

## Ocular sequelae in severe COVID-19 recovered patients of second wave

Taw Dipu, Ruchi Goel, Ritu Arora, Meenakshi Thakar, Akanksha Gautam, Shalin Shah, Yashi Gupta, Mohit Chhabra, Sumit Kumar, Kirti Singh, Suresh Kumar<sup>1</sup>, Sandeep Garg<sup>1</sup>, Harpreet Singh<sup>1</sup>, Rashmi Pant<sup>2</sup>

**Purpose:** To evaluate the retinal microvascular changes in patients, recovered from severe COVID-19 during the second wave of the pandemic in North India. **Methods:** In this observational cross-sectional study, 70 eyes of 35 patients who recovered from severe COVID-19 during the second wave underwent detailed ophthalmic evaluation 4–6 weeks after discharge. Twelve controls were also enrolled, and the difference in the findings between the case and control groups on optical coherence tomography (OCTA) were studied. **Result:** The ages of study participants ranged from 27 to 60 years with the male:female ratio being 1.05:1. The fundus changes suggestive of ischemia in the form of cotton wool spots and vascular tortuosity were seen in 25 eyes (35.71%). Increased venous tortuosity was the most common finding seen in 23 eyes (32.85%), of which 10 eyes (28.57%) had concurrent hypertensive retinopathy (HTR) changes. There was a significant reduction in the mean vascular density (VD) and perfusion density (PD) for both the superficial capillary plexus (SCP) and deep capillary plexus (DCP) at inner, outer ring, and whole ( $P < 0.05$ ). Foveal avascular zone was significantly enlarged in both the SCP ( $P = 0.01$ ) and the DCP ( $P = 0.03$ ). The mean ganglion cell-inner plexiform layer (GC-IPL) was significantly reduced in comparison to controls ( $P < 0.001$ ). **Conclusion:** Severe COVID-19 can result in microvascular changes at the macula in the form of reduction in vascular and perfusion density, which can be evaluated using OCTA. As structural changes precede functional changes, a close watch is recommended in patients showing compromise in retinal microvasculature.

**Key words:** COVID-19, OCTA, perfusion density, vessel density

The second wave of COVID-19 in India unleashed unprecedented devastation across the country, with many experiencing “long COVID” and multiorgan involvement. Tissue damage by SARS CoV-2 has been linked to microvascular angiopathy along with overproduction of cytokine, leading to ischemia, inflammation, tissue edema, and prothrombotic state.<sup>[1,2]</sup> In the retina, presumed S and N COVID-19 proteins have been demonstrated within the endothelial cells of the inner and outer nuclear layer.<sup>[3]</sup> Recent studies have reported a direct association between the severity of COVID-19 and retinal changes.<sup>[4,5]</sup> Retinal findings may be seen in the form of hemorrhages, cotton wool spots, dilated veins, and tortuous vessels or the fundus may appear normal despite underlying microvascular alterations that may persist for 6 months after hospital discharge.<sup>[6,7]</sup>

Optical coherence tomography (OCTA) has been suggested as a biomarker for microvascular changes.<sup>[8]</sup> It is an efficient and noninvasive modality for examining retinal vasculature. OCTA helps in the assessment of superficial and deep capillary plexuses separately. It gives quantitative and qualitative analysis of vessels at macula for assessment of the ischemic changes.

Department of Ophthalmology, Guru Nanak Eye Centre, Maulana Azad Medical College, <sup>1</sup>Department of Medicine, Lok Nayak Hospital, Maulana Azad Medical College, New Delhi, <sup>2</sup>Society for Health Education and Allied Research, New Delhi, India

**Correspondence to:** Dr. Ruchi Goel, Department of Ophthalmology, Gurunanak Eye Centre, Maulana Azad Medical College, New Delhi - 110 002, India. E-mail: gruchi1@rediffmail.com

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The purpose of this study was to evaluate the ocular sequelae, especially the retinal microvascular changes, in patients who recovered from severe COVID-19 during the second wave of the pandemic in North India.

## Methods

An observational cross-sectional study was conducted from June 1 to August 31, 2021 at a tertiary eye center attached to a COVID-19-dedicated hospital. The study was approved by the institutional ethical committee (Protocol no. F.1/IEC/MAMC/84/02/2021/No384 and registration no. CTRI/2021/06/033949) and conducted according to the tenets of the Declaration of Helsinki. Signed informed consent from the participants was taken prior to participation in the study.

