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Optical Coherence Tomography Angiography Features in Post-COVID-19 Pneumonia Patients: A Pilot Study

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• ABSTRACT:• PURPOSE: **This study investigated changes in retinal vessel density in macular and papillary regions in post-SARS-CoV-2 pneumonia patients by means of optical coherence tomography angiography (OCTA).**

• DESIGN: **Prospective, observational, cohort study.**

• METHODS: **Forty eyes of 40 patients (mean age: 49.7 ± 12.6 years old) post-SARS-CoV-2 infection and 40 healthy subjects were enrolled in this study. COVID-19 patients had to be fully recovered from COVID-19 pneumonia and were evaluated 6 months after COVID-19 infection. The primary outcome resulted from OCTA studies of the following vascular structures: vessel density (VD) in the retinal superficial capillary plexus (SCP), deep capillary plexus (DCP), and radial peripapillary capillaries (RPC) compared to those of controls. Structural spectral domain (SD)-OCT parameters were also evaluated: ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL).**

• RESULTS: **The patients showed a significant reduction in VD of the SCP in whole images and in the DCP in all sectors compared to those in healthy subjects (P <.05). COVID-19 patients featured a reduced VD of the RPC compared to that in controls (P <.001). No differences were found in the GCC, whereas the RNFL was reduced in the COVID-19 group compared to that in controls (P = .012). Significant correlations were found between the RNFL and VD of the SCP, DCP, RPC, and FAZ area in the COVID-19 group (P <.05).**

• CONCLUSIONS: **OCTA showed retinal vascular changes in subjects fully recovered from COVID-19 pneumonia. These findings could be a consequence of a thrombotic microangiopathy that affected retinal structures as well as other systemic organs. OCTA could represent a valid, noninvasive biomarker of early vascular dysfunction after SARS-CoV-2 infection. (Am J Ophthalmol 2021;227: 182–190. © 2021 Elsevier Inc. All rights reserved.)**

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SINCE DECEMBER 2019, THE SARS-CoV-2 OUTBREAK has been a dramatic issue all over the world. On March 11, 2020, the World Health Organization declared a pandemic.[1] All countries have been tremendously affected, and all health care systems have been overwhelmed by this calamity. To date, no effective therapy has been developed, and there is no clue as to whether a future vaccine will be able to stop it.[2]

This infection can be completely asymptomatic or it can involve several organs and tissues, eyes included. A hypercoagulable state leading to thromboembolic events and disseminated intravascular coagulation has been observed in many critical patients.[3,4] Recent research has demonstrated diffuse endothelial damage that causes ischemic injury to different regions of the body. Such an impairment of the microcirculatory system may lead to functional disorders in multiple organs.[5,6]

Ocular implications have not been fully studied. Non specific retinal signs, such as microhemorrhages, vein dilation, cotton-wool spots, and flame-shaped hemorrhages, have been reported in many recent studies. However, it has not been possible to clearly establish whether these signs were secondary to COVID-19 infection or just incidental findings, given the high presence of comorbidities in the general population.[7-9] Optical coherence tomography angiography (OCTA), a new non invasive imaging technique, may provide qualitative and quantitative features of retinal and choroidal vascularization and could monitor the changes of vascular perfusion in patients with COVID-19 infection.[10,11]

This pilot study evaluated retinal vessel densities (VD) in patients who fully recovered from COVID-19 pneumonia and compared those findings with densities in healthy controls.

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METHODS

The present study was a prospective, observational, cohort study. The study protocol was registered on clinicaltrial.gov (OCTA Study: Retinal Vascular Changes in Patients With SARS-CoV-2 Infection; NCT04601012). The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. Written informed consent was obtained from all subjects enrolled in the study.

