




Retinal microvascular abnormalities in patients after COVID-19 depending on disease severity

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ABSTRACT

Background Global pandemic SARS-CoV-2 causes a prothrombotic state without fully elucidated effects. This study aims to analyse and quantify the possible retinal microvascular abnormalities.

Materials and methods Case-control study. Patients between 18 and 55 years old with PCR-confirmed SARS-CoV-2 infection within the last 3 months were included. Risk stratification: group 1—mild disease (asymptomatic/paucisymptomatic); group 2—moderate disease (required hospital admission with no acute respiratory distress) and group 3—severe disease (subjects who developed an acute respiratory distress were admitted in the intensive care unit and presented interleukin 6 values above 40 pg/mL). Age-matched volunteers with negative serology tests were enrolled to control group. A colour photograph, an optical coherence tomography (OCT) and an angiography using OCT centred on the fovea were performed.

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. There were no fundoscopic lesions, neither in the colour images nor in the structural OCT. Fovea-centred vascular density (VD) was reduced in group 2 and group 3 compared with group 1 and control group (control group vs group 2; 16.92 vs 13.37; $p=0.009$) (control group vs group 3; 16.92 vs 13.63; $p=0.026$) (group 1 vs group 2; 17.16 vs 13.37; $p=0.006$) (group 1 vs group 3; 17.16 vs 13.63 $p=0.017$).

Conclusion 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.

INTRODUCTION

Pandemic of COVID-19 represents a new global health threat caused by SARS-CoV-2.¹

SARS-CoV-2 infects the cell binding to ACE2 receptor expressed in various organs including lung, heart, kidney, intestine and blood vessels. ACE2 is abundantly expressed on endothelia in virtually all organs.² Systemic vasculitis in SARS-CoV-2 involves recruitment of immune cells into vessel walls and endothelial cellular oedema, either by direct response to viremia or immune reactions. Eventually this may lead to generalised endothelial dysfunction associated with apoptosis.³

Up to date, ocular manifestations in the infection of SARS-CoV-2 are not fully elucidated, although conjunctivitis has been commonly described in patients with COVID-19.⁴ Retinal vascular changes

such as microbleeds and small infarcts at the level of the internal plexus have been reported in patients with COVID-19.⁵

Retinal vasculature can be directly observed in a non-invasive way. This provides accessible and valuable information to monitor, diagnose and study early microcirculatory changes in multiple systemic conditions including viral infections.⁶ Classical direct visualisation (funduscopy) or new techniques via modern optical coherence tomography (OCT) or angiography OCT (OCT-A) allow precise evaluation of retinal microvascular plexus.

There are no published studies assessing the state of the retinal vascularisation in patients after COVID-19. The rationale for this study was to observe possible retinal capillary changes associated to the prothrombotic and inflammatory state in COVID-19. We decided to perform not only a direct retinal observation, but an in-depth analysis of the vascular plexus in order to detect any subclinical abnormality.

MATERIALS AND METHODS

Inclusion and selection of patients

We designed a case-control study. The case participants were patients between 18 and 55 years old with PCR-confirmed SARS-CoV-2 infection during the last 3 months since patient's enrolment. The study was performed at Vall d'Hebron University Hospital (VHUH) (Barcelona, Spain), a 1100-bed tertiary teaching centre, from 3rd of June 2020 until 7th of July 2020. Exclusion criteria were: known prior ophthalmological record, myopia higher than -6 dioptres, diabetes with any sign of retinopathy, active vascular diseases that could lead to retinopathy, such as malignant hypertension, multiple myeloma or hyperglobulinaemia. Cases were divided into three groups: (a) group 1—mild disease: asymptomatic/paucisymptomatic patients with laboratory-confirmed SARS-CoV-2 infection who received outpatient care; (b) group 2—moderate disease: patients who required hospital admission for SARS-CoV-2 pneumonia but did not develop acute respiratory distress or respiratory failure and had interleukin 6 (IL-6) values less than 40 pg/mL during hospital stay; (c) group 3—severe disease: patients who developed acute respiratory distress syndrome and were referred for intensive care unit (ICU) admission with IL-6 values above 40 pg/mL at any time during hospital stay.

