The impact of acute COVID-19 on the retinal microvasculature assessed with multimodal imaging

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Abstract

Purpose To quantify retinal microvascular findings in the acute phase of COVID-19 using multimodal imaging and compare them with healthy, age-matched controls.

Methods Hospitalized patients in the acute phase of COVID-19 without known systemic comorbidities (n = 75) and healthy controls (n = 101) aged 18–65 were enrolled in this prospective cross-sectional study. The retinal microcirculation and microvasculature impairments were assessed using fundus photography, swept-source optical coherence tomography, and swept-source optical coherence tomography angiography in the COVID-19 unit and compared with healthy, age-matched controls.

Results Retinal findings were predominately observed in patients with severe disease (P = 0.006). Patients with severe disease were shown to have increased both mean vein diameter (Coef. = 19.28, 95% CI: 7.34–31.23, P = 0.002) and mean artery diameter (Coef. = 11.07, 95% CI: 0.84–21.67, P = 0.044). Neither blood vessel diameters were correlated with any confounding variables (age, sex, treatment with oxygen, LDH, or ferritin). Patients with severe COVID-19 were shown to have significantly increased retinal nerve fiber layer thickness in the superior and inferior quadrants both in the inner (S: P = 0.046; I: P = 0.016) and outer (S: P = 0.026; I: P = 0.014) ring and significantly increased GCL thickness in the outer temporal quadrant (P = 0.038). There were no statistically significant differences in vessel density or the foveal avascular zone area between the groups.

Conclusion The severity of COVID-19 was significantly correlated with the presence of retinal microangiopathy, which could become a biomarker of angiopathy in patients with COVID-19.

Key messages

- The severity of COVID-19 is correlated with the presence of retinal findings.
- Patients with severe disease had a notable increase in the mean vein as well as the mean artery diameter.
- Patients with severe COVID-19 were shown to have significantly increased RNFL thickness in the superior and inferior quadrants both in the inner and outer ring and significantly increased GCL thickness in the outer temporal quadrant.

Keywords COVID-19 · Retina · OCT · OCTA · SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic affecting millions worldwide.
SARS-CoV2 enters the cell by binding to angiotensin-converting enzyme 2 (ACE2), expressed in various tissues on the host cell surface [1]. In the retina, it is expressed in the vascular endothelium, Müller glia and ganglion cells, and neurons in the inner nuclear layer [2]. Moreover, SARS-CoV-2 viral RNA was detected by real-time polymerase chain reaction (RT-PCR) in the retina of deceased COVID-19 patients [3]. By binding to ACE2, SARS-CoV2 downregulates its activity and creates an imbalance in the signaling effects of the renin–angiotensin–aldosterone pathway. Consequently, a combination of severe inflammatory response with cytokine overproduction and endothelial dysfunction results in the hypercoagulable state, predisposing the patients to thromboembolic events [4, 5]. Several organ systems are affected, and due to its proposed pathophysiological mechanism leading to microvascular thromboses, retinal involvement has been widely suspected. Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) are non-invasive imaging methods that provide high-resolution visualization of the retina and the flow in its superficial and deep capillary plexuses, allowing assessment of the proposed microcirculatory changes in the retina [6]. Changes in the size of the foveal avascular zone (FAZ) assessed with OCTA, particularly its enlargement, have been linked to the macular ischemia [6]. Previous studies, which included only patients who recovered from COVID-19, reported retinal findings, namely flame-shaped hemorrhages, cotton wool spots, dilated veins, and tortuous vessels with a varying frequency (0.01 to 20%) [7, 8]. Pooled analysis of the studies has shown an 8.86-fold increase in the prevalence of retinal micro-vasculopathy in recovered COVID-19 patients compared to healthy controls [7]. The severity of the disease could play a role, as a higher prevalence of findings was reported in patients with moderate and severe course of the disease [5, 7]. One study found that not the severity but the elevated d-dimer value (≥500 ng/ml) during hospitalization was associated with lower vessel density (VD) after discharge [9]. It is important to note that patients with a moderate and severe course of disease requiring hospitalization exhibit a higher rate of comorbidities, especially diabetes and hypertension, that share similar retinal findings [10]. As the studies did not exclude patients with comorbidities, it remains unclear whether the retinal findings appear due to COVID-19 or are just incidental findings in patients with a pre-existing diabetic or hypertensive retinopathy. To the best of our knowledge, this is the first study including patients in the acute phase of COVID-19 without known systemic conditions that could affect the retina. The purpose of the study was to quantify possible impairment of the retinal microcirculation and microvasculature using fundus photography, swept-source optical coherence tomography (SS-OCT), and swept-source optical coherence tomography angiography (SS-OCTA) and compare it with healthy, age-matched controls.

