

Evaluation of the Retina, Choroid and Optic Disc Vascular Structures In Individuals With a History of Covid-19

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Abstract

Introduction

In this study, we aimed to detect changes in posterior segment structures and posterior segment vascular density caused by COVID-19 using the optical coherence tomography angiography (OCTA) device.

Material and Method

The study included 20 eyes of 20 patients without any systemic or eye disease, who were followed up at the Ophthalmology Clinic of Health Sciences University Antalya Training and Research Hospital. The OCTA images of these individuals taken before COVID-19 and at six months after recovery were examined.

Results

The mean choriocapillaris blood flow value of the patients was $2.00 \pm 0.13 \text{ mm}^2$ before COVID-19 and $2.08 \pm 0.23 \text{ mm}^2$ after the disease, the mean subfoveal choroidal thickness value was $247.33 \pm 7.65 \mu\text{m}$ before the disease and $273.08 \pm 4.92 \mu\text{m}$ after the disease, indicating a statistically significant difference ($p = 0.003$, $p = 0.001$, respectively). The mean retinal nerve fiber layer values before and after COVID-19 were 119.33 ± 3.88 and $117.50 \pm 3.92 \mu\text{m}$, respectively, and there was a statistically significant decrease ($p < 0.001$).

Conclusion

This is the first study in the literature to evaluate the post-COVID-19 changes in the eye vascular structures compared to the pre-disease values. We consider that inflammation and increased vascular permeability are effective in changes.

Introduction

Coronaviruses, belonging to the RNA virus family, can cause infections in both humans and animals. Coronavirus disease is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by this virus was named COVID-19, where "CO" stands for corona, "VI" for virus, "D" for disease, and "19" indicates the year in which it occurred. COVID-19 is a systemic disease affecting the whole body and manifesting with the general findings of fever, cough, fatigue, headache, sore throat, loss of taste, loss of smell, and low back pain [1, 2]. In this disease, ocular findings can also be seen and sometimes even present as initial findings. Ocular findings associated with COVID-19 include eye watering, itching, foreign body sensation, double vision, blurred vision, limitation of eye movements, conjunctivitis, Guillain–Barré syndrome, chemosis, lagophthalmia and ischemic optic neuropathy [3, 4].

Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that has recently been used to visualize retinal vascular blood flow. OCTA can measure both the superficial and deep

vessel densities in the macular capillary plexus by detecting motion contrast in blood flow [5]. In previous studies, retinal and choroidal vascular density values in patients with COVID-19 were compared with control groups using OCTA, and statistically significant results were obtained [6, 7]. The current study aimed to compare the retinal, choroidal and optic disc vascular density values, choroidal thickness, and retinal nerve fiber layer (RNFL) of the same individuals before and after COVID-19 using the OCTA device. We conducted this study with the hypothesis that changes in the posterior segment structures and posterior segment vascular density caused by COVID-19 can be detected using the OCTA device.

Material And Method

Patient Selection

The study included 20 eyes of 20 individuals without any systemic or eye disease, who were followed up at the Ophthalmology Clinic of Health Sciences University Antalya Training and Research Hospital. These individuals consisted of healthcare workers who had been selected as a control group for another academic study before the COVID-19 pandemic and later contracted the virus but recovered without the need for intensive care. The complete ophthalmologic examinations and OCTA findings of these patients before COVID-19 and at six-month after recovery from the disease were recorded from their files. This study was carried out between 01.01.20 – 01.01.21. None of the patients in this study received a coronavirus related vaccine.

The exclusion criteria were determined as follows: any eye pathology (e.g., glaucoma, uveitis, diabetic retinopathy, amblyopia, and epiretinal membrane), myopia greater than -6 diopters, axial length greater than 26 mm, history of eye surgery other than uncomplicated cataract surgery, and any systemic disease.

The demographic characteristics of the patients (age, gender, medications, systemic disease, etc.) and examination findings were available in patient files. A full ophthalmological examination and OCTA were performed before COVID-19 and during follow-up at six months after the disease. The findings of the fundus examinations of the patients were evaluated by biomicroscopy. The OCTA images of the patients were examined. A spectral-domain OCTA device (AngioVue; Optovue, Inc, Fremont, CA) was used to obtain OCTA images.