Hospital medical records were reviewed, and 184 severe COVID-19 patients,  $\geq 18$  years, were invited for this study 4–6 weeks after discharge from hospital and with at least one documented negative reverse transcription-polymerase chain reaction (RT-PCR) report. Severe COVID-19 was defined as clinical signs of pneumonia along with the presence of respiratory rate  $>30$ /min or severe respiratory distress, and

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SpO<sub>2</sub> <90% at room air. Exclusion criteria were high refractive error myopia/hyperopia (>6 D), ocular congenital anomaly, macular disease, and media opacity precluding OCTA. The patients were managed as per the government of India guidelines.<sup>[9]</sup>

Twelve age- and sex-matched controls were selected from willing participants, devoid of any systemic illness likely to influence the orbital vascular flow, who had come to the outpatient department for problems related to the ocular surface.

A flowchart showing patient recruitment is presented in Fig. 1.

The study participants underwent a detailed history and bilateral ophthalmic examination including best-corrected visual acuity (BCVA) in logMAR, slit-lamp biomicroscopy, intraocular pressure measurement using Goldman applanation tonometry, and retinal fundus examination. Bilateral fundus photographs were captured using Zeiss Visucam Pro NM (Carl Zeiss Meditec, Dublin, CA, USA).

Visual field analysis was done using Humphrey Field Analyzer III, Swedish interactive threshold algorithm standard 30-2 program (Carl Zeiss Meditec, Dublin, CA, USA). The thickness of the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fiber layer (RNFL) at 3 mm at the macula and

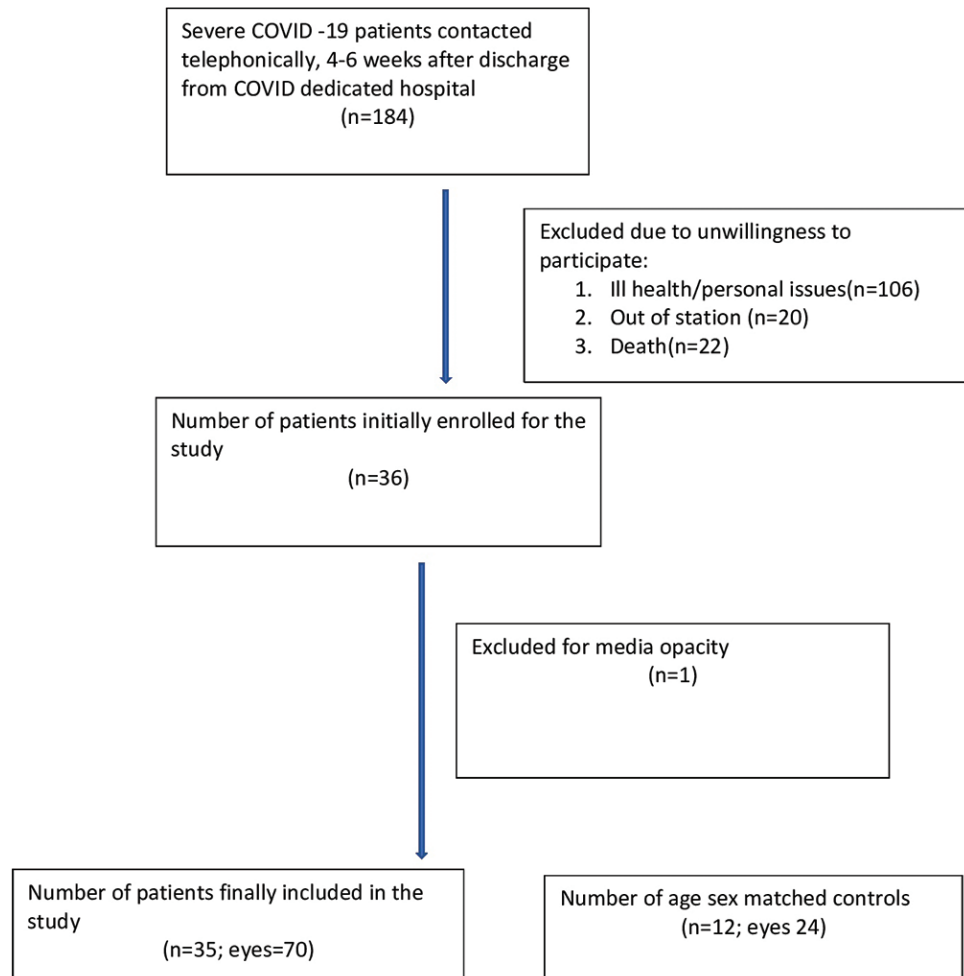
4.5 mm at the disc was recorded using the spectral domain OCT RS-3000 LITE (NIDEK Inc.).