Consecutive patients who had been hospitalized with COVID-19 pneumonia and had fully recovered from the infection were referred after 6 months from discharge to the Eye Clinic of the University of Naples "Federico II" in October 2020 and were assessed for eligibility. The following inclusion criteria had to be satisfied to be enrolled: a) a history of hospital admission for COVID-19 pneumonia, classified as moderate illness, not requiring supplemental oxygen; b) a full recovery; c) 2 consecutive upper respiratory tract samples negative for viral nucleic acid. Moderate illness was defined as evidence of disease affecting the lower respiratory tract with an Spo_2 ≥94%, not requiring administration of supplemental oxygen.[12] Exclusion criteria were congenital eye disease, high myopia and high hyperopia (greater than 6 diopters), retinal vascular diseases, macular diseases, previous ocular surgery except uneventful cataract surgery, history of other ocular disorders, or significant lens opacity to avoid low-quality OCTA images. All subjects with a history of stroke, blood disorders, diabetes, uncontrolled hypertension, and neurodegenerative disease were also excluded. Each patient enrolled in the COVID-19 group was age and sex matched with a healthy control. Each subject underwent a complete ocular assessment including best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated fundus examination. Snellen BCVA measurements were based on the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (converted into logMAR for statistical analysis). Spectral domain-OCT (SD-OCT) and OCTA were performed by 2 independent observers (G.C. and D.M.) who carefully reviewed the OCTA and SD-OCT scans to confirm accurate retinal layer segmentation. Only 1 eye was randomly selected for each participant and included in the analysis.

The primary outcome of this study was the vessel density of macular and papillary regions on OCTA in the COVID-19 group compared with those in the control group. Foveal avascular zone, SD-OCT parameters, such as ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL), were considered secondary outcome measurements, as well as clinical variables, including BCVA and retinal findings.

• **SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY:** All patients were examined using SD-OCT (software RTVue XR version 2017.1.0.151, Optovue Inc., Fremont, California, USA). The optic nerve head (ONH) analysis measurements of the disc area, the rim area, and the cup-to-disc ratio were used to assess the RNFL thickness, calculated along a 3.45-mm diameter circle around the optic disc. The GCC thickness was obtained from a 7 × 7-mm grid of the macula centered 1 mm temporal to the fovea. The GCC thickness is the distance from the internal limiting membrane to the outer boundary of the inner plexiform layer.[13]

• **OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY:** All subjects underwent OCTA scanning. (Optovue Angiovue System, software ReVue XR version 2017.1.0.151, Optovue Inc., Fremont, California, USA). The system is based on a split-spectrum amplitude decorrelation algorithm.[14] The OCTA analysis divided the macular region into whole image, fovea, and parafovea in each vascular network of the retina, according to the ETDRS classification of diabetic retinopathy.[15] The software (AngioAnalytic) automatically calculated the vessel density in different retinal vascular networks: superficial capillary plexus (SCP) and deep capillary plexus (DCP) in a 6 × 6-mm quadrant scan centered on the fovea. Moreover, the software automatically calculated the foveal avascular zone (FAZ) area in the full retinal plexus.[16] The VD of the radial peripapillary capillary plexus (RPC), analyzing the whole papillary region, inside the disc and peripapillary region with an area scan of 4.5 × 4.5-mm, was automatically calculated by the AngioVue disc mode.[17]

The OCTA device included the 3-dimensional (3D) projection artifact removal (PAR) algorithm to remove projection artifacts for improving depth resolution on an OCTA signal and then distinguishing vascular plexus-specific features.[18-20] Each OCTA scan underwent automatic scan quality (1~10), values ≥6 were accepted. OCTA images with a signal strength index (SSI) less than 80, and residual motion artifacts were excluded from the analysis.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using Statistical Package for Social Sciences version 25 software (SPSS, Chicago, Illinois, USA) for Windows (Microsoft, Redmond, Washington, USA). The χ^2 test was used to determine differences in terms of sex. Student *t*-test analysis for independent samples was used to compare structural SD-OCT with OCTA parameters between patients and controls. The multiple linear regression model was used to evaluate the relationship between OCT and OCTA parameters in the post-COVID-19 group. The agreement between 2 observers in the measurement of SD-OCT and OCTA parameters was assessed using the intraclass correlation coefficient. A P value of $<.05$ was considered statistically significant.

TABLE 1. Demographic and Ocular Characteristics of the COVID-19 Group and Controls.

	COVID-19 Group	Control Group
Number of eyes	40.0	40.0
Males/females	29.0/11.0	.029/11.0
Age, yrs	49.7 ± 12.6	48.6 ± 12.2
BCVA, logMAR (Snellen)	0.06 ± 0.06 (20/23)	0.05 ± 0.05 (20/22)
Axial length, mm	23.3 ± 0.3	23.2 ± 0.5
IOP, mm Hg	13.9 ± 2.2	13.6 ± 2.3
SSI	83.5 ± 2.2	84.1 ± 2.1
Recovery time from SARS-CoV-2 infection, months	4.1 ± 1.3	-

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; IOP = intraocular pressure; SSI = signal strength index.