Octa Evaluation

The OCTA measurements of the patients were performed on the 6x6 mm HD angio retina and 4.5x4.5 mm AngioDisc scales. Images with poor shooting quality due to motion and other artifacts were not included in the study. Only images with a signal quality higher than 8/10 were evaluated. The foveal vascular density was measured from a 1-mm circular region, parafoveal vascular density from a 1 mm x 3 mm circular region, perifoveal vascular density from a 1 mm x 3 mm circular region, and total vascular density from a 6 mm circular region in the center of the fovea, and all the values were recorded as percentages. These areas provided the density measurement of the superficial capillary area in automatic

mode in cross-section. The ratio of the vascular image (white areas) in these regions to the whole area was used as percentage density.

The foveal avascular zone (FAZ) was automatically calculated by the device from as a measurement in mm^2 . Choriocapillaris blood flow (CBF) was automatically calculated as the amount of area with blood flow in the choriocapillaris layer with a central radius of 1 mm and an area of 3.142 mm^2 and was recorded in mm^2 [Figure 1, 2]. Optic disc vascular density was obtained as vascular density measured from a 4.5 mm circular region centered on the optic disc and recorded as a percentage. RNFL was automatically measured and recorded by the device from a 3.4 mm scanning circle centered on the optic disc [Figure 3, 4]. Retinal thicknesses were automatically measured between internal limiting membrane and retinal pigment epithelium in the foveal, parafoveal and perifoveal regions and recorded by the device.

Choroidal thickness measurements were performed from the subfoveal area by two different observers using the “Enhanced HD line” image. The average of the measurements of the two observers was calculated. The RPE-sclerachoroidal junction was taken as the boundary of the subfoveal choroidal thickness (SCT).

Statistical Analysis

The analysis of the data was performed using SPSS v. 24.0 software package. Descriptive statistics were given as percentages for categorical variables, and mean, standard deviation and median, minimum and maximum values for numerical variables. The conformity of the numerical variables to the normal distribution was evaluated with the Shapiro-Wilk test. Values were presented using mean and standard deviation. Pre- and post-disease measurements were compared using the Wilcoxon test. The results were evaluated at the 95% confidence interval, and $p < 0.05$ was considered statistically significant.

Results

The mean age of the 20 participants, twelve female and eight male, was calculated as 36.70 ± 1.81 years. None of the patients had pneumonia, and their bleeding profile values (active partial thromboplastin time, prothrombin time, INR, D-dimer, and fibrinogen) were normal. The oxygen saturation of all the patients varied between 94 and 100%, and none required oxygen therapy. All the patients received favipiravir and anticoagulant therapy. None of the patients required hospitalization or received steroid therapy. The demographic characteristics of the patients are given in Table 1.

Table 1
Demographic characteristics of the patients participating
in the study

Variable	Value
Age	36.70 ± 1.81
Female/Male	12/8
Number of doctors	4
Number of nurses	4
Number of medical secretaries	10
Number of other healthcare personnel	2
Total number of patients	20

Burning and stinging were present in six of the 20 patients (30%), redness in four (20%), itching in ten (50%), eye pain in twelve (60%), and visual impairment in four (20%) patients, while four patients did not have any ocular symptoms. Epiphora, conjunctivitis and neuroophthalmologic symptoms were not detected in any of the patients.

Table 2 presents the comparison of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) vascular density values measured by OCTA before and after COVID-19. No statistically significant difference was found in the comparison of the pre- and post-disease vascular density values of SCP and DCP.

Table 2

Comparison of the superficial and deep capillary plexus vascular densities before and after COVID-19

	Group	N	Mean	SD	Min	Max	P
SCP total vascular density (%)	Pre-disease	20	52.78	1.04	48.40	57.50	0.47
	Post-disease	20	52.63	0.99	47.60	56.90	
SCP foveal vascular Density (%)	Pre-disease	20	17.80	1.08	13.10	23.20	0.65
	Post-disease	20	17.04	1.43	11.10	24.80	
SCP parafoveal vascular density (%)	Pre-disease	20	54.93	1.24	48.10	60.10	0.44
	Post-disease	20	54.21	1.39	46.10	59.40	
SCP perifoveal vascular density (%)	Pre-disease	20	53.43	1.10	48.60	58.40	0.74
	Post-disease	20	53.48	1.04	48.50	58	
DCP total vascular density (%)	Pre-disease	20	55.20	0.73	48	58.50	0.36
	Post-disease	20	55.80	1.09	49.50	61.70	
DCP foveal vascular density (%)	Pre-disease	20	35.45	1.89	27.40	46.40	0.89
	Post-disease	20	34.68	2.27	25.10	45.70	
DCP parafoveal vascular density (%)	Pre-disease	20	58.41	0.64	52.20	60.10	0.35
	Post-disease	20	58.87	1.04	53	63.20	
DCP perifoveal vascular density (%)	Pre-disease	20	57.07	0.74	50	60	0.34
	Post-disease	20	57.71	1.11	51	63	
SD: Standard deviation; Min: Minimum; Max: Maximum; SCP: Superficial capillary plexus; DCP: Deep capillary plexus							