**Materials and methods**

**Study design**

We designed a prospective cross-sectional study conducted at the University Medical Center Ljubljana (UMCL) between December 2020 and March 2021. The study was approved by the Slovenian Medical Ethics Committee (protocol ID number: 0120–553/2020/3) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants enrolled in the study.

**Patient selection, inclusion, and exclusion criteria**

Consecutive patients aged 18–65 in the acute phase of COVID-19, with a PCR-confirmed SARS-CoV-2 and without other comorbidities, admitted to the COVID-19 unit of the Department of Infectious Diseases, UMCL, were included in the study. Nasopharyngeal swab RT-PCR was performed at UMCL upon admission; in the case of a positive PCR, the patients were admitted to the COVID-19 unit. Therefore, even otherwise asymptomatic patients or patients with mild disease awaiting any surgical procedure (e.g., trauma surgery) were also admitted and invited to participate in the study. All of the included patients were Caucasian. All hospitalized patients eligible to participate in the study after applying the exclusion criteria were invited to participate. The following exclusion criteria were used: systemic comorbidities (diabetes, arterial hypertension, hyperlipidemia, coronary artery disease, history of stroke), concomitant infectious diseases (HIV, HSV, VZV, CMV), systemic treatment linked to retinal toxicity, smoking, pre-existing ocular pathology (age-related macular degeneration and other retinal diseases), a history of glaucoma, high myopia (>−6), and other conditions that could have affected the retinal morphology. Patients were divided into four groups based on the COVID-19 disease severity classification: (1) asymptomatic (positive PCR, no symptoms), (2) mild (the presence of symptoms but no shortness of breath, dyspnea, or abnormal chest imaging), (3) moderate (evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥ 94% on room air at sea level), and (4) severe disease (SpO2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%) [11]. To facilitate statistical analysis, groups were combined as follows: asymptomatic and mild diseases were classified as
mild; moderate and severe diseases were classified as severe. Volunteers without comorbidities and no history of COVID-19 represented the age-matched control group. To estimate the minimum sample size for adequate study power, we considered an alpha error of 0.05 and a power of 80%. For the anticipated incidence, we used the 22.2% incidence of retinal hemorrhages and cotton wool spots reported by Pereira et al., which was the only study that referred to COVID-19 retinal changes in the acute phase of COVID-19 at the time of the study design [12]. After this calculation, the minimum recommended size was 30 patients.