The control group consisted of healthy subjects with negative serology for SARS-CoV-2 and



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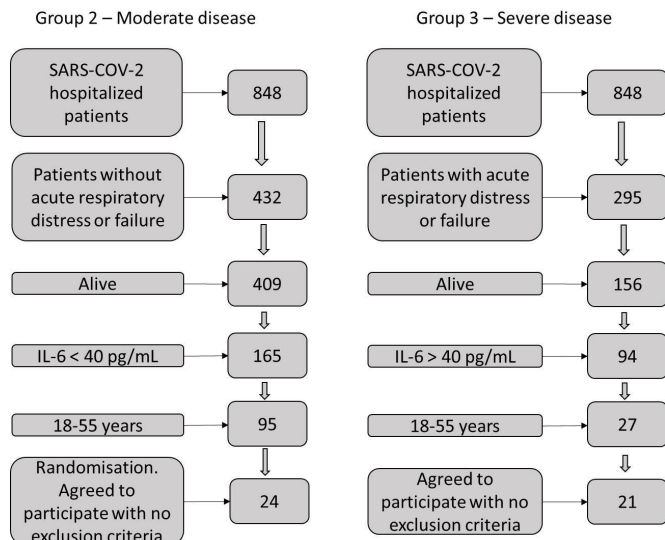


Figure 1 Selection process of patients included in group 2 and group 3. IL-6, interleukin 6.

absence of viral symptoms within 4 weeks prior to enrolment. Control group and group 1 were randomly selected from VHUH healthcare workers with negative and positive serological tests, respectively, and matched 1:1 for age and gender. **Figure 1** shows flow chart of groups 2 and 3 selection process. Selection of a convenience sample of 20 participants per group was decided in order to conduct an exploratory research.

Examinations performed

At the time of the study, all patients had been discharged from the hospital. All participants performed a structured questionnaire collecting comorbidities, chronic medication, use of tobacco, use of alcohol and illicit drug consumption. In-hospital data were retrieved from VHUH COVID-19 cohort study database.

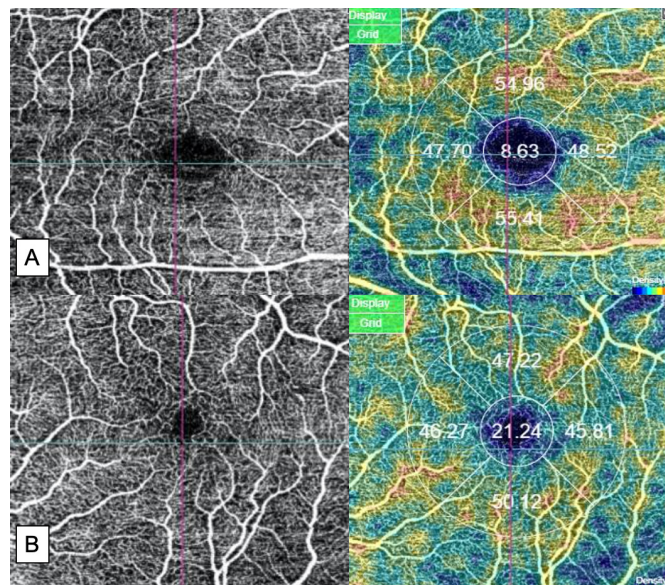


Figure 2 Example of angiography by optical coherence tomography (OCT-A). (A) Image obtained from a group 3 patient. Marked decrease in vascular density is observed in the central area compared with the image below. (B) OCT-A of control group subject.

