Ocular Manifestations of COVID-19 Virus in the Recovered Patients

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Abstract

BACKGROUND

The aim of this study was to evaluate the ocular disorders in patients with Covid-19 after recovery.

METHODS

In this cross-sectional, historically controlled study, fifty one recovered COVID-19 patients were compared with thirty-seven age and gender matched healthy individuals. After complete ophthalmological examination, all participants underwent peripapillary and macular optical coherence tomography and optical coherence tomography angiography (OCTA) measurements (OptoVue Inc, Freemont, CA, USA).

RESULTS

Ophthalmic examination of all the recovered COVID-19 patients was within normal range. None of the peripapillary and macular OCTA parameters were significantly different between the two groups. A good correlation was found between the whole image and all segment of capillary density as well as peripapillary retinal nerve fiber layer thickness in the recovered COVID-19 patients eyes (r = 0.56,P = 0.000) and in healthy eyes (r = 0.36,P = 0.027).

CONCLUSION

None of the COVID-19 recovered patients had any sign of ocular and retinal abnormalities. It seems that this virus does not lead to long-term damages to the eye in patients without comorbidities.

Introduction

Coronavirus disease 2019 (COVID- 19) has quickly spread around the world, affecting various parts of the human body, and ophthalmological manifestations is associated with extraocular disease, such as conjunctivitis .[1]

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) is a non-invasive method to establish subclinical retinal changes as well as visualization of both perfused vascular network and vascular abnormalities without the use of contrast. Some studied reported the retinal finding of COVID-19 in acute phase and after recovery .[2–9]

To the best of our knowledge, there is one report (9)on the effects of COVID-19 in eye during three months, after recovery; hence, the aim was to systematically evaluate the ocular involvement, using examination, OCT and OCT angiography amongst the recovered COVID-19 patients.

Material & Method

This cross-sectional, historically controlled study was conducted in the Ophthalmology department of Feiz Hospital, which is a referral center affiliated with Isfahan University of Medical Sciences, Iran as well as Shahrekord University of Medical Sciences, Iran from March 2020 till June 2020. Fifty eyes of the 50 hospitalized patients after they had recovered from COVID-19 infection, and 37 eyes of age and gender matched healthy individuals were compared. Prior to entering the study and after explaining the study objectives, written informed consent was obtained from the participants. The study and the protocol were approved and reviewed by the institutional ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.105), and was performed according to the Declaration of Helsinki and its later amendments.

All eligible participants underwent a comprehensive ophthalmologic examination, including Best- corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, IOP measurement with Goldmann applanation tonometry, ultrasound pachymetry, axial length measurement and dilated fundus examination.

The historical control group included healthy individuals aged 10 to 70 years old. Ophthalmology examination, OCT and OCT angiography were performed before the outbreak of COVID-19 virus, and maintained as normal database in our center.

Controls were obtained from a OCTA database at Feiz hospital (Isfahan, Iran) from previous research projects (IR.MUI.MED.REC.1398.105 and IR.MUI.MED.REC.1399.713).

Any patient with history of a corneal anomaly, cataract, or glaucoma was excluded from the study.

Exclusion criteria were abnormalities of pupil, refractive surgery or other eye surgery, glaucoma patients, history of trauma, anterior segment inflammation, and systemic diseases with ocular complications.

Inclusion criteria for the study groups were best corrected visual acuity (BCVA) of 20/40 or better, and a refractive sphere between − 5 and + 3 diopters and refractive cylinder within − 3 diopters .

Exclusion criteria included intraocular surgery (except for uncomplicated cataract extraction), history o retinal disease, glaucomatous and non-glaucomatous optic neuropathy, uveitis, or ocular trauma and other ocular or systemic diseases known to affect the eyes. Participants with poor quality of OCT and OCT-A

scans were excluded from the study. If both eyes were eligible, only one eye was randomly selected for analysis.

OCT-A Image Acquisition and Processing

The OCTA scans were obtained, using RTVue-XR spectral domain OCT (AngioVue, Optovue Inc., Fremont, California, USA; version 2017.1.0.151). A 4.5 × 4.5 mm^2 area centered on the optic disc was used for optic disc scan; while a 3 × 3 mm^2 and a 6 × 6 mm^2 area centered on the fovea was used for macular scan.

During the screening process, different layers retinal vascular networks were observed. The ratio of the total area occupied by blood vessels was defined as vessel density (VD).

A blood vessel was defined as pixels having decorrelation values two standard deviations above threshold level (two standard deviations above noise).

In the optic disc scan, the whole image VD an area scan of 4.5 × 4.5 mm2), average VD within the ONH (inside disc VD), and peripapillary VD (measured in a 750 um-wide annulus extending outward from the optic disc boundary) were calculated automatically by a software.