**Study protocol**

The study was conducted in two locations; patients with PCR-confirmed SARS-CoV-2 underwent imaging in the COVID-19 unit of the Department of infectious diseases, UMCL, whereas the control group underwent imaging at the Department of Ophthalmology, UMCL. The primary outcome measures of this study were the SD-OCT parameters—ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) thicknesses. The secondary outcome measures of the study were the OCTA parameters—(vessel densities and the FAZ area) and the retinal findings, including vessel diameters. All enrolled subjects were asked about the presence of ocular symptoms and signs, namely conjunctivitis, photophobia, itching, and diminished visual acuity. After dilating the pupils (1% tropicamide), fundus images, OCT, and OCTA were obtained using SS-OCT (Topcon DRI OCT Triton; Topcon Corp., Tokyo, Japan). The study protocol consisted of 4 images per eye: 2 color fundus images (one centered on the fovea, one on the optic disc), OCT centered on the fovea using the 7 × 7 mm scanning protocol, and OCTA centered on the fovea using the 3 × 3 mm scanning protocol. All the images were obtained by two doctors (KJ, LL). The appropriate full-body protective gown with the FFP 3 mask (3 M™, Maplewood, Minnesota, USA) was worn in the COVID-19 unit. Hospitalized patients’ electronic medical records were reviewed to collect the following relevant demographic, clinical, and laboratory parameters: age, sex, presence of comorbidities (diabetes, arterial hypertension, hyperlipidemia, coronary artery disease, history of stroke), history of smoking, alcohol consumption, concomitant infectious diseases (HIV, HSV, VZV, CMV), time from the symptom’s onset or positive PCR to the day of fundus imaging, the presence of COVID-19 related symptoms, the need for oxygen, COVID-19-related treatment, and outcome. Laboratory parameters included lactate dehydrogenase (LDH), ferritin, CRP, pro-calcitonin, white blood cells, red cell distribution width, platelets, lymphocytes, d-dimer, and 25-OH-D3.

**Image analysis**

Fundus photographs, OCT, and OCTA scans were independently reviewed by three researchers (KJ, AM, and PJM). Only images with a signal strength index above 60 were included in the analysis. Only one eye was included in the analysis, and even though randomization was considered, we have decided to include the eye with a better image quality index, to avoid potential data loss resulting from media opacities. The eye was not included in the analysis if the fundus details were not visible due to media opacities or acquisition artifacts. Fundus photographs were reviewed for the presence of hemorrhages, cotton wool spots, and dilated and tortuous vessels. The vessels were defined as dilated if all three examiners marked them as dilated in their notes. The inter-rater reliability was calculated using Fleiss’ kappa. We have additionally used the Automated Retinal Image Analyser (ARIA, V1-09-12-11), an open-source software of the MATLAB platform (MathWorks Inc., Natick, MA, USA) to objectify the vessel diameter analysis [13, 14]. Images were processed using a previously described method, where the vessel diameters of the four main veins and four main arteries between 0.5 and 1 disc diameter from the optic disc margin were used to calculate the mean vein diameter (MVD) and mean artery diameter (MAD) [13, 14]. OCT and OCTA images were automatically segmented by the built-in software (Topcon Corp., Tokyo, Japan), reviewed for the presence of any abnormalities, and checked for correct auto-segmentation, and manually readjusted if necessary. OCT parameters were measured in the macular area according to the early treatment diabetic retinopathy (ETDRS) grid. The thickness of the RNFL, GCL, and retina in the four quadrants of the inner (3 mm) and the outer ring (6 mm) of the ETDRS grid were exported using OCT Data Collector software (Topcon Inc., Tokyo, Japan). OCTA images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were processed using MATLAB (MathWorks Inc., Natick, MA, USA). The FAZ area was analyzed using a validated, previously published method, [15]. Once the center of FAZ was defined, the ETDRS chart was superimposed to calculate the parafoveal VD in the four quadrants within the 3-mm circle of the center of FAZ. Each quadrant was separately binarized using the Otsu method [16]. VD was expressed in percentages derived from the ratio of the total vessel area (white pixels) to the entire area of the analyzed region (number of pixels in the quadrants) a method previously described by Nicoló et al. [16]. The average vessel densities of the SCP and DCP were used for quantitative analysis.

**Statistical analysis**

Values are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) for numerical variables and as frequency (%) for descriptive variables.
The differences in numerical variables between mild and severe COVID-19 groups were evaluated as appropriate by independent t-test or Mann–Whitney test. The normality was examined with the Shapiro–Wilk test. In descriptive variables, the differences were tested with Fisher’s exact test. Multiple linear regression was performed to assess the association between the mean vein and mean artery diameters and COVID-19 severity, adjusting for age, sex, oxygen, and lab parameters. The differences in OCTA parameters (FAZ, SCP, DCP) were compared using multiple logistic regression adjusted for sex, age, and inflammatory parameters (LDH and ferritin). OCT parameters were compared with linear mixed-effects regression. The side (N, nasal; S, superior; T, temporal; I, inferior) was included as a random intercept to account for multiple measurements in each subject.
values of all pairwise comparisons (mild vs. control, severe vs. control, severe vs. mild) were adjusted using the Benjamini–Hochberg method. Statistical analysis was performed with R statistical software (version 4.1.3, R Development Core Team, Vienna, Austria); additionally, the `lme4` and `multcomp` packages were used [17].

