Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Retinal and peripapillary vessel density increase in recovered COVID-19 children by optical coherence tomography angiography

Noemi Guemes-Villahoz, MD,[a] Barbara Burgos-Blasco, MD,[a] Pilar Perez-Garcia, MD,[a] Jose Ignacio Fernández-Vigo, MD, PhD,[a] Laura Morales-Fernandez, MD, PhD,[a] Juan Donate-Lopez, MD, PhD,[a] Jose Tomas Ramos-Amador, MD, PhD,[b] and Julian Garcia-Feijoo, MD, PhD[c]

PURPOSE To evaluate retinal vascular changes in children who have recovered from coronavirus disease (COVID-19) using optical coherence tomography angiography (OCTA) and to compare the results with age-matched healthy children.

METHODS In this cross-sectional case–control study, children 6-18 years of age with laboratory-confirmed SARS-CoV-2 infection were compared with historic healthy controls. All participants underwent ophthalmological examination, including fundus photography and OCTA of the macular region and optic disk. COVID-19 children were examined 4-8 weeks after COVID-19 diagnoses. Demographic data, medical history, and COVID-19 symptoms were noted. OCTA parameters in the superficial capillary plexus (SCP) were analyzed according to ETDRS sectors and peripapillary quadrants.

RESULTS A total of 72 patients were included: 27 recovered COVID-19 children and 45 controls. Mean age for cases was 11.96 ± 3.8 years (18 females [66%]); for controls, 11.02 ± 2.0 years (29 females [64%]). Macular OCTA of the SCP showed a significant increase in retinal vessel density (VD) in recovered COVID-19 children compared with healthy controls in the inner ring ($P = 0.001$). Macular perfusion density (mPD) was also increased in the inner ring ($P = 0.001$). Peripapillary OCTA evidenced a significant higher flux index (FI) in all four quadrants ($P < 0.001$).

CONCLUSIONS Recovered COVID-19 children present increased retinal VD, mPD, and peripapillary FI shortly after recovery. Since the retinal vasculature is considered a unique window to assess microvascular changes, these findings may represent a potential in vivo biomarker of vascular abnormalities in COVID-19 children in other organs. (J AAPOS 2021;25:325.e1-6)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), has spread throughout the world with unprecedented speed. Although COVID-19 primarily affects the respiratory system, there is growing evidence that it may affect virtually all organs, including the eye.[1-3] Several studies have reported not only conjunctivitis associated with COVID-19,[4] but also retinal vascular abnormalities in adults that persist even after recovery.[5-8] However, to our knowledge, no studies to date have evaluated retinal microvasculature changes in children who have recovered from COVID-19.

Optical coherence tomography angiography (OCTA) noninvasively provides three-dimensional visualization of the retinal circulation without the need for intravenous dye injection.[9] Given that microvascular retinal abnormalities have been described in adults with SARS-CoV-2 infection[10-12] and that differences in disease course and prognosis have been documented in children and adults,[13-15] there is a rationale for assessing retinal vasculature changes in children who have recovered from COVID-19. The aim of this study was to qualitatively and quantitatively evaluate the retinal vasculature of these children and to compare the findings with those of healthy children.

Author affiliations: [a]Ophthalmology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain; [b]Pediatrics Department, Hospital Clínico San Carlos, Madrid, Spain; [c]Ophthalmology Department, Hospital Clínico San Carlos, Departamento de Inmunología, Oftalmología y ORL, Facultad de Medicina, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Oftared, Madrid, Spain

Submitted March 22, 2021.
Revision accepted June 22, 2021.
Published online October 20, 2021.

Correspondence: Noemi Guemes-Villahoz, MD, Hospital Clinico San Carlos. Servicio de Oftalmología, Calle del Profesor Martin Lagos. 28040 Madrid, Spain (email: noemiguemes@gmail.com).

1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2021.06.004

Subjects and Methods

This case–control study, conducted at Hospital Clinico San Carlos (HCSC), Madrid, Spain, was approved by the hospital's Clinical Research Ethics Committee and adhered to the tenets of the Helsinki Declaration. Parents provided written informed consent. In children aged ≥12 years, written informed assent of the participants was also obtained.

The inclusion criteria for the case group were as follows: (1) age 6-18 years; (2) laboratory-confirmed SARS-CoV-2 infection, testing positive to SARS-CoV-2 by reverse transcriptase–polymerase chain reaction (RT-PCR) from nasopharyngeal swab; (3) spherical equivalent within ±6.00 D; and (4) treatment at the hospital's Pediatric Emergency Department between August 15 and November 30, 2020. Patients' sociodemographic data (age, sex, race), medical history and clinical data of COVID-19 were retrieved from the medical record.