OCTA was performed at 4.5 mm × 4.5 mm at the disc and 3 mm × 3 mm at the macula with the inner ring at 1.5 mm from the center of the fovea and the outer ring between 1.5 and 3 mm. Vessel density (VD) and perfusion density (PD) were automatically calculated by the algorithm using the early treatment of diabetic retinopathy study (ETDRS) chart. VD was defined as the total length of perfused vasculature per unit area in the region of measurement. PD was defined as the total area of perfused vasculature per unit area in the region of measurement. Foveal avascular zone (FAZ) was measured using the machine algorithm. All OCTA images have been taken in dilated pupils under standard lighting and protocol.

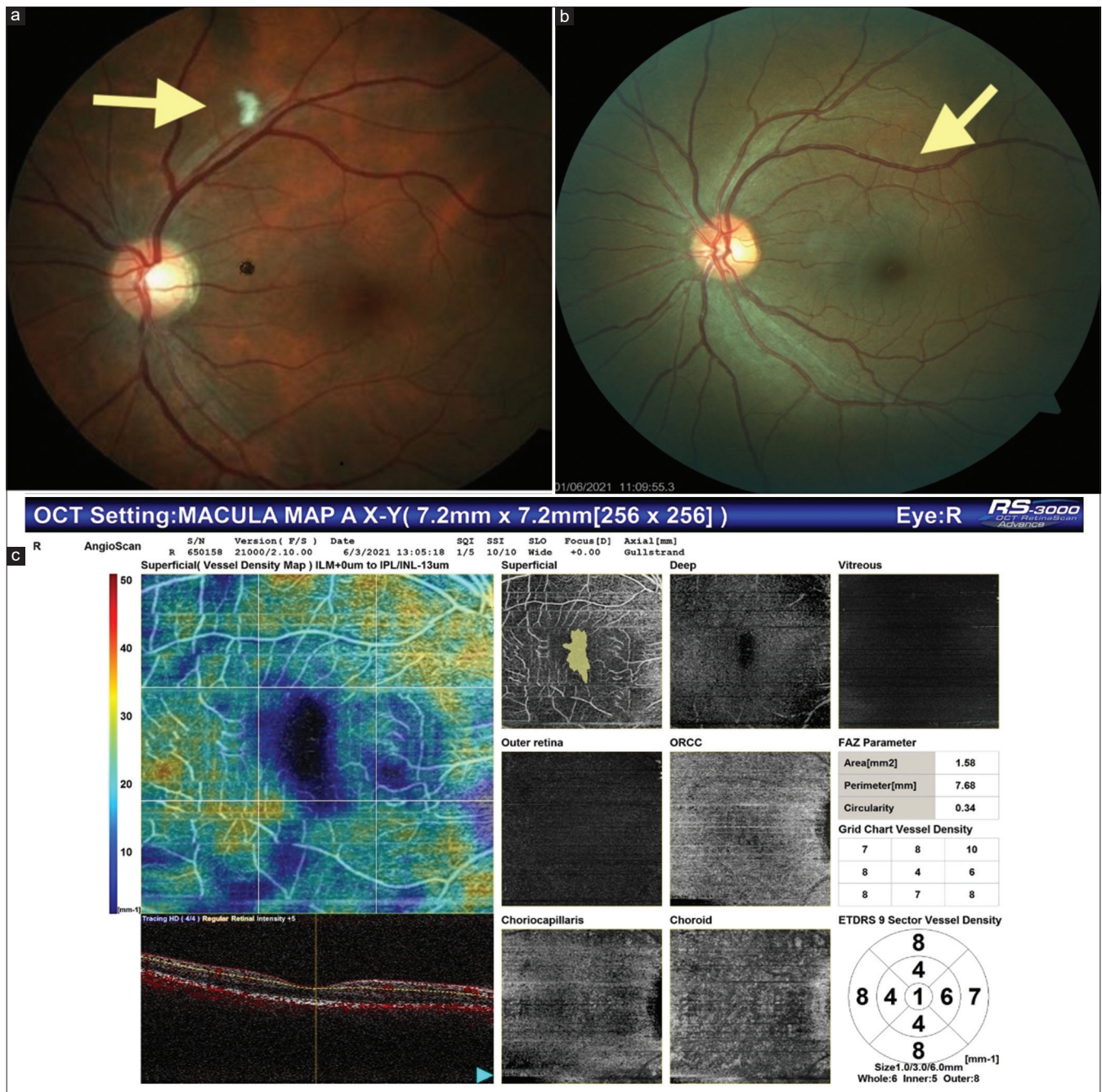
The primary outcome measure was the difference in VD and PD between the case and control groups. The secondary outcomes included analysis of changes in FAZ, GC-IPL, RNFL, and VD/PD of the radial peripapillary capillary plexus (RPCP) between the case and control groups, and the correlation of minimum oxygen concentration at room air with the macular VD/PD in the cases group.