The peripapillary VD was analyzed from the radial peripapillary capillary segment, extending from the internal limiting membrane (ILM) to the posterior boundary of the RNFL. The peripapillary region was divided into 8 sectors, every 45 degrees.

An experienced OCTA technician performed all the OCTA examinations.

In the macular scan three-dimensional OCTA scans were acquired over 3 × 3 mm^2 and 6 × 6 mm^2 regions. Macular vessel densities analyzed in this study were of the superficial vascular plexus (span from the ILM to the lower border of IPL and deep capillary plexus (DCP) (span from the inner nuclear layer (INL) to the outer plexiform layer (OPL)).

The angio-retina scans were automatically inserted in three concentric circles at the fovea with diameters of 1, 3 and 6 mm.

The small circular area with a diameter of 1 mm was defined as foveal zone.The area between the inner (1-mm) and middle (3-mm) rings was considered as parafovea and perifovea was defined by an area of the outer circle, with a diameter of 6 mm.

The parafoveal and perifoveal regions were automatically divided into 2 sectors of 180 degrees each (superior and inferior sectors) and four quadrants: the superior, inferior, temporal, and nasal quadrants.

Parafoveal and perifoveal values were calculated, using the average vessel density of the four quadrants. Measurement of the foveal avascular zone (FAZ) area in the SCP was obtained, using the non-flow assessment tool, and the FAZ area, including the full retinal vasculature, FAZ perimeter, acircularity index (AI) of the FAZ, and foveal density-300, which were measured, using the FAZ assessment tool. In addition, retinal thickness were derived from the optical coherence tomography (OCT) images. Measurements of subfoveal choroidal thickness measurements were performed, using enhanced depth imaging optical coherence tomography (EDI-OCT).

From the participant data, one eye was randomly selected for the statistical analysis.

Images with lower quality (defined as having a signal strength index < 5 or signal strength index (SSI) < 45), Segmentation errors due to artifacts, or any residual motion artifacts were excluded. The RNFL thickness measurement was generated at 3.45-mm-diameter circle relative to the disc center for each sector on the ONH map, and macular ganglion cell complex (GCC) thickness was measured from the internal limiting membrane (ILM) to the outer inner plexiform layer (IPL) boundary in the superior, inferior hemiretina and overall GCC map.

Statistical analysis

Statistical analyses were performed, using the statistical software SPSS, version 22 (SPSS, Inc., Chicago, IL, USA). P values < 0.05 were considered to be statistically significant. Continuous variables are expressed as mean ± standard deviation. Categorical data were reported as numbers (percentages). The distribution of numerical data was tested for normality, using the Kolmogorov–Smirnov test. Independent samples t-test was used to compare the vessel density between groups. The two-tailed statistical significance of Pearson's correlation coefficient was used to test the correlation between different parameters.

Results

In this study, fifty one eyes from 51 *recovered COVID-19 patients* were compared with thirty-seven eyes of 37 healthy participants (Table 1, and Table 2). In total, 53 (60.22%) were male and 35 (39.78%) females. The age range was between 9 to 67 years with mean age of 43.03 years (SD: 13.24). There was no statistically significant difference in age or gender between the *recovered COVID-19 patients* and the healthy controls. Thirty-two (62.7%) of the recovered COVID-19 patients and 21 (56.75%) of the healthy participants were male (p=0.57). The *time between* the initial *onset* of symptoms and ophthalmologic examination was 63.31+/- 15.21 (40- 95 days). A complete ophthalmologic examination was performed one month after the patients were discharged with recovery, and PCR negativity was confirmed.

Majority of the eyes 79 (89.77%) had normal vision (VA 20/20) and 8 eyes (10.22%) had mild visual impairment (VA 20/25–20/30). The recovered COVID-19 eyes were examined 40-95 days after COVID-19 symptom onset. None of the recovered COVID-19 eyes had related ocular disorders.

None of the recovered COVID-19 patients had symptoms or signs of intraocular inflammation, and the *examination* of the *anterior segments and dilated fundus examination were within normal range*.

The structural OCT of the normal and the recovered COVID-19 eyes did not show any significant abnormalities, and the image quality was good. High quality images obtained from OCTA, showed clear and organized microvascular networks in the two groups without any blood flow alterations, vessel tortuosity and dropout, vasodilation, vascular remodeling, microaneurysms, looser networks with larger and sparser mesh.

Descriptive measures for peripapillary parameters in both study groups are summarized in Table 3. None of the optic disc parameters (cpVD and RNFL thickness) was statistically significantly between the groups.

Table 4 shows the comparisons of macular parameters in both study groups. None of the macular parameters (superficial and deep VD, RNFL thickness, ganglion cell complex, FAZ parameters) were statistically different between the groups.