Without pharmacological mydriasis, a 50° colour photograph of the retina posterior pole, a macula-centred high-definition OCT (scan radial 12 mm) and an automatically fovea-centred OCT-A were performed to all study participants (4.5×4.5 mm). The equipment used in all patients was the DRI OCT Triton Swept Source (Topcon Corporation, Tokyo, Japan). This system is based on motion contrast measure using a ratio method named OCT Angiography Ratio Analysis. Scattered light by red blood cells and adjacent tissue structures form an interference that is turned into a speckle pattern whose variation is detected as flow.⁷ Automatic segmentation generated the superficial capillary plexus in the macular region and a specified software calculated vascular density (VD), defined as the percentage of a region occupied by blood vessels in the OCT-A en-face images.⁸ Following the ETDRS grid, VD data were collected from central, superior, inferior, nasal and temporal perifoveal areas. **Figure 2** shows an example of the VD analysis. The images of the fundus and tomographic scans were analysed for presence of haemorrhagic or exudative lesions in both the external and inner retina by two different ophthalmologists (SBG, MAZ). A third ophthalmologist double evaluated images (GA). Images with visually recognised motion artefacts, signal strength index below 40 or incorrect segmentation were excluded.

Foveal avascular zone (FAZ) images were analysed by three different observers (SBG, MAZ, GA) and manually delineated by means of ImageJ Software (National Institutes of Health). Area means were then statistically analysed.

Statistical study

Statistical analyses were performed with the SPSS (V.23.0). Data from only left eye were considered. The normality of the variables was tested with the test of Kolmogorov-Smirnov. The quantitative variables that followed a normal distribution were studied with analysis of variance (ANOVA) using Bonferroni correction. Kruskal-Wallis test was performed to compare quantitative variables not normally distributed. Qualitative variables were examined using the X² test.

RESULTS

Study population

We included a total of 96 patients. The control group was formed by 27 subjects. Among patients with laboratory-confirmed SARS-CoV-2 infection, group 1 included 24 subjects, group 2 consisted of 24 participants and group 3 included 21 patients. Demographic, clinical and image characteristics are summarised in **table 1** for each group. Mean days from PCR-confirmed diagnosis to ophthalmological examination time were 72 and 70 days (group 2 and group 3, respectively). There were no statistically significant differences between groups in terms of age, gender, smoking, diabetes history or treatment with ACE inhibitors (ACEI) or angiotensin II type-I receptor blockers (ARB). There was a significant difference (p=0.001) in the proportion of patients with Latin American origin in groups 2 and 3.

Funduscopy and structural OCT findings

No visual injuries attributable to SARS-CoV-2 were found, neither in the colour fundus images nor in the structural OCT sections. Only one patient presented a small haemorrhage in the posterior pole without other accompanying abnormalities. According to the researchers, this finding could be due to a Valsalva manoeuvre or the fact that this subject was currently under treatment with heparin for presenting a thromboembolic episode during his stay in ICU. During the examination,

Table 1 Distribution of the subjects within groups, characteristics and vascular density

		Control group	Group 1—mild disease	Group 2—moderate disease	Group 3—severe disease	Significance among all groups
Gender	Male	10	12	10	12	0.520*
	Female	17	12	14	9	
Age (years)	Mean	39	41	42	44	0.333†
Diabetes	No	27	24	22	19	0.189*
	Yes	0	0	2	2	
Smoker	No	22	21	24	19	0.186*
	Yes	5	3	0	2	
Race	Caucasic	27	23	19	11	0.001*§
	Latin	0	1	5	9	
	Other	0	0	0	1	
ACEI use	No	26	24	24	20	0.550*
	Yes	1	0	0	1	
Days from PCR	Mean	–	–	72	70	–
Central VD	Mean	16.90	17.16	13.37	13.63	0.000†§
	SD	3.10	3.48	4.90	3.78	
Inferior VD	Mean	50.37	49.55	49.67	48.78	0.827†
	SD	3.25	2.63	4.88	4.56	
Superior VD	Mean	49.72	48.82	49.03	49.46	0.733†
	SD	3.43	2.99	2.70	3.28	
Nasal VD	Mean	43.92	44.26	43.86	44.21	0.970†
	SD	2.59	4.41	2.80	7.74	
Temporal VD	Mean	47.77	45.99	48.41	47.87	0.020†§
	SD	2.20	3.46	4.19	3.97	
FAZ	Mean	0.25	0.20	0.35	0.31	0.000†
	SD	0.07	0.08	0.15	0.10	
Image quality	Mean	64,96	64.13	66,88	65,95	0.441†
	SD	5,21	6,61	4,25	4,75	

* χ^2 test.