The inclusion criteria of the control group consisted of healthy subjects 6-18 years of age and with spherical equivalent within ±6.00 D who had been recruited for a previous study conducted at the same ophthalmology department at HCSC from May to August 2019. A historical control group was preferred in this study because of the difficulty of ensuring the absence of past SARS-CoV-2 infection in children, a population with a particularly high prevalence of asymptomatic cases. In addition, seroconversion in children with confirmed SARS-CoV-2 infection is not 100%,[16] which means that the presence of negative antibodies results (IgM and IgG) cannot rule out with certainty a previous infection. Subjects included in the control group were completely healthy; they had no history of any known systemic disease, including diabetes mellitus and other cardiovascular conditions and psychiatric, neurological, and other systemic diseases. Control subjects had undergone the same ophthalmological examination with the same device and software used in this study.

Subjects with ophthalmological diseases were excluded. Individuals with previous diagnosis or diagnosis made during the examination of optic nerve head disease, macular disease, retinal vascular disorders, or uveitis were excluded, as were those with previous ophthalmic procedures. Additionally, patients with amblyopia were excluded. The same exclusion criteria were applied to both groups.

Ophthalmological Examination

In all study participants, eye examination included color fundus photography and OCTA of the macular region and optic nerve head, without pharmacological mydriasis, under scotopic conditions. Examination was performed in the Pediatrics Department, on the same day as COVID-19 follow-up, 4-8 weeks after SARS-CoV-2 infection diagnosis. Eidon true-color confocal scanner camera (Centervue, Padova, Italy) was used to capture a 60° wide-field image in a single exposure for each eye of each subject. The presence of retinal hemorrhages, cotton wool spots, and other retinal abnormalities that have been previously reported in COVID-19 adults[6-8,17] were assessed. OCTA images were captured using the Zeiss Cirrus 5000 spectral domain OCTA with AngioPlex (Carl Zeiss Meditec Inc, Dublin, CA). Macular OCTA and peripapillary OCTA were performed in both eyes for each subject. Macular angiography images were obtained using the 6 × 6 mm Macular Cube protocol. A 4.5 × 4.5 mm scan centered on the optic nerve head was also captured to assess the peripapillary vasculature. The inclusion crieria for acceptable signal strength was 7 or more. The complex optical microangiography (cOMAG) algorithm analyzed changes in the complex signals and the results were processed using Cirrus OCTA software (AngioPlex, version 11.0). ZEISS AngioPlex Metrix software provides automatic quantitative analysis of retinal vessels in the superficial capillary plexus (SCP), whose limits are preset from the internal limiting membrane (ILM) to the inner plexiform layer (IPL), where IPL is estimated to be at 70% of the thickness between the ILM and the retinal pigment epithelium The macular OCTA parameters analyzed were vessel density (VD), perfusion density (mPD), and the area, perimeter, and morphology (circularity) of the foveal avascular zone (FAZ). VD was defined as the total length of perfused vasculature per unit area in the region of measurement (mm/mm2). PD was defined as the percent total area of perfused vasculature in a given region of measurement (%).[18] The built-in analytic algorithm automatically outlined the FAZ boundary along the innermost capillaries (area and perimeter). FAZ circularity was defined as FAZ boundary similarity to a circle (range, 0-1, where 1 = FAZ perfect circle and 0 = very different from a circle).[18]

The macular region was segmented according to the nine sectors of the Study of Early Treatment of Diabetic Retinopathy (ETDRS): central circle of 1 mm in diameter; inner ring, inner diameter of 1 mm and outer diameter of 3 mm, with four quadrants (superior, nasal, inferior, and temporal); outer ring, inner diameter of 3 mm and outer diameter of 6 mm, with 4 quadrants (superior, nasal, inferior, and temporal). See eSupplement 1 (available at jaapos.org).

In peripapillary OCTA, two vascular indices were also automatically obtained considering four quadrants: superior, nasal, inferior, and temporal. See eSupplement 2 (available at jaapos.org).

Peripapillary perfusion density (pPD) and flux index (FI) were measured from the ILM to the retinal nerve fiber layer. The pPD was defined similar to mPD in the macular region. FI measures the number of red blood cells passing through a retinal vessel cross-sectional area per unit time and was defined as the total area of perfused vasculature per unit area in a region of interest (unitless ratio).

The subjects' right eye was included, unless it did not meet the inclusion and exclusion criteria, in which case the left eye was included. OCTA images and fundus photographs were obtained by the same trained examiner and reviewed individually by two ophthalmologists (NGV and BBB) for quality assessment; low-quality images were excluded. Segmentation errors were checked and manually corrected if detected.