Discussion

Coronaviruses are known to involve organs and systems *other than* the *respiratory tract*, including the digestive *system*, *nervous system* and ocular tissues.[10,11] Substantiating the previous reports, suggest ocular infection in the recent SARS-CoV-2 epidemic, and *ocular transmission* might a *potential route* of SARS-CoV-2 infection.[12,13] Despite the fact that several months has gone by since the epidemic, not much is published with regards to the SARS-CoV-2 pathogenic mechanisms, especially with respect to the ocular tissues. This study, evaluated the ocular findings detected in the recovered COVID-19 patients, using clinical examination, OCT, and OCT angiography imaging, after mean time of two months , which were compared with normal population .

In this study of 51 patients with confirmed COVID-19 infection, it is noteworthy to say that all 51 patients (100%) had a normal ophthalmology examination and imaging.

None of the recovered COVID -19 patients had ocular or retinal finding. Visual acuity and pupillary reflexes were normal in all eyes, and we did not detect any symptoms or signs of intraocular inflammation.

Marinho reported more prominent hyper-reflective lesions at the level of ganglion cell and inner plexiform layers at the papillomacular bundle in the symptomatic populations, using dilated fundus examination and OCT[2]. Previous studies of state of the retinal vascularisation in patients after COVID-19 are summarized in Tables 5. Turker et al.[4] examined the 54 eyes from 27 hospitalized patients with COVID -19 within 1 week of discharge and compared with 54 eyes of 27 volunteers and reported a reduced vessel density of the retinal capillary plexus in COVID-19 patients.

Abrishami et al.[5] evaluated the macular density of 31 patients at least 2 weeks after recovery from systemic COVID-19 using optical coherence tomography angiography (OCTA) analysis and compared with 23 healthy normal controls, and suggested that recovered patients displayed alterations in the retinal microvasculature, including a significantly lower vessel density in the superficial and deep capillary plexus.

González-Zamora et al.[6] evaluated the presence of retinal and microvascular alterations in hospitalized COVID-19 patients compared to age- and sex-matched controls using OCT angiography, 14 days after hospital discharge and suggested that ,COVID-19 patients presented lower vessel density in the foveal region and a greater FAZ area than controls.

Savastano et al.[7] compared OCT angiography and structural OCT of 70 post-COVID-19 patients after 1-month hospital discharge and 22 healthy control subjects and found no or minimal retinal vascular involvement by SARS-CoV-2.

Hazar et al.[8] compared 50 patients with SARS CoV2 pneumonia 55 healthy age- and gender-matched controls using OCT angiography one month after discharged with recovery.and reported low vessel density in some sectors in both superficial and deep layers with no change in FAZ.

These different findings could be attributable to the different period between acute infection and ophthalmological examination. Our investigation revealed that the frequency of ocular findings might be related to infection time, as our patients were on a mean time approximately 63 days (40 to 95 days) after the onset of COVID-19. *Among these studies in recovered patients, time from onset of infection* were not the same and *no longer than* one *month* (between 1 week to one months), which might have led to higher number of retina findings.

Zapata and associates,[9] analyzed and quantified retinal microvascular by OCT angiography in COVID- 19 infected patients during the last 3 months *since onset of disease* and found patients with moderate and severe disease had decreased central retinal vessel density as compared with that of asymptomatic or paucisymptomatic cases or control subjects. and *difference in time of imaging from disease onset.*

In mentioned report, mean days from PCR-confirmed diagnosis to ophthalmological examination time were 72 days in moderate disease and 70 days in severe disease which it is almost the same as our study. *The discrepancy may* be *due* to the *difference in disease severity,* differences in device and image analysis. *Also, in our study, for evaluated the net retinal effect of COVID-19, we excluded the comorbidity diseases* (smoking, diabetes history or treatment with ACE inhibitors) which effect on vascular density and patients who need ICU care, but in past study all of patients included in the study. Importantly, our recovered COVID- 19 subjects are significantly higher than the aforementioned report; besides we have a comparative control healthy populations before the COVID-19 pandemic.

Genomic and structural analyses shows that SARS-CoV-2 infect host cells via the angiotensin-converting-enzyme-2 (ACE2) receptor on endothelial cells[14] and viral replication can cause inflammatory cell infiltration, endothelial cell apoptosis, which can have microvascular prothrombotic effects. [15]

COVID-19 endotheliitis can *contribute* to *microcirculatory impairment* and clinical *sequelae,* such as thrombosis and ischemia, cerebrovascular complications in younger patients, myocardial ischemia and micro- and macrocirculatory thromboembolic complications that can be explained by The endotheliopathy. [15-17]

An active local *intraocular renin– angiotensin system* (RAS) exist *in the human eye*, and systemic *antihypertensive drugs* that inhibit *RAS can reduce IOP.*ACE-2 does exists in the aqueous humour and retina, but not on conjunctival or corneal epithelia.[18] Furthermore, additional investigation is warranted to explore the hypothesis of SARS-CoV-2 ocular infection via ACE2.