Data are expressed as mean ± SD.

RESULTS

A total of 40 eyes of 40 patients were included in the COVID-19 group (mean age: 49.7 ± 12.6; 11 females and 29 males) and a total of 40 eyes of 40 age- and sex-matched healthy subjects in the control group (mean age: 48.6 ± 12.2). Demographic and ocular characteristics of enrolled patients are reported in Table 1. Mean BCVA was 0.06 ± 0.06 logMAR (Snellen: 20/23) and 0.05 ± 0.05 logMAR (Snellen: 20/22) in the COVID-19 group and the control group, respectively. All patients included in the COVID-19 group presented unremarkable ocular examinations on the slit lamp as well as normal fundus examination. None of the patients complained of eye symptoms at the time of enrollment, and no participant had a history of eye symptoms during hospital admission for COVID-19 pneumonia. All patients were phakic in both the COVID-19 and the control groups. Recovery time from SARS-CoV-2 infection, confirmed by 2 consecutive negative oropharyngeal swabs, was 4.1 ± 1.3 months. There was no significant correlation between OCTA parameters and recovery time after SARS-CoV-2 infection ($P = .732$).

On OCTA imaging, SSI values were comparable between the 2 groups ($P = .921$). SCP vascular density was decreased in the COVID-19 group compared to that in the control group only in the whole image ($P = .038$). DCP vascular density showed a significant reduction in all macular sectors in the COVID-19 group compared to that in the control group ($P = .029$; $P = .016$; and $P = .027$ in the whole image, parafovea, and fovea, respectively). A significant reduction of the RCP vessel density in the whole image was found in the COVID-19 group compared to that in the control group ($P < .001$) (Table 2, Figure 1). The FAZ area did not show any significant changes between the 2 study groups ($P > .05$) (Table 2, Figure 1). The structural SD-OCT showed no significant differences in GCC averages ($P = .309$), whereas the RNFL averages were decreased ($P = .012$) in the COVID-19 group compared to those in the control group (Table 2, Figure 1).

The agreement between 2 observers for measuring the SD-OCT and OCTA parameters was excellent, with an intraclass correlation coefficient of >0.8 (Table 3)

Multiple regression analyses revealed in all COVID-19 patients a significant relationship between reduced average thickness of the RNFL and impaired OCTA parameters ($r = 0.818$; $P = .001$), particularly with SCP parafovea ($P = .004$), DPC whole image ($P = .006$), DCP parafovea ($P = .002$), RPC whole image ($P = .001$), RPC inside ($P = .012$), and FAZ area ($P = .008$). No significant relationships were found between GCC average thicknesses and OCTA parameters ($r = 0.712$; $P = .057$) (Table 4).

DISCUSSION

To the best of the authors' knowledge, this is the first report that investigated macular and peripapillary vessel density changes using OCTA in subjects who had recovered from COVID-19 infection. Results show a significantly altered retinal vascular density in post-COVID-19 subjects compared with healthy controls: DCP vessel density was reduced in all macular regions, whereas SCP and RCP vessel densities were reduced only in the whole image. These findings could be explained by the multiple pathogenic mechanisms linked to the SARS-CoV-2 infection, including thromboinflammatory microangiopathy and angiotensin-converting enzyme (ACE) 2 disruption.[6,21]

Complement-mediated thrombotic microangiopathy (TMA) has been assumed to be one of the main factors involved in COVID-19-related microvascular damage.[22] Complement activation plays a central role in the pathophysiology of TMA determining platelet activation, leukocyte recruitment, endothelial cell dysfunction, and coagulation.[23,24] Complement cascade activation is, in turn, a response to an endothelial injury secondary to local renin-angiotensin system disruption.[6,21] Endothelial cells express high levels of ACE2 receptors, which are used by SARS-CoV-2 to gain entry into the cell that is then disrupted.[25] Endothelial damage and subsequent thromboinflammatory microangiopathy lead to a hypercoagulative state that may explain the microvascular occlusion and the consequent multiorgan failure that characterizes advanced disease.[21,26]

Although severe respiratory complications are the main clinical features, COVID-19-associated coagulopathy predisposes to a wide spectrum of thromboembolic events, including pulmonary embolism, large-vessel ischemic strokes,

TABLE 2. Differences in OCTA and SD-OCT Parameters Between COVID-19 Group and Healthy Subjects.