Statistical Analysis

Statistical analyses were performed with the SPSS software, version 24.0 (IBM, New Castle, NY). Continuous variables are

Table 1. Demographic data and characteristics of the patients included in the study

Characteristics	Recovered COVID-19 children	Healthy controls	*P* value
Total, no.	27	45	
Age, years, mean ± SD (range)	11.96 ± 3.8 (6-16)	11.02 ± 2.0 (8-15)	0.263
Sex, no. (%)			0.847
Male	9 (33)	16 (36)	
Female	18 (67)	29 (64)	
Refractive error, mean ± SD (range)	−1.05 ± 1.8 (+2.4 to −3.9)	−0.68 ± 1.8 (+3.1 to −2.9)	0.542

COVID-19, coronavirus disease; *SD*, standard deviation.

presented as mean and standard deviation (SD), while numbers and percentages are used for categorical variables. Differences in age and sex between groups were compared using the χ^2 test and *t* test. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. Differences in quantitative variables between groups were analyzed using the *t* test, with Bonferroni correction. With 19 OCTA parameters compared between COVID patients and controls, differences were considered statistically significant when $p<0.0026$.

Results

The total study population included 72 subjects: 27 recovered COVID-19 patients and 45 healthy controls. Among the children diagnosed with COVID-19 in the Pediatric Emergency Department during the study period, 35 patients met inclusion criteria. Of those, 2 patients were lost to follow-up after emergency department discharge, 1 child did not have parental consent for participation, 1 child presented myopia >6 D, and 4 were excluded because OCTA did not meet the quality criteria. Demographic data and patient characteristics are provided in Table 1. There were no statistically significant differences between groups in terms of age, sex, and refractive error.

Clinical characteristics of COVID-19 children are summarized in Table 2. Regarding COVID-19 severity, it should be noted that the 7 asymptomatic patients included in the study came to the pediatric emergency department accompanying their siblings or parents with COVID-19 symptoms, and therefore PCR was also performed on them as close contacts of a confirmed-COVID-19 patient. None of them required systemic treatment with antivirals or corticosteroids, requiring only symptomatic treatment with acetaminophen. The only child who required hospital admission because of poor gastrointestinal tolerance responded favorably with supportive treatment with intravenous fluids; no additional treatments were required.

Ophthalmologic examination of children with recent history of SARS-CoV-2 infection was unremarkable. No retinal hemorrhages, cotton wool spots, nor other retinal abnormalities were found on fundus examination. None of the children endorsed visual loss or other visual symptoms during the acute phase of the infection and thereafter up to the date of evaluation. Mean days from PCR-confirmed diagnosis to ophthalmological examination were 37.6 ± 12.9 (range, 29-60 days). Macular OCTA revealed statistically significant differences in VD and mPD between COVID-19 patients and healthy controls. Patients recovered from COVID-19 had increased mPD compared with healthy children in the inner ring ($P = 0.001$). Significantly higher VD was also found in the inner ring ($P = 0.001$). FAZ circularity was the only FAZ-related parameter that evidenced differences between the two groups ($P = 0.001$). Table 3 shows macular OCTA parameters in recovered COVID-19 children and healthy controls.

Table 2. Clinical characteristics of COVID-19 children

Characteristics	COVID-19 children
Days from diagnosis to examination, mean ± SD (range)	37.6 ± 12.9 (29-60)
COVID-19 severity, no. (%)	
Asymptomatic	7 (25.9)
Mild	19 (70.3)
Hospital admission/moderate COVID-19	1 (4)
ICU admission, no. (%)	0 (0)
COVID-19 symptoms, no. (%)	
Temperature	
37-38°C	5 (19)
>38°C	9 (33)
Arthralgias/myalgia	5 (19)
Asthenia	6 (22)
Cough	6 (22)
Odynophagia	4 (15)
Rhinorrhea	5 (19)
Respiratory distress	1 (4)
Abdominal pain	2 (7)
Vomits	1 (4)
Diarrhea	2 (7)
Headache	12 (44)
Anosmia/ageusia	9 (33)
Other symptoms	4 (15)

COVID-19, coronavirus disease; *ICU*, intensive care unit; *SD*, standard deviation.

Likewise, peripapillary OCTA exhibited differences between COVID-19 children and healthy controls, demonstrating a higher FI in all four quadrants ($P < 0.001$) in patients with history of COVID-19 compared with controls. Table 4 summarizes peripapillary OCTA results in recovered COVID-19 children and healthy controls.