Vascular abnormalities in OCT angiography were rare in COVID -19 participants, which can be an underestimation; whereas vascular variations can be detected, using fluorescein angiography that allows for a dynamic assessment of the *retinal* and choroidal *vasculature*.

The present *study did not* find a *significant* difference in the average and sectoral peripapillary vessel density between the two groups. In addition, the deep and superficial layer macular vessel densities were evaluated and superficial and deep foveal, parafoveal and perifovel VDs were found to be similar between eyes in the recovered COVID-19 vs. the healthy eyes.

Since human ocular studies of Corona virus infections are rear in the literature, studying the ocular manifestation of Corona viruses in various animals is of value. Animal studies have revealed that ocular lesions *might* present itself in the form of *optic neuritis*, *neuroretinitis* .[19,20]

The retina is an *extension* of the *brain and retinal* anatomy, function, response to injury, and *immune responses similarly* to those in the *brain* and *spinal cord*. A *retinal ganglion cell* (*RGC*) is a type of neuron located in the ganglion cell layer of the *retina* and in the thalamic region form direct synaptic connections with the CNS. [21]

According to The Lancet, ganglion cell and plexiform layer might be associated with central nervous system manifestations that were previously described in animal studies and in COVID-19 neurological findings.[20,22]

The *macula* has the *highest density* of (retinal ganglion cells) *RGCs,* which *exist in* the inner retinal layer and gets *its oxygen supply* from superficial *retinal capillary plexuses*[23-24]. The central macular and parafoveal and perifovel superficial as well as deep VD did not differ between the recovered COVID-19 eyes and healthy controls. Microvascular dropouts, secondary to retinal *neurodegenerative* changes, such as GCC thinning, which might be *one possible explanation* for coordination between neural atrophy and vascular insufficiency was not observed in this study.

To the best of our knowledge, this is the first study to assess the ocular findings of COVID-19 patients without comorbidities after recovery to 3 months. It is worth noting that our groups were matched in terms of age and gender, and historical control participants examination and imaging were performed before the COVID-19 outbreak.

The latest version of built-in software was used in this study, which automatically provides VD at various retinal layers, and removes large vessels from peripapillary images. Also, our regional analysis coverage of involved area is higher, using large scan size (whole6×6mm^{2}scanning field).

This study has several limitations, and the main one is the small number of recovered COVID-19 patients which none of them needed intensive care, as well as the limited follow-up time. Further studies with larger sample size are required to reassess our findings. Another limitation is that all of the patients were of Iranian origin, which cannot reflect upon the entire population of recovered COVID-19 patients. In addition, some patients may have received medical intervention once they were suspected of having or confirmed to have infection, which could have affected the ocular findings, but this was not accounted for in this study. Since BCVA of 20/40 or better were used, this might have skewed the outcomes and would potentially introduce bias and select for patients with less disease. Finally, OCT-A is a relatively new technique and its limitations must be taken into account. Apart from the artifacts, the obtained images and data analyzing techniques, might in fact lead to different results and must be taken into account when comparing the results of different studies.

In conclusion, the recovered COVID19 patients without comorbidity had similar peripapillary and (superficial and deep) macular VDs in comparison with the healthy eyes matched for age and gender. The results suggest that the pathogenic mechanisms affecting vascular damage may not be involved in the eyes' tissue. Finally, the theory that vascular changes in COVID -19 is significant should be further investigated in larger prospective studies.

Abbreviations

AI : Acircularity index

DCP :deep capillary plexus

FAZ : Foveal avascular zone

GCC : ganglion cell complex

ILM :internal limiting membrane

INL: inner nuclear layer

IPL : inner plexiform layer

OCTA : optical coherence tomography angiography

OPL : outer plexiform layer

RNFL: retinal nerve fiber layer

VD: vessel density

Declarations

Ethics approval and consent to participate

The Isfahan university of medical sciences approved this study .This study followed the tenets of the Declaration of Helsinki.

Consent for publication : Not applicable.