**Statistical analysis**

Descriptive analysis of age and other clinical data were performed for numeric data in terms of mean, median, and



**Figure 1:** Flowchart showing patient recruitment



**Figure 2:** (a) Fundus image showing cotton wool spots along supero-temporal arcade. (b) Fundus image showing vascular tortuosity and sluggish blood flow. (c) Optical coherence tomography angiography showing enlarged FAZ (1.58 mm) and decreased vessel density

standard deviation. The categorical variables were reported as counts and percentages. The OCTA parameters between the cases and controls were compared using the student *t* test assuming unequal variances in the two groups. The correlation analysis was done using the Karl Pearson correlation coefficient and *P* values were reported at a 5% significance level.

**Results**

The study included 70 eyes of 35 cases and 24 eyes of 12 controls. The ages of cases and controls ranged from 27 to 60 years, and the male: female ratio was 1.05:1. Out of 35 cases, 17 had no comorbidities, four had hypertension, four had type

2 diabetes mellitus, (T2DM), and 10 had both type 2 diabetes mellitus(T2DM) and hypertension. None of the subjects had a history of smoking. Six cases had been given the first dose, and the remaining 29 had not been vaccinated against COVID-19. All the patients had received injection methylprednisolone, tablet remdesivir, low-molecular-weight heparin, and supportive therapy as per the prescribed guidelines.<sup>[9]</sup> None of the cases had been administered tocilizumab or blood transfusion. The mean D-dimer level on admission was 1269.62 ± 576 ng/mL.

**Best-corrected Visual Acuity:** It ranged from logMAR 0.00 to 0.20 in the COVID-19-recovered patients. The difference between the groups was statistically insignificant.

**Table 1: Fundus findings in patients recovered from severe COVID-19**

Fundus findings	No. of patients (eyes)	Presence of hypertension
Venous tortuosity	12 (24)	4
Cotton wool spots	3 (5)	2
Venous dilatation, blot hemorrhages suggestive of impending CRVO	1 (2)	No
Disc hyperaemia	1 (2)	No
Disc pallor	1 (1)	1
Neurosensory detachment	1 (1)	No