Table 3 shows the comparison of the FAZ, CBF, SCT and retinal thickness values measured using OCTA before and after COVID-19. No statistically significant difference was found in the comparison of the pre- and post-disease FAZ and retinal thickness values. The mean CBF value of the patients was 2.00 ± 0.13 mm² before COVID-19 and 2.08 ± 0.23 mm² after the disease. When the pre- and post-disease CBF values were compared, there was a statistically significant increase ($p = 0.003$). The mean SCT value was 247.33 ± 7.65 μm before COVID-19 and 273 ± 4.92 μm after the disease, indicating a statistically significant increase ($p = 0.001$).

Table 3

Comparison of foveal avascular zone, choriocapillaris blood flow, subfoveal choroidal thickness and total retinal thickness before and after COVID-19

	Group	N	Mean	SD	Min	Max	P
Foveal avascular zone (mm ²)	Pre-disease	20	0.32	0.36	0.16	0.49	0.16
	Post-disease	20	0.32	0.38	0.16	0.50	
Choriocapillaris blood flow (mm ²)	Pre-disease	20	2	0.13	1.90	2.04	0.003
	Post-disease	20	2.08	0.23	1.94	2.18	
Subfoveal choroidal thickness (µm)	Pre-disease	20	247.33	7.65	205	286	0.001
	Post-disease	20	273.08	4.92	249	296	
Total retina parafoveal thickness (µm)	Pre-disease	20	239.75	2.48	226	252	0.92
	Post-disease	20	239.67	2.94	221	253	
Total retina foveal thickness (µm)	Pre-disease	20	314.50	3.40	303	332	0.79
	Post-disease	20	313.67	3.74	301	337	
Total retina perifoveal thickness (µm)	Pre-disease	20	293.50	1.71	286	301	0.91
	Post-disease	20	293.17	2.28	284	306	
SD: Standard deviation; Min: Minimum; Max: Maximum							

Table 4 presents the comparison of the optic disc vascular density and RNFL values measured before and after COVID-19. No statistically significant difference was found in the comparison of the optic disc vascular density values before and after COVID-19. While the mean RNFL value was 119.33 ± 3.88 µm before COVID-19, it was measured as 117.50 ± 3.92 µm after the disease, indicating a statistically significant decrease ($p < 0.001$).

Table 4

Comparison of the optic disc total vessel vascular density and retinal nerve fiber layer thickness values before and after COVID-19

	Group	N	Mean	SD	Min	Max	P
Optic disc total	Pre-disease	20	57.87	0.39	56	59.60	
vascular density (%)	Post-disease	20	57.52	0.34	54.80	59.20	0.44
Inside-disc vascular density (%)	Pre-disease	20	61.83	0.56	59.60	64.80	0.50
	Post-disease	20	60.40	0.67	57.10	63.70	
Peripapillary vascular density (%)	Pre-disease	20	59.45	0.42	57.30	61.40	0.30
	Post-disease	20	59.57	0.54	55.70	61.20	
Retinal nerve fiber layer (μm)	Pre-disease	20	119.33	3.88	101	127	<0.001
	Post-disease	20	117.50	3.92	98	124	
SD: Standard deviation; Min: Minimum; Max: Maximum							