### Results

A total of 75 consecutive patients in the acute phase of COVID-19 without known systemic comorbidities and 101 healthy controls were included in the study. Baseline demographics and clinical characteristics are presented in Table 1. We initially included 77 patients with COVID-19, but two patients were excluded due to poor image quality. The median age of the COVID-19 group was 57 years (range 21–65), and the median age in the control group was 54 (range 21–65). There was no statistically significant difference between the two groups regarding age ($P=0.092$). The median duration of symptoms before imaging was 4 days (interquartile range: 1–8) in patients with mild disease and 10 days (interquartile range: 8–13) in patients with severe disease. Patients with a severe course exhibited higher activity of LDH ($P<0.001$) and higher concentrations of ferritin ($P=0.002$). None of the COVID-19 patients reported ocular symptoms such as itching, photophobia, foreign body, conjunctivitis, or diminished visual acuity.
Retinal findings

Retinal findings were predominately observed in patients with severe disease ($P = 0.006$) and are presented in Fig. 1. Retinal hemorrhages were seen in 5 patients (8.5%), cotton wool spots in 3 patients (4.0%), and dilated veins in 44 patients (74.6%) with severe disease. Dilated veins were noted in 6 (37.5%) patients with mild disease. The inter-rater reliability was 1 for retinal hemorrhages and cotton wool spots and 0.96 for dilated veins. MVD was 123.5 μm (SD = 13.2) in the mild group and 133.8 μm (13.8) in the severe group. MAD was 93.1 μm (9.1) in the mild group and 96.5 μm (11.9) in the severe group. Disease severity was a significant predictor of both MVD ($P = 0.002$; Coef. = 19.28, 

Fig. 2 Retinal vessels according to the disease severity. Retinal vessel analysis was done with the ARIA (automatic retinal image analyzer) software. The mean diameters (in μm) of the four main veins (blue) and four main arteries (red) were measured between 0.5- and 1-disc diameter from the optic disc margin. A Mild disease. B Severe disease. C Boxplot of the diameter of retinal vessels according to the disease severity. Diamond symbol, average; filled circles, the distribution of the raw data; the frame of the boxplot (median, first and third quartile); the whiskers extend to minimum/maximum value within 1.5*IQR range (from first/third quartile)
95% CI: 7.34–31.23) and MAD (\( P = 0.044, \text{ Coef.} = 11.07, 95\% \text{ CI: 0.84–21.67} \)) when accounting for age, sex, treatment with oxygen, LDH, and ferritin (Table 2, Fig. 2). All other variables (age, sex, treatment with oxygen, LDH, and ferritin) were not significant.

OCT parameters of COVID-19 patient groups based on disease severity and healthy controls are summarized in Table 3. Patients with severe COVID-19 were shown to have significantly increased RNFL thickness in the superior (S) and inferior (I) quadrants compared with healthy controls both in the inner ring (S: \( P = 0.046; I: P = 0.016 \)) and in the outer ring (S: \( P = 0.026; I: P = 0.014 \)). Furthermore, significantly increased GCL thickness in the outer temporal ring was observed in patients with severe COVID-19 (T: \( P = 0.038 \)). The mean differences for RNFL and GCL of all groups with 95% CI are presented in Fig. 3. There were no statistically significant differences in the entire retinal thickness. There were no statistically significant differences in OCTA parameters, including FAZ area and vessel density of the SCP and DCP, between the groups (Table 4). There was also no difference within the COVID-19 group when adjusted for severity of laboratory values of d-dimer (\( P = 0.974 \)) and immune-inflammatory parameters. Figure 4 shows a comparison of OCT and OCTA images between a healthy control and a COVID-19 patient.