**Table 2: Comparison of OCTA parameters in cases and controls**

OCT/OCTA parameters	COVID-19 group Mean ( $\pm$ SD)	Control group Mean ( $\pm$ SD)	P
SCP VD			
Inner	11.31 $\pm$ 4.58	16.00 $\pm$ 1.29	<0.001
Outer	18.22 $\pm$ 3.79	20.75 $\pm$ 1.45	<0.001
Whole	13.26 $\pm$ 3.63	16.04 $\pm$ 1.00	0.00
DCP VD			
Inner	9.40 $\pm$ 3.76	11.25 $\pm$ 2.75	0.02
Outer	17.26 $\pm$ 4.83	20.00 $\pm$ 2.92	<0.001
Whole	11.88 $\pm$ 3.67	14.00 $\pm$ 2.38	<0.001
SCP PD			
Inner	29.55 $\pm$ 12.75	42.29 $\pm$ 6.65	<0.001
Outer	46.45 $\pm$ 10.17	53.33 $\pm$ 4.72	<0.001
Whole	34.28 $\pm$ 9.96	42.63 $\pm$ 4.31	<0.001
DCP PD			
Inner	23.86 $\pm$ 9.40	28.63 $\pm$ 8.56	0.03
Outer	42.83 $\pm$ 11.79	47.83 $\pm$ 6.89	0.02
Whole	29.69 $\pm$ 9.21	33.88 $\pm$ 6.89	0.03
RPCP VD	19.08 $\pm$ 2.12	19.67 $\pm$ 1.13	0.11
RPCP PD	55.03 $\pm$ 5.05	54.79 $\pm$ 2.32	0.76
FAZ SCP	0.37 $\pm$ 0.11	0.31 $\pm$ 0.07	0.01
FAZ DCP	0.54 $\pm$ 0.14	0.47 $\pm$ 0.11	0.03
GC IPL	101.28 $\pm$ 10.33	108.93 $\pm$ 7.04	<0.001
RNFL	101.11 $\pm$ 13.40	95.17 $\pm$ 19.35	0.17

SCP=superficial capillary plexus; DCP=deep capillary plexus, RPCP=radial peripapillary capillary plexus; FAZ=foveal avascular zone, GC-IPL=ganglion cell- inner plexiform layer; RNFL=retinal nerve fiber layer. Statistically significant if  $P<0.05$

**Visual Field:** No defect was seen in any of the study participants.

**Fundus:** Abnormal retinal findings were seen in 44 of the 70 eyes [Table 1]. The fundus changes suggestive of ischemia in the form of cotton wool spots and vascular tortuosity were seen in 25 eyes (35.71%) [Fig. 2a]. Increased venous tortuosity was the most common finding seen in 23 eyes (32.85%), of which 10 eyes (28.57%) had concurrent hypertensive retinopathy (HTR) changes: arteriolar attenuation, arteriovenous crossing changes, and cotton wool spots [Fig. 2b].

**Vessel and Perfusion density:** There was a significant reduction in the mean VD and PD for both the SCP and DCP. The mean VD and PD of the RPCP, though reduced, were statistically not significant [Table 2].

**Other OCT parameters:** FAZ was significantly enlarged in both the SCP ( $P = 0.01$ ) and the DCP ( $P = 0.03$ ). FAZ was enlarged at the SCP level in 15 patients and at the DCP level in 13 patients [Fig. 2c]. The mean GC-IPL was significantly reduced in comparison to controls in 40 eyes (57.14%) from the cases group. A positive correlation was seen between the GC-IPL and the VD/PD at both the SCP and the DCP level [Table 3]. The mean RNFL thickness changes between the groups were not significant [Table 2].

Correlation analyses showed that average minimum oxygen saturation at room air was not significantly associated with any of the macular OCT parameters [Table 4].

## Discussion

The study was conducted to investigate retinal microvascular changes in severe COVID-19-recovered patients during the second wave. To the best of our knowledge, there are no published studies from India on vascular alteration at the macula and optic disc following COVID-19.

The mean diameter of arteries and veins increases in COVID-19 patients. Also, the mean vein diameter has been found to be negatively correlated with the time from COVID-19 symptom onset and positively correlated with disease severity.<sup>[5]</sup> In our study, bilateral dilated tortuous veins were observed in 33% (23/70) eyes and constituted the most common finding on fundus examination. The blood flow tends to adapt to the physiological needs of the retinal tissue by pressure autoregulation and induction of changes in the diameter of retinal vessels.<sup>[10]</sup> The larger retinal venular diameter has also been associated with rising serum levels of the inflammatory markers C-reactive protein, fibrinogen, and lipoprotein-associated phospholipase A 2.<sup>[11]</sup>

Other fundus findings noted in our study were cotton wool spots (CWS), disc pallor, disc hyperemia, neurosensory detachment (NSD), and vitreous fibrillary degeneration. Similar fundus findings were also seen in previous studies.<sup>[5,12-14]</sup> A state of hypercoagulability occurs secondary to an inflammatory response to the SARS-CoV-2 virus, leading to microangiopathy, which tends to worsen with hypertension and diabetes.<sup>[15]</sup> Sim *et al.*<sup>[16]</sup> excluded previously known cases of hypertension and diabetes mellitus in their series and attributed the retinal findings to a transient rise in blood pressure during COVID-19. In our series, we did not follow strict exclusion criteria; however, retinal microangiopathic changes were observed in seven cases without any other comorbidity.