	Post COVID-19 Group	Healthy Subjects	*P* Value
OCTA parameters			
SCP, %			
Whole image	48.86 ± 4.32	50.94 ± 4.49	.038
Parafovea	52.34 ± 5.29	52.59 ± 6.72	.858
Fovea	25.21 ± 5.28	25.30 ± 4.22	.929
DCP, %			
Whole image	52.42 ± 7.18	55.79 ± 6.35	.029
Parafovea	56.27 ± 6.31	59.72 ± 6.20	.016
Fovea	44.08 ± 7.16	47.80 ± 7.57	.027
RPC, %			
Whole image	46.43 ± 4.01	50.44 ± 4.67	<.001
Inside disc	52.40 ± 3.42	53.61 ± 4.34	.171
Peripapillary	48.02 ± 4.80	50.02 ± 5.03	.073
FAZ area, mm^2	0.225 ± 0.07	0.223 ± 0.07	.883
SD-OCT parameters			
GCC average, μm	99.17 ± 6.81	100.77 ± 7.15	.309
RNFL average, μm	98.27 ± 6.64	101.92 ± 6.06	.012

SCP = superficial capillary plexus: superficial capillary plexus; DCP = deep capillary plexus; RPC= radial peripapillary capillary plexus; FAZ = foveal avascular zone; GCC = ganglion cell complex; RNFL = retinal nerve fiber layer.

Student *t*-test was used for independent samples. Statistical significance *P* value <.05.

Data are expressed as mean ± SD.

venous thrombosis, renal failure, and cardiomyopathy, which can culminate in multiple organ dysfunction.[21,27,28]

It should be noted that immunohistochemical studies conducted on the human eye reported that also the ciliary body, choroid, retina, and retinal pigment epithelium showed significant levels of ACE2 receptors.[29] Therefore, SARS-CoV-2 could cause microvascular damage to retinal and choroidal vessels.[9]

Several retinal findings have been reported in COVID-19 patients, such as cotton-wool exudates, retinal flame-shaped hemorrhages, central retinal artery occlusion, and sectorial retinal pallor. All these could be considered signs of retinal vascular impairment following thrombotic complications.[7-9,30,31] Hitherto, only a report conducted by Savastano and associates[32] used OCTA imaging in COVID-19 patients. The authors demonstrated a reduction of perfusion density of the radial peripapillary capillary plexus in COVID-19 patients compared to that in healthy controls after 1 month from infection. The present results on RCP are in line with those of Savastano and associates. However, OCTA imaging was focused mainly on the study of RCP, with no information about other regions or plexuses. Furthermore, the present study has shed light on vascular changes affecting capillary plexuses of the macula area as well. The present analysis also revealed a significant relationship between RNFL and OCTA parameters, which could be explained by the anatomical localization of the RCP in the peripapillary RNFL.[33] COVID-19-related thrombotic microangiopathy could have caused vascular perfusion damage to the SCP and RPC, leading to interference in axoplasmic flow and subsequent retinal structural loss. The anastomoses that interconnect the SCP with the DCP may explain the possible correlation between this plexus and the RNFL.

Interestingly, the present findings showed no significant changes in GCC thicknesses. Ganglion cell layer is expected to get reduced when there is a thinning of RNFL, as the latter consists mainly of ganglion cell axons. Probably, the vessel density of SCP was not compromised enough to cause such a reduction of metabolic support to GCC that would have determined an anatomic thinning of this layer.

OCTA highlighted a much more significant impairment of the DCP than the SCP in COVID-19 patients in controls, as also occurs in diabetic retinopathy and other systemic vasculopathies.[34,35] The vascular structure of the deep plexus is characterized by a fine capillary network that makes it more vulnerable to thrombotic events than