Discussion

COVID-19 is a systemic disease that affects the whole body, especially the respiratory tract. The main symptoms of COVID-19 are fever, cough, sore throat, and loss of smell and taste. Ocular symptoms can also be seen and sometimes even present as initial findings [8]. Bertoli et al. reported conjunctivitis, Kawasaki disease, Guillain-Barré syndrome, polyneuritis, encephalopathy, dry eye, exposure keratopathy, chemosis, infectious keratitis, ischemic optic neuropathy, and Horner syndrome in patients with COVID-19 [4]. Wu et al. found ocular symptoms, including conjunctivitis, conjunctival hyperemia, epiphora, chemosis and increased secretion in 12 (31.6%) of 38 patients with COVID-19 [9]. In another study, Zhou et al. noted the presence of conjunctival symptoms, such as chemosis, conjunctival hyperemia, itching, foreign body sensation, and watering in eight (6.6%) of 121 COVID-19 cases [10]. Hon et al., evaluating 56 patients with COVID-19, observed ocular symptoms in 15 (27%) patients and summarized these symptoms as itching, redness, foreign body sensation, dry eyes, watering and floating objects. The authors also noted that six (11%) patients had developed ocular symptoms prior to respiratory system symptoms [11].

Marinho et al. examined 12 patients with COVID-19 and found soft exudate in the retina, retinal hemorrhage, and hyperreflectivity in ganglion cells and inner plexiform on optical coherence tomography [12]. In another study, Virgo et al. observed acute macular neuroretinopathy in a patient with COVID-19 and paracentral moderate acute retinopathy in another case [13]. Tostmann et al. described eye pain in

31 (34.4%) of 90 patients with COVID-19 [14] while Mao et al. reported visual loss in three (1.4%) of 214 patients [15]. In COVID-19 cases, Guillain-Barré syndrome manifesting with diplopia, third or sixth nerve involvement, and nystagmus, as well as its eye component, Miller Fisher syndrome, have also been described [16, 17]. However, although literature studies have shown that coronaviruses cause anterior uveitis, retinitis, vasculitis and choroiditis in animals, these findings have not been found in humans [18].

The etiopathogenesis of ocular findings seen in COVID-19 has been investigated in various studies but has not yet been fully elucidated. Considering the pathogenesis of conjunctivitis symptoms, it is thought that the virus uses the ocular surface as an entry point through the mediation of angiotensin-converting enzyme 2 receptors [19]. Peripheral nerve damage, demyelination and inflammation in diplopia are held responsible for visual impairment [20]. In Guillain-Barré and Miller Fisher syndromes, the autoimmune mechanism has been suggested to be effective against Schwann cells and myelin antigens [16, 17, 20].

Savastano et al. compared the OCTA findings of 80 patients with COVID-19 to 30 healthy controls. The authors reported the mean RNFL value as $94.09 \pm 10.77 \mu\text{m}$ for the COVID-19 group and $96.50 \pm 7.78 \mu\text{m}$ for the control group. Although this difference was not statistically significant, the RNFL value of the COVID-19 control was found to be lower than the control group ($p = 0.26$) [21]. In the current study, the mean RNFL was $119.33 \pm 3.88 \mu\text{m}$ before COVID-19 and $117.50 \pm 3.92 \mu\text{m}$ after the disease. The decrease in the RNFL value after the disease was statistically significant ($p < 0.001$). We consider that the reason for this is inflammation and retinal nerve fiber damage, as also described in previous studies [20].

Various OCTA studies have been conducted in relation to COVID-19 and its vascular etiopathogenesis. Abrishami et al. compared the OCTA findings of 30 patients with COVID-19 (nine requiring hospitalized treatment) obtained at two weeks after recovery to 23 healthy individuals. The total, parafoveal and foveal vascular density values of SCP and DCP were found to be statistically significantly lower in the COVID-19 group ($p = 0.001$, $p = 0.002$, $p = 0.004$, $p = 0.001$, $p = 0.011$, and $p = 0.003$, respectively) [6]. Similarly, Cennoma et al. evaluated the OCTA values at six months after recovery in 40 patients who had developed pneumonia due to COVID-19 and compared them to 40 healthy individuals. The authors reported that the total vascular densities of the optic disc and SCP and the total, parafoveal and foveal vascular densities of DCP were statistically significantly lower in the COVID-19 group compared to the control group ($p < 0.001$, $p = 0.038$, $p = 0.029$, $p = 0.016$, and $p = 0.027$, respectively).⁷ In another study, Savastano et al. found the radial peripapillary plexus perfusion density to be statistically significantly lower in individuals with COVID-19 compared to the control group, and this difference statistically significant ($p = 0.041$) [21].