Vascular occlusion of the central retinal vein, central retinal artery, branch retinal vein, and branch retinal artery have been variably observed in COVID-19.<sup>[17-19]</sup> Also, acute macular neuroretinitis (AMN) and paracentral acute middle maculopathy (PAMM) have been reported. AMN is hypothesized to occur following ischemic changes in DCP and PAMM due to reduced blood flow at the SCP, intermediate capillary plexus, and DCP levels.<sup>[20]</sup> Other reported findings are papillophlebitis, optic neuritis, vitritis, serpiginous choroiditis,

**Table 3: Correlation of OCTA and OCT parameters**

	RNFL	GC-IPL
Macular vessel disease (Superficial)		
Whole		
<i>r</i>	-0.0825	0.3127
<i>P</i>	0.4614	0.0042
Inner		
<i>r</i>	-0.0641	0.3394
<i>P</i>	0.5675	0.0018
Outer		
<i>r</i>	0.0104	0.2061
<i>P</i>	0.9261	0.0632
Macular vessel disease (Deep)		
Whole		
<i>r</i>	0.0314	0.2622
<i>P</i>	0.7791	0.0173
Inner		
<i>r</i>	-0.025	0.2513
<i>P</i>	0.8239	0.0228
Outer		
<i>r</i>	0.0478	0.1887
<i>P</i>	0.6696	0.0896
Macular PD (Superficial)		
Whole		
<i>r</i>	-0.0833	0.2538
<i>P</i>	0.457	0.0214
Inner		
<i>r</i>	-0.0946	0.2943
<i>P</i>	0.3976	0.0073
Outer		
<i>r</i>	-0.0328	0.1702
<i>P</i>	0.7698	0.1263
Macular PD (Deep)		
Whole		
<i>r</i>	0.0312	0.2025
<i>P</i>	0.7805	0.0681
Inner		
<i>r</i>	0.0261	0.2405
<i>P</i>	0.8159	0.0295
Outer		
<i>r</i>	0.0648	0.1176
<i>P</i>	0.5632	0.2928

GC-IPL=ganglion cell-inner plexiform layer; RNFL=retinal nerve fibre layer.  
Statistically significant if  $P<0.05$

and endogenous endophthalmitis.<sup>[21-23]</sup> None of these findings were seen in our series except for bilateral impending CRVO in one case. In a recently published review, retinal signs on clinical examination were variably observed till about 36 days after discharge.<sup>[6]</sup> Fewer retinal changes in our study could be related to the long interval between COVID-19 recovery and fundus examination.

The disparity in VD/PD and FAZ can occur due to age, sex, axial length, and refractive error.<sup>[24,25]</sup> To overcome these biases,

**Table 4: Correlation of OCTA parameters with minimum O<sub>2</sub> saturation**

	Minimum O <sub>2</sub> levels
Macular vessel disease (Superficial)	
Whole	
<i>r</i>	-0.0527
<i>P</i>	0.6947
Inner	
<i>r</i>	-0.0964
<i>P</i>	0.4716
Outer	
<i>r</i>	0.0566
<i>P</i>	0.673
Macular vessel disease (Deep)	
Whole	
<i>r</i>	0.2018
<i>P</i>	0.1287
Inner	
<i>r</i>	0.1394
<i>P</i>	0.2967
Outer	
<i>r</i>	0.2065
<i>P</i>	0.1199
Macular PD (Superficial)	
Whole	
<i>r</i>	-0.061
<i>P</i>	0.6492
Inner	
<i>r</i>	-0.0962
<i>P</i>	0.4723
Outer	
<i>r</i>	0.0264
<i>P</i>	0.8442
Macular PD (Deep)	
Whole	
<i>r</i>	0.204
<i>P</i>	0.1246
Inner	
<i>r</i>	0.1653
<i>P</i>	0.2149
Outer	
<i>r</i>	0.2212
<i>P</i>	0.0952

*r*=correlation coefficient, Statistically significant if  $P<0.05$

we included age- and sex-matched controls and excluded patients with high refractive errors.

