.9 ± 0.3 (0.3 to 1.6)	1.0 ± 0.2 (0.7 to 1.5)	0.254	
OA PSV (cm/s)	59.3 ± 18.4 (25.1 to 87.3)	58.3 ± 19.7 (19.2 to 98)	70.8 ± 21.9 (22 to 107)	<**0.001**	1.00[a], **0.025**[b], **0.016**[c]
OA EDV (cm/s)	19±9.2 (4.5 to 37.4)	21.6 ± 9.6 (6.8 to 43.7)	24.2 ± 10.4 (5.7 to 52)	0.120	
OA RI	0.7 ± 0.1 (0.5 to 0.8)	0.6 ± 0.1 (0.3 to 0.8)	0.7 ± 0.1	0.127 (0.3 to 0.8)	
OA PI	1.3 ± 0.3 (0.8 to 1.8)	1.2 ± 0.4 (0.5 to 2.2)	1.3 ± 0.4	0.673 (0.5 to 2.4)	

CRA: Central retinal artery, OA: Ophthalmic artery, PSV: Peak systolic velocity, EDV: End-diastolic velocity, RI: Resistive index, PI: Pulsatility index.
[a] : p value between Group 1 and Group 2.
[b] : p value between Group 1 and Group 3.
[c] : p value between Group 2 and Group 3. Boldfaced values are statistically significant.

obesity, and rheumatoid arthritis have been found to cause a decrease in the choroidal thickness by triggering inflammation in the body [14–16]. In our study, choroidal thickness was found to be significantly lower at all measurement points in both groups with COVID-19 when compared to the control group. Choroidal thickness and total choroidal area have been found to be significantly lower in the early postinfectious period in COVID-19 patients compared to healthy individuals in the literature [9, 10].In contrast, the study where patients with mild COVID-19 infection were compared to a healthy control group found no significant difference in terms of choroidal thickness and CMT [11]. We think that the difference in the duration between the COVID-19 infection diagnosis and the ophthalmology examination in this study (14 to 60 days) and the differences in inflammatory cytokine density may have caused this contrasting result. On the other hand, studies exist on the early and late stage effects of COVID-19 infection on the ocular vascular structures [10, 17] but whether these changes are permanent is not known. The included patients in our study were within the 3-month period folowing the COVID-19 diagnosis.

Various proinflammatory cytokines are known to increase in COVID-19 infection, and tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, interferon-γ, and granulocyte-colony stimulating factor are the main cytokines that cause inflammation and coagulation. This situation, called cytokine storm, affects vascular endothelial structures and causes microangiopathy [18]. Hypercoagulation results in local thrombus formation and large vessel thrombosis, resulting in major thromboembolic complications and multiorgan dysfunction with possibly fatal outcomes [18].

The ACE-2 receptor acts as the key cell surface receptor for SARS-CoV-2. ACE-2 receptors are found in the retina, ciliary body, and choroid, in addition to vascular endothelial cells [19]. Consumption of ACE-2 through viral entry also causes an increase in Angiotensin-II (Ang-II), which is a vasoconstrictor agent. The prothrombotic process begins with vasoconstriction, platelet activation, and increased proinflammatory cytokines [20]. Central retinal artery and vein occlusion, serpiginous choroiditis, macular hemorrhage, acute macular neuroretinopathy, paracentral acute middle maculopathy, vitritis, and acute retinal necrosis have been reported to develop in COVID-19 patients, as a result of direct viral invasion of the ocular vessel wall and the thromboembolic process [21]. Invernizzi et al. have reported COVID-19 to affect retinal vascular structures and cause retinal hemorrhages, cotton wool spots, and dilated and tortuous vessels [22]. The vascular density of the parafoveal superficial and deep capillary plexus was found to be lower in a study conducted with Optical Coherence Tomography Angiography (OCT-A) in patients with COVID-19 infection [12].

Steroid treatment to suppress inflammation was administered to all Group 2 and some Group 1 patients in our study. Han et al. have reported that systemic steroid treatment did not affect choroidal thickness [23]. The lower choroidal thickness in the groups with COVID-19 infection in our study indicates that COVID-19 could affect choroidal perfusion by triggering the thromboembolic process in the presence of inflammation.