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Authors' contributions: ANB collected, analyzed, and interpreted the data and took the lead on writing the manuscript. ZNB helped design the study, collected and analyzed the data, and wrote a portion of the manuscript. FK and AD helped with methodology and conducted the analyses. HD and ZH and EM oversaw the entirety of the study, including design, interpretation, and editing of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic Details, Clinical Characteristics, and Lab data of patients in acute phase of COVID-19 disease. F= Female, M= Male

Calcium= Ca, erythrocyte sedimentation rate= ESR, C-reactive protein= CRP, hematocrit= HCT, Hemoglobin= HB, lactate dehydrogenase= LDH, Lymphocyte count, /µL= Lymph, mean corpuscular hemoglobin concentration= MCHC, mean cell hemoglobin=MCH

Mean cell volume= MCV, Mixed cell= MXD count, Neutrophil Count×103/µL = Neut , Platelet count, =Plt, red blood cell= RBC count, RBC distribution width-variation coefficient= Rdw-cv, RBC distribution width-standard deviation= Rdw-sd, White blood cell count, /µL = WBC

Duration of onset of disease to the study	WBC	PLT	Rdw-sd	Rdw-cv	RBC	NEUT count	MXD	MCV	MCH	MCHC	Lymph count	LDH	Hb	HCT	CRP	ESR	Ca
60	6100	305000	38.1	12.2	5.19	3.2	0.6	86.5	31.2	36.1	2.3	-	16.2	44.9	6	16	9.0
95	11000	166000	47.0	12.9	4.84	7.4	1.3	92.1	33.1	35.9	2.3	-	16.0	44.6	-	18	8.9
90	9900	281000	41.3	12.9	5.06	6.0	0.7	85.6	31.2	36.5	3.2	-	15.8	43.3	-	-	-
62	3400	135000	42.0	12.6	4.7	2.7	0.1	87.7	31.1	35.4	0.6	-	14.6	41.2	-	64	8.3
74	3600	164000	42.6	12.8	3.85	2.0	0.3	88.4	31.9	36.1	1.2	-	14.5	40.2	17	73	8.6
74	12200	146000	45.7	20.1	3.77	10.6	0.4	64.5	18.6	28.8	1.2	-	7.0	24.3	18	40	7.2
60	8200	207000	46.7	14.7	4.95	0.0	0.2	87.8	25.3	29.0	1.6	1472	12.8	46.6	-	-	8.3
62	6600	241000	42.5	13.1	4.88	3.3	0.4	84.0	27.0	32.2	2.9	-	13.2	41.0	8	11	-
76	10900	101000	51.8	14.9	2.84	9.3	0.8	96.5	32.7	33.9	0.8	521	9.3	27.4	15	91	-
40		840000	52.9	15.4	3.53	28.1	0.4	89.3	31.8	34.9	1.0	606	13.0	37.3	-	86	
75	12900	109000	46.1	13.6	4.34	9.4	1.2	88.0	29.7	33.8	2.3	-	12.9	38.2	-	17	8.5
64	21600	290000	48.9	13.9	5.32	5.3	13.5	93.6	32.5	34.7	2.8	-	17.3	49.8	1	44	9.3
60	8200	277000	47.3	13.6	4.26	4.9	1.0	93.4	32.2	34.4	2.3	-	13.7	39.8	8	25	9.1

73	10100	175000	42.6	13.1	4.77	8.2	0.3	87.8	27.5	31.3	1.6	-	13.1	41.9	-	16	8.2
95	6600	352000	40.8	13.1	5.41	5.2	0.2	82.8	29.6	35.7	1.2		16.0	44.8	8		
95	5600	239000	42.0	13.4	4.93		0.5	81.6	28.8	35.6	2.1	748	15.4	43.6	-	30	8.6
90	18400	241000	42.9	12.9	3.94	15.3	0.7	86.8	31.0	35.7	2.4	1065	12.2	34.2	-	-	7.8
60	5900	271000	49.4	14.5	3.79	3.7	0.2	93.4	34.0	36.4	2.0	-	12.9	35.4	-	32	8.9
76	9200	361000	47.4	14.8	4.02	6.0	1.3	86.1	27.4	31.8	1.9	-	11.0	34.6	-	123	-
95	8100	470000	43.8	14.1	4.98	0.0	0.0	81.7	28.3	35.2	0.7	-	14.7	42.9	-	28	8.4
62	6700	138000	45.9	13.3	5.06	3.9	0.6	89.9	31.2	34.7	2.2	-	15.8	45.5	-	-	-
55	5200	174000	45.9	13.2	4.73	3.9	0.2	89.4	32.6	36.4	1.1	501	15.4	42.3	4	19	8.8
44	12000	158000	40.4	12.8	4.14	10.1	0.6	86.5	29.7	34.4	1.3	399		35.8	-	80	-
55	14400	128000	43.2	13.2	3.67	11.6	0.6	85.7	28.4	33.2	2.2	570	12.1	36.5	22	32	-
64	3800	137000	47.3	12.8	4.12	2.1	0.5	96.6	34.7	35.9	1.2	456	14.3	39.8	4	47	7.9
50	8500	232000	43.8	13.5	4.31	6.3	0.6	84.0	24.4	29.0	1.6		10.5	36.2	-	32	-
43	8600	74000	74.1	20.2	5.7	7.1	0.5	99.6	31.1	31.2	1.0	640	17.7	56.8	-	13	8.6