†ANOVA test and Bonferroni correction.

‡Kruskal-Wallis and Mann-Whitney U test.

§Statistically significant $p < 0.05$.

ACEI, ACE inhibitor; ANOVA, analysis of variance; FAZ, foveal avascular zone; VD, vascular density.

two patients were found to have asymptomatic small pigment epithelial detachments not presumably related to the viral infection. Hyper-reflectivity in the internal retina at the level of the ganglion cell layer was observed in some patients in the structural OCTs.⁵ Blood vessels parallel to the OCT direction were

found to correspond to these findings from the fundus image. [Figure 3](#) shows examples of this fact in both a participant from the control group and a subject from group 3.

OCT-A and VD

At macroscopic scale, no alterations were observed in the vascular architecture of the superficial or deep plexus. Ischaemic zones or vascular dilations were not observed, neither in cases nor in controls. There were no visible anatomical alterations in terms of the size, shape or circularity of FAZ. A tendency to a bigger FAZ area was noted ([figure 4](#)). FAZ mean area (non-normally distributed data) was analysed by Kruskal-Wallis test and posteriorly a Mann-Whitney U test was used for pair comparison. [Table 1](#) and [figure 5](#) show the mean VD for each group and studied areas. VD had a normal distribution in central, superior and nasal areas. Mean VD in control group for the central area was 16.92 (SD 3.10), in group 1 was 17.16 (SD 3.48), in group 2 was 13.37 (SD 4.90) and group 3, standing for the most severe cases, was 13.63 (SD 3.78). In ANOVA analysis, after Bonferroni correction for multiple measurements, we obtained, statistically significant higher central VDs in control group and group 1 were found (control group vs group 2, $p=0.009$; control group vs group 3, $p=0.026$; group 1 vs group 2, $p=0.006$; group 1 vs group 3, $p=0.017$). VD data for inferior and temporal areas were non-normally distributed. After analysis with Kruskal-Wallis, a statistically significant difference in mean temporal VD was found ($p=0.02$) but in Mann-Whitney U test, statistical differences were only found in control group versus group 1 ($p=0.04$) and control group versus group 2 ($p=0.08$); whereas control

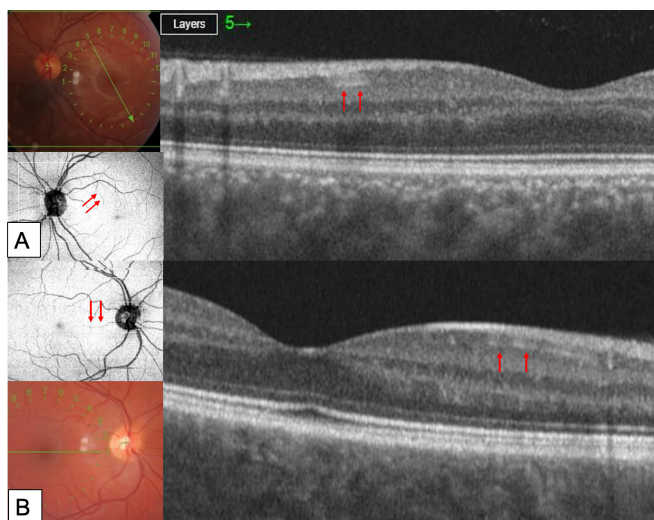


Figure 3 (A) Vessel image in a parallel section of the optical coherence tomography in a group 3 participant. The red arrows point the vessel forming the image. (B) Image of the vessel parallel to the optical coherence tomography section in a control patient. The red arrows indicate the vessel that generates the image.