We evaluated the changes in the retrobulbar blood flow by using the CDU device. Impaired ocular perfusion is reflected by low PSV and EDV values, and vascular resistance by the RI and PI parameters [24]. The OA PSV value was found to be significantly lower in patient groups with a history of COVID-19 infection than the control group in our study. Besides, the OA EDV value was also lower in the groups with COVID-19 infection than the control group, despite not being statistically significant. However, no significant difference was observed between the groups in terms of CRA PSV and EDV values.

A lower blood flow rate has been detected in the middle cerebral artery at rest and after breath-holding in patients with COVID-19 infection when cerebral vasoreactivity was evaluated with transcranial Color Doppler [25]. We found that ocular perfusion was affected by the decrease in OA PSV value while there was no change in the CRA blood flow in the groups with COVID-19 infection in our study. While the outer third of the retina is supplied by the choroid, the inner two-thirds is supplied by the CRA. Due to the high metabolic activity of retinal cells, an attempt is made to keep the retinal blood flow constant via the autoregulation mechanism despite the changing conditions [26]. This autoregulatory mechanism is based on the ability of the tissue blood flow to adapt to the metabolic needs of the tissue and is regulated by local vasoactive factors released from the retinal tissue and endothelial cells [27]. However, the choroidal circulation is controlled by sympathetic, parasympathetic, and trigeminal sensory nerve fibers and does not contain an autoregulatory mechanism [28]. Evaluation of our results reveals an attempt to regulate retinal arterial perfusion by the activation of autoregulatory mechanisms in the presence of a systemic disease affecting vascular structures, such as COVID-19. However, patients who have experienced a COVID-19 infection are more severely affected by the decreased ocular perfusion as a result of the lower OA PSV value in the choroidal circulation created by the posterior OA branch in addition to the decrease in the choroidal circulation on an inflammatory background, and this decrease cannot be stabilized due to the absence of choroidal autoregulatory mechanisms.

Lower systemic vascular function and higher arterial stiffness have been found in DU measurements of young adults with COVID-19 infection compared to a control group [29]. No significant difference was found between the groups in terms of OA CRA PI and RI values in our study. RI and PI values are the most reliable and commonly used vascular resistance parameters that indicate resistance to blood flow in an organ [24]. RI is suitable for the evaluation of low-resistance vascular structures while PI is suitable for the evaluation of high-resistance ones, and RI has been reported to be the value least affected by errors for orbital vascular structures with low resistance [24]. However, a study where a resistance increase was induced with 100% O_2 inhalation has

emphasized that the RI value in CRA is not an adequate retinal vascular resistance indicator [30]. The group 2 patients in our study were monitored in the hospital with oxygen support, possibly affecting the RI value. Besides, there may be different outcomes in cases with more severe COVID-19 infection.

Our study had various limitations. It was conducted at a single center and with a small sample group. Another limitation was the lack of measurements of the COVID-19 patients in the acute period and our inability to compare these measurements with the post-COVID period. Besides, patients who required an intensive care stay were not included in the study groups. However, our study is the first to evaluate the retrobulbar blood flow rate in COVID-19 patients in the literature. We therefore believe that it should be supported with other studies on larger groups.

In conclusion, we found that the choroidal thickness and the retrobulbar ocular parameter of OA PSV were lower in patients with COVID-19 infection. We did not observe a statistically significant relationship between such changes and the severity of the disease. Based on this information, we believe the microangiopathy triggered by the COVID-19 infection affects the choroid, which is one of the most vascular structures of the human body, and the retrobulbar blood flow, creating a potential for ocular vascular complications, as seen in other organs.

Disclosure statement

The authors declare that they have no conflict of interest.

Ethical approval

This study was approved by the Ethics Committee of the Amasya University .All procedures were conducted in accordance with the Declaration of Helsinki.

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Availability of data and materials

In this study data supporting findings can be found in Sabuncuoglu Serefeddin Training and Research Hospital, Department of Ophthalmology and Department of Radiology.

CRediT authorship contribution statement

Melek Tufek: Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Mustafa Capraz:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Ahmet Turan Kaya:** Writing – review & editing, Visualization, Software, Data curation, Conceptualization. **Nihat Aydin:** Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Pinar Nalcacioglu:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Conceptualization.

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