We found a significant decrease in vessel and perfusion density in the inner ring, outer ring, and whole of the macula at both SCP and DCP levels. The relation between change in VD and PD and severity of COVID-19 has been variably reported. Though the study participants were exclusively severe COVID-19-recovered in our series, reduction in both VD and PD has been observed in mild and moderate COVID-19-recovered

cases in absence of systemic illness likely to influence retinal Vasculature.<sup>[8]</sup> Zapata *et al.*<sup>[4]</sup> found a greater reduction in VD in patients with moderate and severe COVID-19 compared to mild disease, linking the reduction in VD with COVID-19 to the severity of COVID-19. However, Savastano *et al.*<sup>[12]</sup> could not find a significant reduction in VD or PD in mild and moderate post-COVID-19 patients at 1 month and suggested reversibility of macular capillary plexus damage over the time. In another study, Hazar *et al.*<sup>[26]</sup> found reduced VD in both SCP and DCP in mild and moderate cases with no systemic illness after 30 days of discharge. They explained that the parallel organization between SCP and DCP, also called “the Hammock,” may be affected in COVID-19, resulting in reduced VD in both layers. This was similar to our study as we found a reduction in both SCP and DCP. Studies have shown more impairment of DCP than SCP in diabetic retinopathy and other systemic vasculopathies.<sup>[27]</sup> An increase in the mean FAZ at both the SCP and DCP level was seen in our study similar to the published reports.<sup>[4,14]</sup> In a prospective study, the comparison of OCTA findings 14 days and six months after discharge, showed persistence of reduced VD, without further deterioration and further enlargement of FAZ.<sup>[7]</sup>

Structural SD-OCT showed a significant reduction in GC-IPL layer thickness, and a positive correlation was seen between GC-IPL and VD/PD at both the SCP and DCP levels in our study. Oren *et al.*<sup>[28]</sup> found thinning of GCL and inner nuclear layer and increased central macular thickness (CMT). Their subjects consisted of mild cases, and the examination was performed 14–30 days after the onset of symptoms. They concluded that the viral infiltration and inflammation in the early phase causes thickening, which eventually clears with progressive loss of the ganglion cell complex and the photoreceptors, resulting in thinning. They also suggested that the edematous increase in CMT may be due to the presence of virus in the external limiting membrane and the inner/outer segments of the photoreceptors. Thinning of GC-IPL in our study could be attributed to delayed post-COVID-19 examination. In another study by Cennamo *et al.*,<sup>[8]</sup> they found no difference in ganglion cell complex between the groups.

Changes in RNFL have been inconsistent in various studies. Gonzalez-Zamora *et al.*<sup>[14]</sup> noted the reduced thickness of GCL and increased thickness of RNFL among moderate and severe COVID-19 patients 14 days after discharge. They suggested the occurrence of subclinical changes in RNFL resulting from axoplasmic flow interruption. Cennamo *et al.*<sup>[8]</sup> also found reduced RNFL thickness in the COVID-19 group as compared to the control. An increase in RNFL and GC thickness was reported in another study.<sup>[29]</sup> The authors postulated that inflammation caused by the virus can account for the thickening of some layers and the atrophy of other layers. Another study performed 6 months after discharge demonstrated further thinning of parafoveal RNFL and GCL as compared to 0 months ( $P < 0.001$  in both cases).<sup>[7]</sup> The study by Ornek *et al.*<sup>[30]</sup> noted a localized thinning in the inferonasal sector in patients with COVID-19. They suggested that subclinical damage may occur in patients with COVID-19, which may cause localized rather than diffuse axonal loss. In our study, we found a slight increase in the RNFL thickness in all four quadrants. This may be related to increased inflammatory markers leading to thickening.

We did not find visual field defects in any of the participants. Correlation analysis did not show any significant association between macular VD and PD and average minimum oxygen saturation at room air. Because all our subjects had  $SpO_2 < 90\%$  at room air, possibly variability in oxygen saturation was too narrow to elicit a difference.

The limitations of our study were the small sample size, the inclusion of patients with comorbidities, and the absence of follow-up data. Also, there is a possibility of missing severe retinal changes in sicker patients who expressed their inability to participate in the study.

## Conclusion

In summary, our study further emphasizes that severe COVID-19 can result in microvascular changes at the macula in the form of a reduction in vascular and perfusion density. These OCTA parameters can be useful for monitoring the progress of retinal ischemia. As structural changes precede functional changes, a close watch is recommended in patients showing compromise in retinal microvasculature.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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