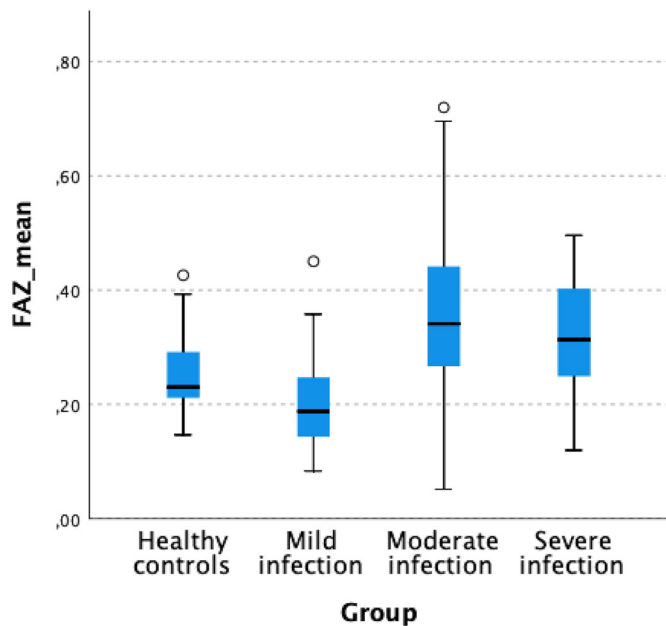


Figure 4 Box plot of the Kruskal-Wallis test for values of FAZ mean area. An upward trend for bigger FAZ mean areas for groups 2 and 3 than in control group and group 1 can be distinguished. FAZ, foveal avascular zone.

group versus group 3 had a $p=0.58$. No difference in nasal VD data was found.

Regardless of group assignment, women and Latin American origin had lower central VD (men 16.81 vs women 14.15; $p=0.002$) (Caucasian 15.81 vs Latino 13.25; $p=0.03$). There was no clear correlation between age and central VD mean

(Pearson correlation -0.193 ; $p=0.06$), but there seemed to be a negative trend.

DISCUSSION

The main finding of the study is decreased VD in central retina related to severity of COVID-19 infection. Despite the

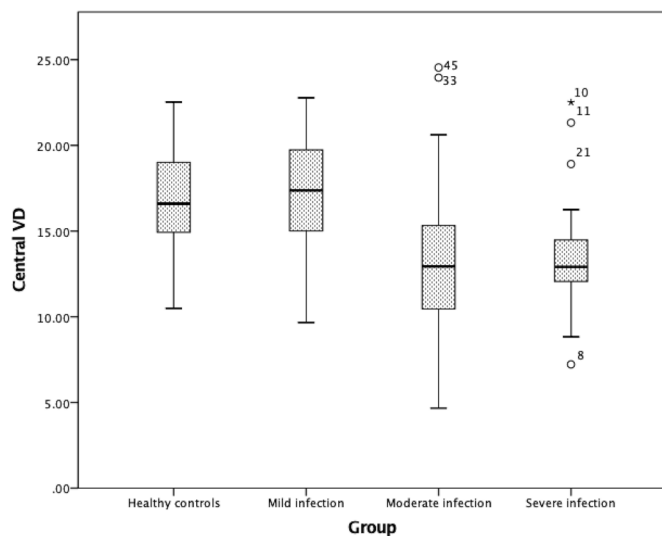


Figure 5 Measurement of the vascular density (VD) of the superficial plexus in the central fovea according to disease risk groups. The VD is defined as the percentage area occupied by vessels in the analysed region.

exponential increase of manuscript publications about COVID-19 in the last months, effects of the virus on the vascular system are unclear. SARS-CoV-2 has been found to cause a prothrombotic state which long-term outcomes remain unknown.^{9–11} Accordingly, macroscopic lesions were expected to be found in the retina. Subjects requiring admission in ICU, who received treatment with anticoagulant drugs and mechanical ventilation, were expected to show small haemorrhages or cotton wool exudates from small infarcts in the nerve fibre layer. However, normal fundus without haemorrhages, ischaemic areas or exudates were observed. A previous study by *Marinho et al* reported these lesions in patients with COVID-19.⁵ These different findings could be attributable to the shorter period between acute infection and ophthalmological examination. Although it is true that we have not collected data from the cases in the acute phase of infection, these types of findings frequently last longer in the fundus. If they were to be a direct effect of SARS-CoV-2, we would have detected them given the sample size of our study. The abnormalities described within the ganglion cell layer correspond to the retina internal vessels in a tomographic parallel section, which is a standard anatomical finding.