In a study evaluating OCTA findings in 27 patients with a history of COVID-19 at one week after recovery from the disease compared to a healthy control group, Turker et al. observed a statistically significant decrease in the parafoveal vascular density values of SCP and DCP in the COVID-19 group ($p < 0.05$). However, the foveal vascular density did not statistically significant differ between the two groups. In the same study, the CBF value was reported to be $2.15 \pm 0.23 \text{ mm}^2$ for the COVID-19 group and $2.08 \pm 0.11 \text{ mm}^2$ for the control group, indicating a statistically significant difference ($p = 0.042$) [22]. In our study,

when we compared the retinal and optic disc vascular density values of the same patients before and after COVID-19, we found no statistically significant results. While the mean CBF value of the patients was $2.00 \pm 0.13 \text{ mm}^2$ before COVID-19, it was $2.08 \pm 0.23 \text{ mm}^2$ after the disease. When the pre- and post-disease CBF values, there was a statistically significant increase in the post-disease CBF value ($p = 0.003$).

In an autopsy performed on a person who died due to COVID-19, SARS-CoV-2 ribonucleic acid was detected in the retina [23]. Since there are ACE2 receptors in the retina and choroid, these tissues also have binding sites for the SARS-CoV-2 virus [6]. Studies have shown that COVID-19 causes vascular endothelial damage and vascular complications. Although endothelial damage, tissue edema, inflammatory cell migration, intravascular coagulation cascade, and endotheliitis are considered to be involved in vascular pathogenesis, the exact mechanism of this cascade remains unknown [24–26]. Inflammation and increased vascular permeability caused by COVID-19 are held responsible for the increase in CBF [22, 27]. We consider that despite the increase in the CBF value, the vascular density values of the retina and optic disc were not altered by the disease due to the autoregulation mechanism in the retina [6]. In addition, the retina contains a blood retinal barrier, but there is no such barrier in the choroid. Therefore, while inflammation and increased vascular permeability cause an increase in CBF, no change is observed in retinal vascular density values. It has been suggested that individuals that have had severe COVID-19 can develop hypoxia, ischemia, and microvascular damage in the retina [6, 22, 28]. The absence of significant changes before and after COVID-19 in our study despite the decrease in retinal vascular density values in the literature may be related to the patients in previous studies suffering from a more severe form of the disease requiring hospitalization.

Savastano et al. found the mean SCT value as $310.463 \pm 81.60 \text{ }\mu\text{m}$ in the patients with COVID-19 and $293.5 \pm 86.56 \text{ }\mu\text{m}$ in the control group. Although not statistically significant, the mean SCT value was higher in individuals who had a history of COVID-19 ($p = 0.34$) [21]. In our study, the mean SCT value was measured as $247.33 \pm 7.65 \text{ }\mu\text{m}$ before the disease and $273.08 \pm 4.92 \text{ }\mu\text{m}$ after the disease, and this increase was found to be statistically significant ($p = 0.001$).

Tan et al. listed the causes of an altered choroidal thickness as age-related changes, gender differences, sympathetic system activity, metabolic diseases (diabetes mellitus, hypercholesterolemia, etc.), changes due to choroidal hyperperfusion (hypertension), systemic inflammatory conditions (ankylosing spondylitis, Raynaud's phenomenon, Vogt-Koyanagi-Harada disease, Behçet's disease, and sarcoidosis), cerebral vasculature changes (Alzheimer's disease), microarteriolar occlusions (sickle cell disease), choroidal tumors and choroidal metastases [29]. We also consider that the increase in the choroidal thickness of our patients was caused by inflammation, increased vascular permeability, and increased CBF.

Considering the limitations of this study, it can be stated that the major limitation was the small number of patients. Another limitation is that none of the patients in this study required intensive care during active infection, and none had a severe form of the disease. Although the patients in our study did not

experience severe COVID-19, we found changes in their CBF, SCT and RNFL values compared to the pre-disease period. The retina, choroid and optic disc may be affected more in severe COVID-19, and this may be reflected in results in the presence of larger data. We consider that our study will contribute to the literature by guiding further research to be conducted with larger samples.

Conclusion

This is the first study in the literature to evaluate the pre- and post-disease changes in the vascular values of the retina, choroid and optic disc in people that recovered from COVID-19. We consider that in individuals with a history of COVID-19, inflammation and increased vascular permeability are effective in increased CBF and SCT values compared to the pre-disease period. In addition, inflammation and destruction of the retinal nerve fiber may be responsible for the decrease in RNFL in these patients.