44	5400	169000	44.7	12.4	4.75	3.9	0.5	89.7	31.4	35.0	1.0	-	14.9	42.6	9	117	8.6
42	24800	137000	49.9	12.6	4.52	5.5	0.4	96.4	35.9	36.2	4.1	-	16.1	45.0	-	12	-
69	10600	237000	49.6	14.4	4.19	9.6	0.2	85.7	26.4	30.5	0.8	-	11.2	35.9	-	-	8.2
69	17800	270000	51.3	13.8	3.56	0.0	0.0	97.5	33.4	34.3	1.6	157	11.9	34.7	-	80	8.2
60	3900	129000	47.6	17.2	4.28	2.9	0.2	77.3	24.6	32.6	0.7	649	14.7	46.2	19	25	8.0
43	6700	349000	47.5	13.1	3.32	6.4	0.0	94.0	32.7	34.1	1.4	609	15.5	46.7	2	66	6.4
60		158000	49.3	14.0	4.64	3.5	0.4	90.5	33.1	35.8	0.4	425	14.8	42.0	-	11	8.0
42	9700	122000	46.2	14.3	4.52	7.6	0.8	85.2	27.2	31.9	1.3		-	38.5	23	44	8.0
42	6600	243000	47.3	14.1	4.65	4.4	0.4	86.7	29.3	33.7	2.9		14.1	41.8	10	27	10.9
62	4800	109000	45.9	12.8	4.74	3.0	0.2	93.0	32.1	34.5	1.6	557	15.2	44.1	15	50	8.5
62	3300	63000	50.0	16.6	4.39	1.6	0.7	83.5	28.2	33.8	1.5	967	13.2	39.1	-	20	-
62	4400	255000	42.4	12.6	4.46	3.6	0.1	88.1	28.5	32.3	0.7	1352	12.7	39.3	12.0	96.0	8.0
50	3800	149000	40.6	12.4	4.55	3.1	0.1	84.8	29.0	34.2	0.6		13.2	38.6	-	17.0	8.0
62	7100	121000	46.4	12.2	4.52	5.2	0.5	94.7	32.3	34.1	1.4		14.6	42.8	23.0	27.0	8.0
62	7300	169000	54.0	14.5	5.07	5.3	0.6	97.8	32.5	33.3	1.4	1116	16.5	49.6	9.0	18.0	9.5

65	17400	141000	49.1	13.8	4.26	15.3	1.2	93.2	33.8	36.3	0.9	-	14.4	39.7	-	27.0	-
65	13900	205000	48.7	12.1	3.56	0.0	0.0	102.3	35.7	34.9	3.2	-	12.6	36.1	16.0	24.0	-
62	4700	196000	50.0	14.7	4.42	3.5	0.1	91.4	25.6	28.0	1.1	-	11.3	40.4	-	25.0	-
40	16100	275000	49.6	19.8	5.62	11.7	1.0	69.0	19.0	27.6	3.4	1346	10.7	38.8	2.0	13.0	8.2
42	16200	146000	52.8	16.0	3.68	12.3	1.5	94.3	31.3	33.1	2.4	1509	11.5	34.7	-	45.0	8.9
75	11900	304000	49.0	14.1	4.13	8.4	0.6	91.3	31.0	34.0	2.9	458	12.8	37.7	36.0	50.0	
62	11900	228000	52.4	14.8	4.67	8.4	0.5	96.1	33.2	34.5	3.0	371	15.5	44.9	6.0	6.0	9.3
73	7400	242000	46.8	13.3	4.45	4.5	0.5	93.5	33.7	36.1	2.4	-	15.0	41.6	-	11.0	9.0
65	5600	245000	49.6	16	4.42	4.5	1	96	31	34.5	3	-	12.4	37.8	15	35	7.8

Table 2. *Comparison of baseline characteristics of participants between study groups* cup disc ratio=CD ratio

Investigated trait	*Recovered COVID-19 eyes*	Healthy eyes	Level statistical significance
age	41.13± 12.6	45.64 ± 13.7	0.11
Sex (male/ female)	32/19	21/16	0.57
CD ratio	0.19± 0.22	0.24± 0.28	0.41
Spherical equivalent	0.41±1.5	0.23± 1.3	0.59
Axial length, mm	22.9± 0.7	23.03± 0.6	0.47
Central corneal thickness (μm)	549± 10.8	546± 15.7	0.41
Retinal nerve fiber layer thickness (μm)	115± 16.9	111± 11.8	0.231