Regarding OCT-A findings, decreased central VD in patients with severe and moderate disease seems to be a consistent finding. Several factors may contribute to those findings, persistent hypoxemia and immune-mediated inflammatory milieu are the most plausible explanations for this phenomenon. However, parafoveal areas did not appear to show decreased VD.

VD has been related to several factors, the first one being age.^{12 13} In our series, there were no significant differences in regard to age among groups, with a slight trend downwards for cases.

The second factor associated with VD is smoking. Various studies have linked smoking to effects at the level of retinal VD.^{14 15} *Çiloğlu et al* described a larger area of FAZ and reduced central VD in the OCT-A of smoker subjects compared with non-smokers. In another study by *Dogan et al*, decrease in VD of the deep retina plexus in smokers was found. No differences were seen in our study, although it is true that the overall percentage of smokers was low and probably not representative of the general population.

The origin or ethnicity of the participants could also influence the VD findings. Some authors described specific inter-racial differences in the central retina thickness and specifically in VDs between white and black,^{16–18} although there are no further studies among other ethnicities. *Chun et al* theorise that such differences could account for a greater likelihood of diabetic retinopathy among black people, although there is no evidence for this relationship. In our study, Latin American origin was more common in moderate and severe infection groups and seemed to be an independent factor for VD. Further research in these inter-racial differences is needed.

The use of ACEI or ARB could have influenced our VD findings. In the first moment, viral dynamics and clinical severity were postulated to be related to these drugs, but this has not been confirmed in subsequent studies.¹⁹ In our study, despite its small power to answer this question, we did not find any relation between ACEI and ARB intake and VD.

Leaving possible confounding factors aside, the difference between densities and severity of infection seems clear. There may be several explanations for this fact. First, it could be an indirect consequence of the infection. It has been shown that hypoxia can increase retina VD²⁰ and that hyperoxia, on the other hand, can decrease it.^{21 22} Many of the patients in the moderate and severe disease groups presented subnormal oxygenation levels and required therefore supplemental oxygen for an extended period. This could

account for central VD decrease in patients with moderate and severe disease. However, our study was performed once symptoms resolved completely and posterior to hospital discharge. Direct effects of hyper/hypoxia seem to linger just a few minutes in some cases^{20,22} or even a few days.²¹ Further research is needed to solve the uncertainties related to our findings.

SARS-CoV-2 targets endothelial cells among others, leading to virus-mediated capillary closure (micro-thrombotic events). If this is just a local finding or similar changes could be found in other organs remains an unsolved question. Other studies have suggested VD in central retina as a possible vascular biomarker and examined its relationship with systemic conditions: diabetes,²³ chronic kidney disease,²⁴ inflammatory bowel disease,²⁵ amyloidosis²⁶ or Alzheimer,²⁶ so could VD be considered a biomarker for microvascular abnormalities after the infection of SARS-CoV-2? Longitudinal studies over time will be necessary to assess vascular outcomes in COVID-19.

Several limitations of our study require consideration. Small sample size limits our power to detect small differences. Selection bias was minimised by random selection of patients with inclusion criteria. No severe comorbidities were observed in our population sample. A bias may have occurred as patients with grievous diseases may have not been possible to include in the study due to raised risk of severe COVID-19 disease and lower surveillance rates. Delay time from active infection until ophthalmological examination due to non-portable tomography equipment is also a limitation to be highlighted. Transfer of hospitalised patients to external consultations with proper isolation in order to perform OCT and OCT-A would have been a complex requirement in our case. Last reference should be made to the cross-sectional nature of the study. Findings in the present document are believed to contribute to the implementation of better designed studies on COVID-19 and its effects in the retina and other tissues.

In conclusion, a decrease in retinal central VD in moderate and severe cases of SARS-CoV-2 pneumonia was found, which demonstrates the complexity of the disease and its multiorganic involvement.

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