Declarations

Funding No funding was received for conducting this study.

Conflict of interest All authors declare no funding was received and no conflict of interest/competing interests.

Data availability The data supporting the findings of the study are available from the corresponding author upon request.

Code availability Not applicable.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MKE, BG and OY. The first draft of the manuscript was written by BG and OY. MKE, BD, FD and ES read, revised, and approved the final manuscript.

Ethical approval The study protocol was approved by the Health Sciences University Antalya Training And Research Hospital (Date: 18.03.21 No:3/17). This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Written consent was acquired by all participants.

Consent for publication Written consent was acquired by all participants.

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Figures



Figure 1

Pre-COVID-19 choriocapillaris blood flow value of a patient (measured as 1.908 mm²)

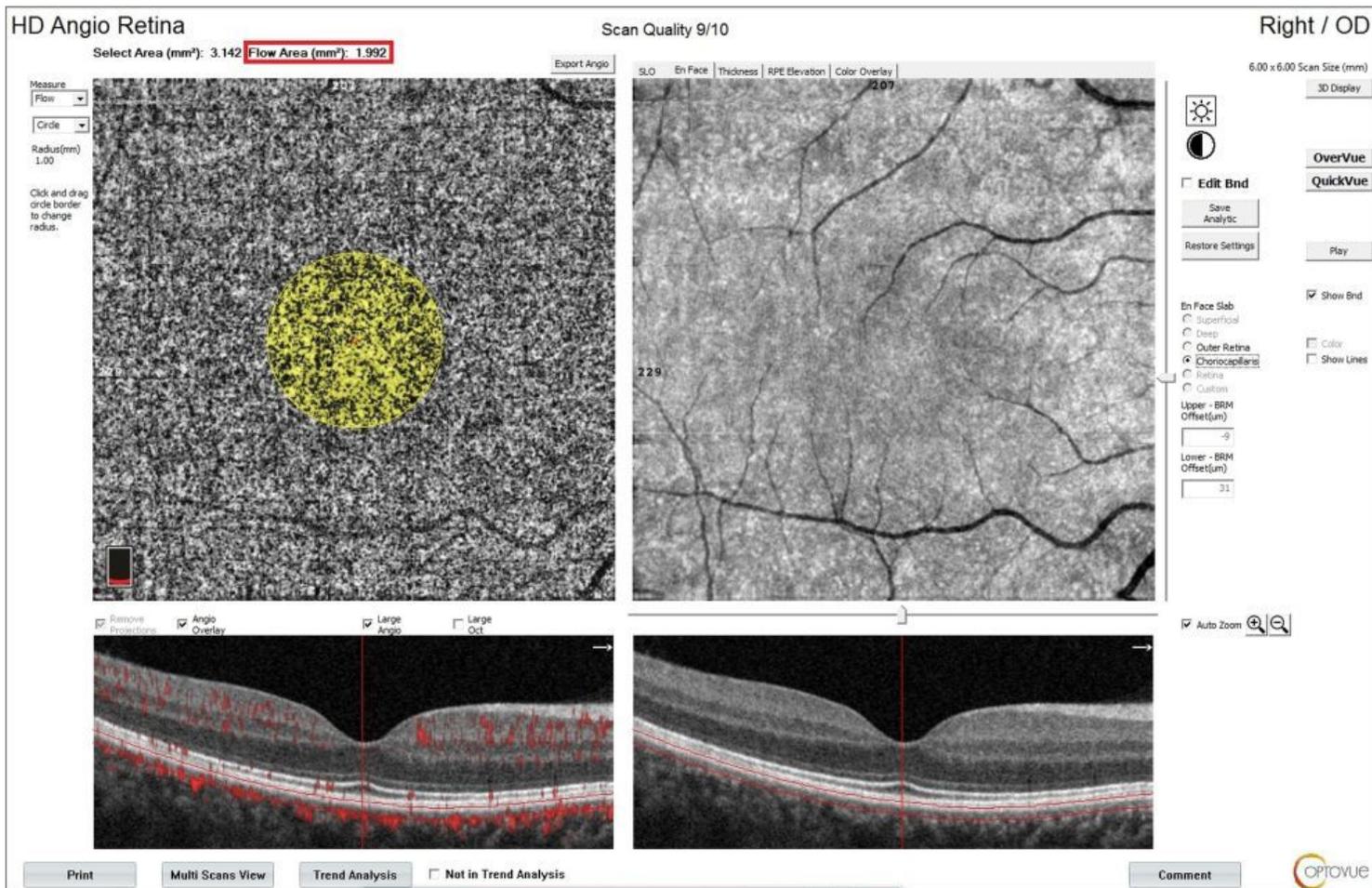


Figure 2

Post-COVID-19 choriocapillaris blood flow value of the patient presented in Figure 1 (post-disease value measured as 1.992 mm²)