Table 3 Comparison of circumpapillary vessel density (cpVD) and retinal nerve fiber layer (RNFL) thickness value between *Recovered COVID-19 patients* and healthy eye

Investigated trait	*Recovered COVID-19 patients*	healthy eyes	P value
pRNFL Thickness	115± 17.3	109± 6.8	0.1
Superior	138.4± 27.4	128± 12.7	0.09
Nasal	108± 21.6	100± 26.8	0.17
Inferior	144.2± 22.5	136±16.4	0.12
Temporal	75.4± 10.9	75.6± 9.4	0.93
Whole image VD	49.14± 2.7	49.6793± 3.07634	0.43
Inside disc VD	49.36± 4.8	48.6517± 7.24030	0.6
Peripapillary VD	51.29± 3.4	51.5690± 3.89845	0.74
Superior VD	49.61± 5.36	51.6071± 5.83945	0.13
Nasal VD	52.1± 5.17	51.6429± 5.97039	0.7
Inferior VD	52.67±4.7	53.9231± 6.71668	0.36
Temporal VD	51.02± 5.7	50.54± 7.03	0.76

Table 4-Comparison of macular vessel density (VD) and retinal nerve fiber layer (RNFL) thickness values between *recovered COVID-19 eyes and healthy eyes*

Foveal avascular zone=FAZ , *FAZ perimeter* (*PERIM*), choriocapillary flow area (CCF), acircularity index (*AI*), foveal density (FD)

P value	Healthy eyes	*Recovered COVID-19 eyes*	Investigated trait
0.47	58.0.256± 10.4	60.3± 11.01	Fovea Inner retinal thickness (ILM-IPL)
0.81	110± 8.5	111.1± 13.4	Superior Parafovea Inner retinal thickness
0.73	107± 12	108.5±10.34	Nasal Parafovea Inner retinal thickness
0.32	109±13.9	111.4± 9.1	Inferior Parafovea Inner retinal thickness
0.23	99.7± 8.5	101.9± 8.2	Temporal Parafovea Inner retinal
0.75	99± 9.4	99.7±8.3	Superior Perifovea Inner retinal thickness
0.83	116± 12.9	116.7± 11.1	Nasal Perifovea Inner retinal thickness
0.33	95.03±14.2	97.6±9.95	Inferior Perifovea Inner retinal thickness
0.94	86.7± 9.3	86.8± 8.06	Temporal Perifovea Inner retinal thickness
0.66	250±27.5	252± 24.58	Fovea Total retinal thickness
0.07	332± 16.3	332± 16.23	Superior Parafovea Total retinal thickness
0.22	323±24.5	328± 17.3	Nasal Parafovea Total retinal thickness
0.057	320± 23.4	328± 15.7	Inferior Parafovea Total retinal thickness
0.49	309±22.8	313± 30.6	Temporal Parafovea Total retinal thickness
0.3	285± 19.1	289± 13.5	Superior Perifovea Total retinal thickness
0.66	301± 21.4	303± 17.8	Nasal Perifovea Total retinal thickness
0.14	272± 18.5	277± 12.8	Inferior Perifovea Total retinal thickness
0.11	268± 18.1	274± 14.6	Temporal Perifovea Total retinal thickness
0.5	48.8± 4.1	49.5± 4.2	Whole image Superficial vessel density
0.08	19.02± 7.7	22.5± 9.08	Fovea Superficial vessel density
0.49	51.9± 5.3	52.7± 4.7	Parafovea Superficial vessel density
0.14	51.4± 5.08	53.05± 4.3	Temporal Parafovea Superficial vessel density
0.57	52.4± 5.3	53.1± 5.5	Superior Parafovea Superficial vessel density
0.28	51.2± 5.4	52.4± 5.02	Nasal Parafovea Superficial vessel density
0.41	51.4± 6.1	52.5± 5.4	Inferior Parafovea Superficial vessel density
0.58	49.4± 4.5	50± 4.3	Perifovea Superficial vessel density
0.34	46.2± 4.2	47.3± 4.9	Temporal Perifovea Superficial vessel density
0.72	49.3± 4.5	49.7± 4.4	Superior Perifovea Superficial vessel density
0.42	52.7± 3.5	53.5± 4.1	Nasal Perifovea Superficial vessel density
0.08	48.1± 3.8	49.8± 4.3	Inferior Perifovea Superficial vessel density
0.47	49.8± 7.2	50.9± 5.8	whole image Deep vessel density
0.28	38.4± 7.9	40.2± 6.6	fovea Deep vessel density
0.46	54.4± 7.3	55.4± 4.7	Parafovea Deep vessel density
0.87	56.3± 6.2	56.5± 4.3	Temporal Parafovea Deep vessel density
0.42	54.3± 7.2	55.4± 5.08	Superior Parafovea Deep vessel density
0.46	56± 6.2	56.9± 4.5	Nasal Parafovea Deep vessel density
0.7	53.1± 8.2	53.7± 5.9	Inferior Parafovea Deep vessel density
0.33	50.8± 7.8	52.4± 6.6	Perifovea Deep vessel density
0.61	54.1± 6.6	54.8± 5.3	Temporal Perifovea Deep vessel density
0.53	50.08± 7.9	51.1± 7.07	Superior Perifovea Deep vessel density
0.57	50.1± 7.5	51.2± 7.8	Nasal Perifovea Deep vessel density