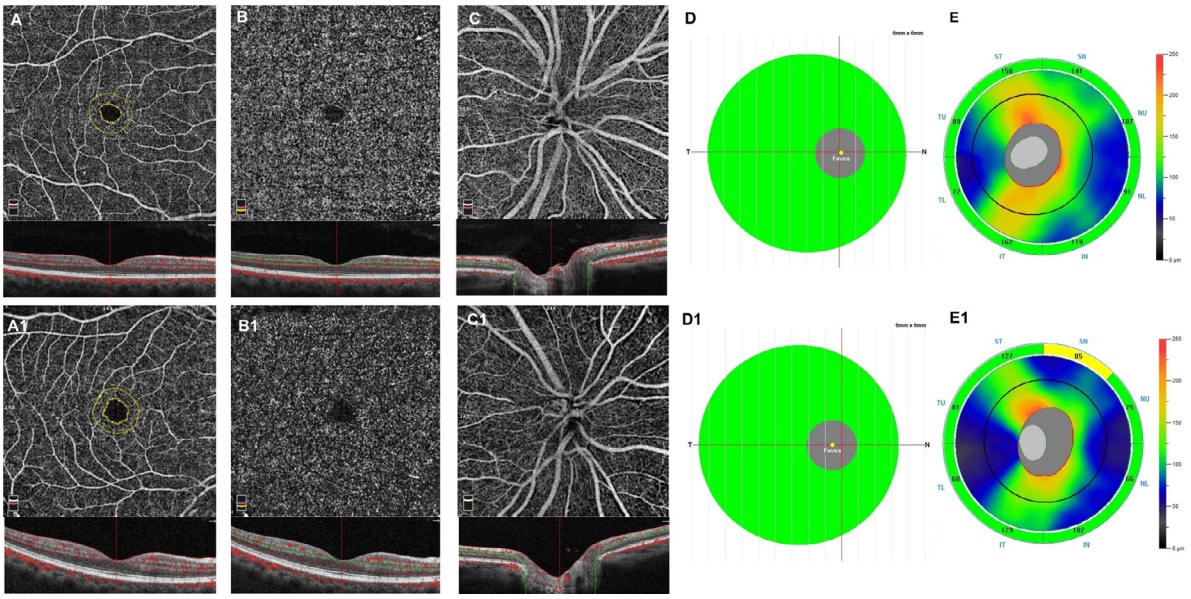

FIGURE. 1. Right eye of an healthy 44-year-old female shows on Optical Coherence Tomography Angiography (OCTA), (SSI:83) a normal vascular texture of the superficial capillary plexus (SCP), Foveal Avascular Zone (FAZ) area (A), the deep capillary plexus (DCP) (B), and the radial peripapillary capillary plexus (RPC) (C). SD-OCT shows a normal ganglion cell complex (GCC) (D) and retinal nerve faber layer (RNFL) thicknesses (E). On OCTA (SSI:82) the right eye of a post-COVID-19 patient (45-year-old female)reveals a focal reduction of SCP with normal FAZ area (A1), a diffuse rarefaction of the vascular texture in DCP (B1), and some alterations in the RPC (C1). SD-OCT shows normal ganglion cell complex (D1) and a focal reduction in RNFL thicknesses (E1).
SSI = signal strength index.

to the greater vascular caliber of the SCP.[36] Of note, the present OCTA findings showed that the loss of perfusion was diffuse, with no specific pattern. Similarly, no specific pattern was demonstrated in RNFL thinning, which was a diffuse reduction of the whole area. There was no sectorial co-localization but a significantly correlation between damages in OCT and OCTA parameters. There was no pattern of retinal structural and perfusion loss and no sectorial co-localization of damages in OCT and OCTA parameters

All patients enrolled in the COVID-19 group of the present study had no reduction in visual acuity, no visual symptoms, and their ocular examination proved unremarkable. They also had no history of any eye symptoms during their admission. The presence of retinal microvascular changes on OCTA imaging in otherwise healthy and asymptomatic eyes has a great scientific relevance. This may support the hypothesis of widespread microvascular damage that could be clinically silent. Idilman and associates[37] found deficits in lung and kidney perfusion in patients affected by mild to moderate COVID-19 disease.[37] Dual-energy computed tomography angiography showed lung perfusion deficits in 26% of cases, most of which had no detectable emboli in pulmonary arteries and did not overlap with areas of consolidation or ground glass opacity. Kidney perfusion deficits were demonstrated in 50% of cases in the absence of major kidney dysfunction.[37] Similarly, retinal microvascular changes did not cause clinical symptoms. It would be useful to know whether these microvascular deficits are associated with alterations on microperimetry and electrodiagnostic testing. On the other hand, a study conducted by Bussani and associates[38] reported a persistence of virus-infected cells in lung pneumocytes and endothelial cells several weeks from COVID-19 diagnosis.[38] These findings could explain the retinal vascular changes as long-term consequences of SARS-CoV-2 infection. More importantly, long-term follow-up is needed to see whether this subclinical microvascular impairment could be responsible for the development of ischemic diseases or a choroidal neovascular membrane. Further studies are warranted for such purposes.