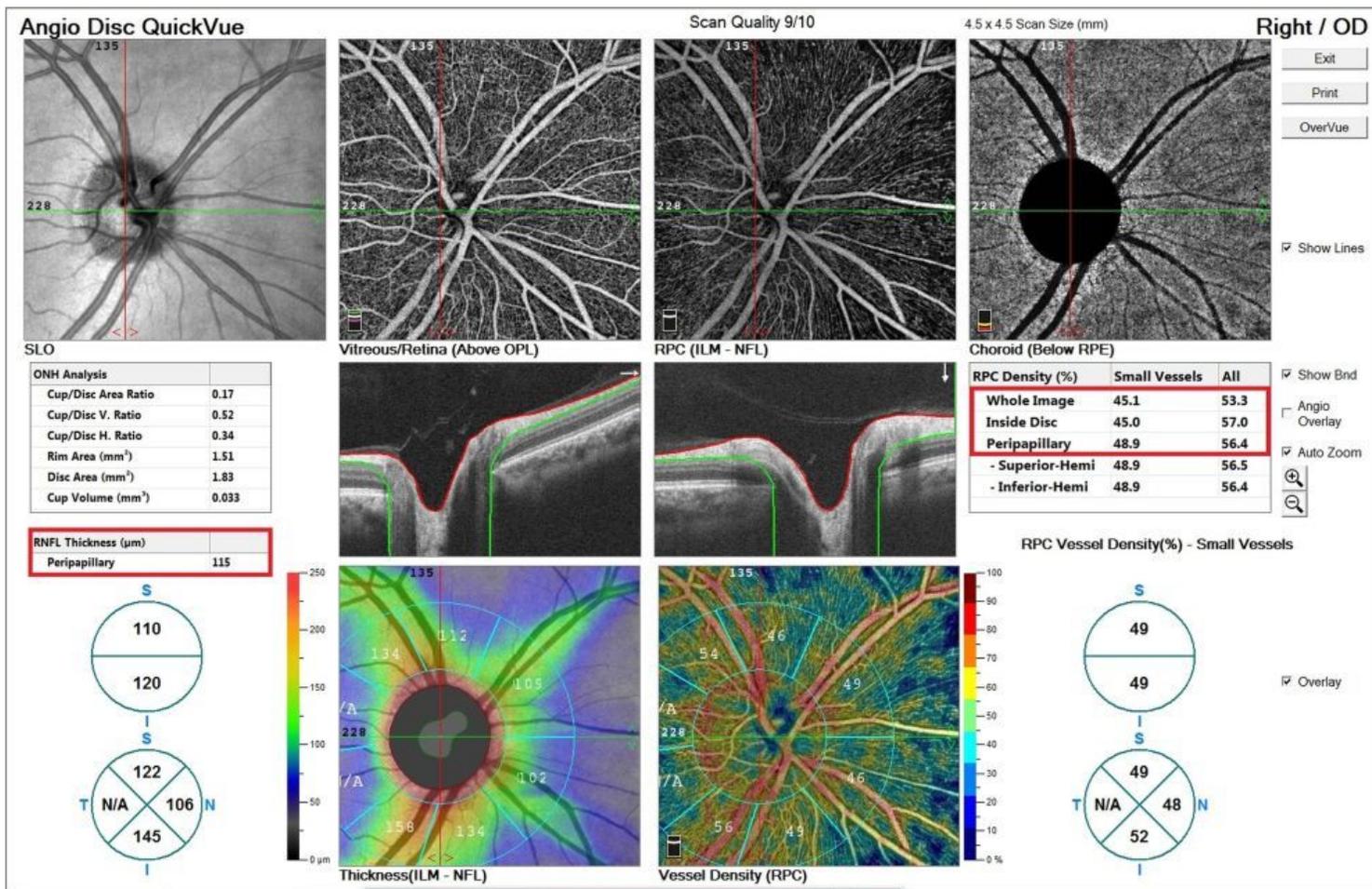


Figure 3

Pre-COVID-19 retinal nerve fiber thickness value of a patient (measured as 115 μm)