0.25	50.5± 7.7	52.5± 7.2	Inferior Perifovea Deep vessel density
0.15	0.37± 0.53	0.25± 0.08	FAZ area
0.96	1.9± 0.39	1.9± 0.38	Perim
0.06	1.07± 0.02	1.09± 0.06	Ai
0.76	54.1± 6.03	54.5± 5.4	FD
0.09	2.1± 0.1	2.01± 0.46	CCF area
0.8	99.7± 9.7	99.88±9.9	GCL
0.7	267± 21.1	265± 22.35	Subfoveal choroidal thickness

Table 5-Previous studies of retinal finding in recovered COVID-19 patients using OCT angiography.

study	patients	Disease severity	Study time	OCT angiography machine	results
Turker et al [4]	54 eyes of 27 patients 54 healthy eyes (volunteers for for routine ophthalmo-logic examination)	All patients were hospitalized	within 1 week of discharge after complete recovery as indicated with conversionto PCR-negative status	AngioVue Imaging System versio 2017.1 (Optovue, Inc, Fremont, Calif).	Reduced vessel density of the retinal capillary plexus was detected in COVID-19 patients who may be at risk for retinal vascular complications.
Abrishami et al [5]	31 recovered COVID-19 patients 23 healthy normal controls (2019 as part of a prior study to build a local OCTA normative database	Mild to moderate 29% hospitalized No intubation	at least 2 weeks after recovery from systemic COVID-	AngioVue (RTVue XR Avanti, Optovue, Fremont, Calif; Software Version 2018.0.0.14)	Patients recovered from COVID-19 displayed alterations in the retinal microvasculature, including a significantly lower VD in the SCP and DCP. Patients with coronavirus infection may be at risk of retinal vascular complications
González-Zamora et al [6]	50 eyes (25 patients and 25 controls)	Hospitalized patients	14 days after hospital discharge	(DRI OCT Triton SS-OCT Angio, Topcon Medical Systems, Inc. Oakland, NJ, USA)	COVID-19 patients presented significantly thinner ganglion cell layer (GCL) ($p = 0.003$) and thicker retinal nerve fiber layer (RNFL) compared to controls ($p = 0.048$), In both SCP and DCP, COVID-19 patients presented lower VD in the foveal region ($p < 0.001$) and a greater FAZ area than controls ($p = 0.007$).
Savastano et al [7]	70 post-COVID-19 patients 22 healthy control subjects.	haspitalized patients	1-month hospital discharge and	OCT and OCTA analysis (Zeiss Cirrus 5000-HD-OCT Angioplex, sw version 10.0, Carl Zeiss, Meditec, Inc., Dublin, USA).	Macula and perimacular vessel density and perfusion resulted unaltered in mild post-COVID-19 patients at 1-month hospital discharge, suggesting no or minimal retinal vascular involvement by SARS-CoV-2.
Hazar L [8]	50 patients with SARS CoV2 pneumonia 55 healthy age- and gender-matched controls were compared using OCTA.	mild to moderate pneumonia	one month after the patients were discharged with recovery, and PCR negativity was confirmed	AngioVue OCTA device (Optovue, Fremont, CA; software version 2016.2.0.35)	In COVID-19 disease, VD is low in some sectors in both SF and deep layers, but no change in FAZ.
Zapata[9]	Results Control group included 27 subjects: group 1 included 24 patients, group 2 consisted of 24 patients and 21 participants were recruited for group 3	Mild Moderate Severe	Mean days from PCR-confirmed diagnosis to ophthalmological examination time were 72 and 70 days (group 2 and group 3, respectively).	DRI OCT Triton Swept Source (Topcon Corporation, Tokyo, Japan)	Patients with moderate and severe SARS-CoV-2 pneumonia had decreased central retinal VD as compared with that of asymptomatic/paucisymptomatic cases or control subjects.