Discussion

This is the first study to report retinal findings assessed with retinal imaging modalities in the acute phase of COVID-19 patients without comorbidities. Our results show that the severity of COVID-19 plays a role in the presence of retinal microvascular findings as they were significantly more common in patients with a severe course. Similar findings were previously reported [5, 7]; however, as only patients without comorbidities were included in this study, the association with COVID-19 seems more plausible. The presence of hemorrhages and cotton wool spots could be explained either by SARS-CoV-2 induced pyroptosis or by dysregulation in the renin–angiotensin–aldosterone system and the resulting endothelial dysfunction [18, 19]. The retina is part of the central nervous system, and its energy demands have been linked to those of the brain, making it particularly susceptible to the effects of ischemia and oxidative stress [20, 21]. Due to the blood-retinal barrier, its intrinsic autoregulatory response maintains a constant blood flow, not influenced by either autonomic innervation or hormonal mediators and neurotransmitters [22, 23].

This study found significantly increased mean vessel diameter of both veins and arteries in patients with severe COVID-19, the difference being higher in the venular

Table 3 Comparison of the OCT parameters between the healthy controls and patients in the acute phase of COVID-19

| Quadrant | Retina | Control (n = 101) | Mild (n = 16) | Severe (n = 59) |
|----------|--------|-----------------|--------------|----------------|
| Inner ring | T | 19.59 (2.96) | 19.97 (2.91) | 19.74 (2.85) |
| S | 28.28 (2.3) | 29.14 (1.67) | 29.62 (1.67) |
| N | 23.8 (2.49) | 24.86 (1.67) | 24.22 (1.67) |
| I | 28.6 (2.5) | 29.65 (2.54) | 30.22 (2.43) |
| Outer ring | T | 21.65 (2.6) | 22.3 (2.21) | 22.91 (2.94) |
| S | 40.07 (4.76) | 40.51 (4.82) | 42.82 (4.21) |
| N | 50.45 (7.11) | 50.84 (6.82) | 52.68 (6.84) |
| I | 41.66 (5.42) | 41.49 (4.57) | 44.79 (5.91) |

\( P < 0.05 \) when compared to the control group

RNFL retinal nerve fiber layer, GCL ganglion cell layer, T temporal, S superior, N nasal, I inferior
Several mechanisms can explain vascular changes and differences. Firstly, it is known that retinal veins dilate in response to impaired drainage, and arteries dilate in response to either hypoxia or hypercapnia [13, 23]. Furthermore, studies have shown the potential role of inflammatory mediators on the increased diameter of both veins and arteries [22]. Nevertheless, none of our study’s confounding variables, including age, gender, treatment with oxygen, and increased inflammatory mediators, were shown to affect the vessel diameter. Autopsy studies of COVID-19 patients have reported micro thrombosis, small vessel thickening, and angiogenesis; therefore, another possible explanation could be the resulting dysfunctional vasoregulation [24, 25]. The more significant impact on venular diameter could reflect higher compliance or a different expression of inflammatory or ACE-2 receptors in the venular vessel wall. Similar vascular alterations were observed in the retina of patients recovered from the COVID-19 [13, 26]; moreover, vessel dilatation was also observed in the lungs of patients with the COVID-19 pneumonia [24], which could indicate SARS-CoV-2-induced vascular remodeling and angiopathy. Even though the measured differences in our study are small, especially in the MAD, they are clearly visible in the fundus photographs. Fundus photography is a non-invasive imaging method that could be used to assess micro vasculopathy in hospitalized patients. This is especially important considering the fact that the expression of ACE-2 receptors was reported in several other tissues, including the kidney, heart, and brain; hence, similar microvascular alterations in those tissues are likely [5]. Patients in the acute phase of severe COVID-19 exhibited increased RNFL thickness of the superior and inferior quadrants in the inner and outer ring of the ETDRS grid and increased GCL thickness in the outer temporal ring. The superficial layer of the retinal capillaries lies in the RNFL and GCL layers of the retina. The retinal plexuses are composed of terminal vessels without anastomotic connections, making them more susceptible to ischemia. In addition, the retina has high metabolic demands, which makes it more vulnerable to the stress induced by acute COVID-19 [22]. Therefore, the thickening of GCL and RNFL could reflect ischemic edema resulting from a combination of endothelial damage and micro-thrombi-induced end-capillary closure.