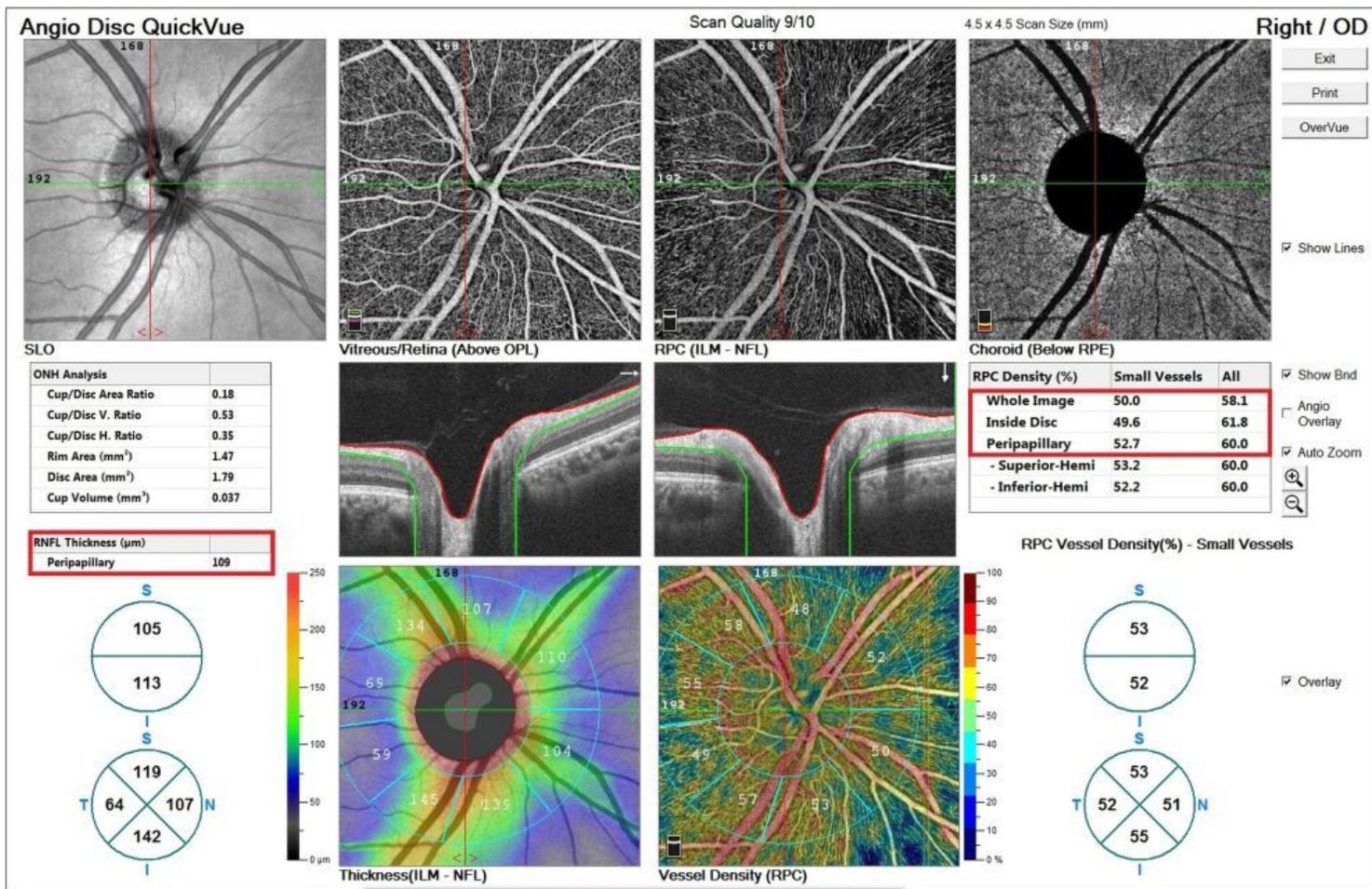


Figure 4

Post-COVID-19 retinal nerve fiber thickness value of the patient presented in Figure 3 (post-disease value measured as 109 μm)