The present trial has some limitations. First, the sample size was relatively small. Second, no data for vascular changes at the time of acute infection were available. There is no information for long-term follow-up. However, this is a novel coronavirus disease, and more time is needed to get longer follow-ups. No fluorescein angiography was performed to investigate the retinal periphery. However, the

TABLE 3. Intraclass Correlation Coefficients of OCTA and SD-OCT Parameters in COVID-19 Group and Healthy Subjects

	Post COVID-19 Group ICC (95% CI)	Healthy Subjects ICC (95% CI)
OCTA parameters		
SCP, %		
Whole image	0.759 (0.711-0.852)	0.841 (0.804-0.945)
Parafovea	0.814 (0.795-0.908)	0.816 (0.792-0.916)
Fovea	0.825 (0.783-0.913)	0.822 (0.780-0.919)
DCP, %		
Whole image	0.797 (0.781-0.806)	0.844 (0.781-0.933)
Parafovea	0.772 (0.744-0.811)	0.881 (0.851-0.914)
Fovea	0.783 (0.752-0.837)	0.856 (0.795-0.907)
RPC, %		
Whole image	0.755 (0.721-0.811)	0.885 (0.794-0.943)
Inside disc	0.874 (0.830-0.954)	0.873 (0.826-0.950)
Peripapillary	0.802 (0.773-0.930)	0.804 (0.780-0.915)
FAZ area, mm^2	0.823 (0.700-0.901)	0.822 (0.714-0.892)
SD-OCT parameters		
GCC average, μm	0.840 (0.731-0.912)	0.843 (0.727-0.925)
RNFL average, μm	0.764 (0.728-0.910)	0.883 (0.756-0.934)

ICC = intraclass correlation coefficient; CI = confidence interval; SCP= superficial capillary plexus; DCP = deep capillary plexus; RPC = radial peripapillary capillary plexus; FAZ = foveal avascular zone; GCC = ganglion cell complex; RNFL = retinal nerve fiber layer.

Statistical significance *P* value <0.05.

purpose of the study was to analyze macular and peripapillary regions by using a dyeless methodology. Further longitudinal studies are needed to evaluate the correlation between the OCTA parameters and both the onset and the duration of SARS-CoV-2 infection.

In conclusion, OCTA detected retinal microvascular changes following SARS-CoV-2 infection, helping to highlight the presence of microvascular damage in clinically asymptomatic eyes. In this clinical scenario, which has puzzled physicians and scientists about how to deal with an utterly new viral infection, new insights in pathogenetic mechanisms could be meaningfully appreciated. This noninvasive imaging technique could represent a valid biomarker of systemic vascular dysfunction as well. Longitudinal studies on larger cohorts are needed to detect the possible progression of retinal vascular alterations on long-term follow-up.

TABLE 4. Multiple Linear Regression Model Between SD-OCT and OCTA Parameters in the COVID-19 Group.

	r Value	ANOVA *P* Value	β Value	*P* Value
GCC average	.712	.057		
SCP whole image			0.178	.830
SCP parafovea			−0.771	.378
SCP fovea			−0.165	.550
DCP whole image			2.166	.028
DPC parafovea			−1.911	.012
DCP fovea			−0.479	.269
RPC whole image			1.232	.154
RPC inside			0.545	.097
RPC peripapillary			−0.421	.644
FAZ area			0.203	0.341
RNFL average	.818	.001		
SCP whole image			0.851	.217
SCP parafovea			−2.259	.004
SCP fovea			0.200	.377
DCP whole image			2.255	.006
DPC parafovea			−2.023	.002
DCP fovea			0.091	.796
RPC whole image			2.584	.001
RPC inside			0.702	.012
RPC peripapillary			−1.442	.061
FAZ area			0.924	.008

SCP = superficial capillary plexux; DCP = deep capillary plexus; RPC= radial peripapillary capillary plexus; FAZ = foveal avascular zone; GCC = ganglion cell complex; RNFL = retinal nerve fiber layer.

Multiple linear regression model; ANOVA = analysis of variance; statistical significance *P* value <.05.

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