**Table 4** Comparison of the OCTA parameters between the healthy controls and COVID-19 patients using multiple linear regression

| Parameter                | OR  | 95% CI   | P value |
|--------------------------|-----|----------|---------|
| FAZ area (cm²)           | 0.51| 0.20–1.16| 0.127   |
| Vessel density in SCP    | 1.51| 0.90–2.78| 0.146   |
| Vessel density in DCP    | 0.73| 0.47–1.09| 0.121   |

Analysis adjusted to age, sex, LDH, and ferritin

FAZ foveal avascular zone, SCP superficial capillary plexus, DCP deep capillary plexus
where thinning of both RNFL and GCL was reported over time [27–31]. Another possible explanation for the thickening is that it reflects the aforementioned vessel dilatation [23]. Even though only healthy patients without comorbidities were included in the study and the analysis was adjusted for confounding variables, it remains possible the observed differences are not necessarily related to COVID-19. The results of our study suggest that there is not any difference between OCTA parameters, including FAZ area, perimeter, circularity, axial ratio, and vessel density of the SCP and DCP between patients in the acute phase of COVID-19 and healthy controls. Previous studies on recovered patients were inconclusive; while some reported no difference in VD [32] and FAZ area [33], others reported decreased VD [28, 33–35] and an increase in the FAZ area [28] that were even more pronounced after a 3–6-month follow-up [29, 36]. It is noteworthy that our study included only patients in the acute phase of COVID-19; therefore, one possible explanation of our results is that the changes in the acute phase are too subtle to reach statistical significance. Another important consideration is that no differences were observed in the OCTA parameters even though increased MVD and MAD were observed, which could lead to a higher-vasculosity index due to vasodilatation. Therefore, our results might indicate endothelial dysfunction and the resulting hypertrophy of the vessel wall by the increased mitotic activity and resulting hypertrophy [37]. Therefore, the dilatation could reflect microvasculopathy and thickening of the vessel wall (also reflected in the thickening of the RNFL layer) rather than vasodilatation per se— which would result in the increased perfusion area [37]. Our study had some limitations. First, the sample size of patients with the mild disease is relatively low. Yet, we found significant differences within the COVID-19 group, suggesting the size sample was sufficient to address the study questions. The study was performed in extreme conditions of the COVID-19 unit and was limited to the patients admitted to the hospital in the study period. Second, the study is not gender-matched, but previous OCT and OCTA studies found no gender-based differences. Third, fundus photography, OCT, and OCTA imaging studies have a limited evaluation area. Lastly, a lack of follow-up is another limitation of our study.

In conclusion, this is the first study to show changes in the retinal microvasculature and structure in the acute phase of COVID-19. The severity of COVID-19 was significantly correlated with retinal microangiopathy, which could become a biomarker of angiopathy in patients with severe COVID-19. Since the findings were subclinical, an ophthalmological examination may be warranted in patients after severe COVID-19. Further longitudinal studies are needed to assess the sequelae of COVID-19-related microangiopathy over time.

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**Author contribution** All authors contributed to the study’s conception and design. Data collection was performed by Kristina Jevnikar and Luka Lapajne, and analysis by Kristina Jevnikar, Andrej Meglič, and Polona Jaki Mekjavić. The first draft of the manuscript was written by Kristina Jevnikar, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Declarations**

**Ethical approval** The study was performed in accordance with the ethical standards of the Slovenian medical ethics committee (protocol ID number: 0120–553/2020/3) and with the 1964 Helsinki declaration and its later amendments.

**Conflict of interest** The authors declare no competing interests.
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