Discussion

Differences in the course and prognosis of COVID-19 have been described in children and adults, with children

Table 3. Macular OCTA parameters in recovered COVID-19 children and healthy controls

Parameters	COVID-19 (n = 27), mean ± SD (range)	Control group (n = 45), mean ± SD (range)	*P* value	Mean difference	95% CI	
					Inferior	Superior
VD						
Central	11.65 ± 2.98 (4.3-16)	10.96 ± 4.04 (2-18.5)	0.408	−0.69	−2.35	0.96
Inner ring	18.84 ± 0.76 (16.2-19.8)	17.68 ± 2.07 (11.5-19.7)	0.001	−1.16	−1.84	−0.48
Outer ring	19.15 ± 0.75 (16.9-20)	18.73 ± 1.33 (12.9-20.3)	0.09	−0.42	−0.91	−0.06
Full area	18.86 ± 0.73 (16.4-19.7)	18.26 ± 1.46 (12.4-19.7)	0.024	−0.60	−1.11	−0.08
mPD						
Central	26.56 ± 6.96 (9.3-36.2)	24,47 ± 9.32 (4.2-42.7)	0.282	−2.09	−5.95	1.76
Inner ring	44.91 ± 1.83 (39.3-48.2)	41.99 ± 5.05 (36.3-47.1)	0.001	−2.92	−4.58	−1.25
Outer ring	47.45 ± 1.61 (42.8-49.1)	46.04 ± 3.35 (30.5-49.1)	0.019	−1.41	−2.58	−0.23
Full area	46.26 ± 1.65 (41-48.4)	44.49 ± 3.67 (39-48)	0.007	−1.76	−3.03	−0.50
FAZ						
Area	0.22 ± 0.12 (0.02-0.53)	0.22 ± 0.11 (0.01-0.53)	0.929	−0.002	−0.06	0.05
Perimeter	1.83 ± 0.54 (0.61-2.89)	1.91 ± 0.70 (0.1-3.73)	0.588	−0.08	−0.22	0.39
Circularity	0.77 ± 0.04 (0.69-0.85)	0.68 ± 0.18 (0.01-0.87)	<0.001	−0.09	−1.16	−0.01

CI, confidence interval; *COVID-19*, coronavirus disease; *FAZ*, foveal avascular zone; *OCTA*, optical coherence tomography angiography; *mPD*, macular perfusion density; *VD*, vessel density.

presenting a milder course of the disease and better outcomes overall.[13-15] Since the onset of the COVID-19 outbreak in December 2019, numerous studies have been published on the ocular manifestations and complications of the disease in adults.[3,19-21] However, there is no data regarding the effects of SARS-CoV-2 infection on retinal microvasculature in the pediatric population.

Previous research has reported a reduction in retinal VD and other vascular parameters of OCTA in adults with SARS-CoV-2 infection.[5,11,12,22] On the contrary, our study indicates that children recovered from COVID-19 have significantly greater macular VD and mPD and peripapillary FI than healthy children. The reason for this paradoxical response in children is not precisely understood, although the apparent differences in immune response to SARS-CoV-2 infection and the anatomical and structural differences between the adult and pediatric retina might partially account for these findings.[23-25]

Asikgarip and colleagues[10] recently reported retinal vessel diameter changes in COVID-19 infected adults, finding that the diameters of the retinal arteries and veins were significantly increased in COVID-19 patients during the acute phase of the disease compared with healthy controls. This vascular enlargement has been also evidenced in other organs, such as the pulmonary arteries.[26,27] These findings seem to be supported by the theory that elevated inflammatory cytokines during the infection may manifest as endothelial damage and vessel dilation. An association of inflammatory markers with increased retinal vein diameter has been previously documented in the Beaver Dam Eye Study, suggesting that retinal venular caliber may be a marker of systemic inflammation.[28] To justify how this retinal vascular dilatation in COVID-19 patients translates into the presence of a lower retinal VD found by OCTA in adults is not straightforward. Endothelial dysfunction and thrombotic microangiopathy has been extensively documented in COVID-19 patients.[29,30] Furthermore, dilated vascular segments with low blood flow velocity are prone to thrombus formation.[31] Therefore, these abnormalities may affect the retinal vascular parameters, accounting for the findings observed with OCTA in adult patients with COVID-19.[5,11,12,22] Other plausible mechanisms might involve COVID-19-associated vascular dilatation, leading to a lower vascular flow and resulting in a decrease in blood

Table 4. Peripapillary OCTA parameters in recovered COVID-19 children and healthy controls

Parameters	COVID-19 (n = 27), mean ± SD (range)	Control group (n = 45), mean ± SD (range)	*P* value	Mean difference	95% CI	
					Inferior	Superior
Superior pPD	45.06 ± 1.77 (41.7-49.2)	44.17 ± 2.5 (37.4-48.1)	0.084	−0.89	−1.91	0.12
Superior FI	0.46 ± 0.02 (0.42-0.54)	0.44 ± 0.02 (0.39-0.48)	<0.001	−0.02	−0.03	−0.01
Nasal pPD	45.26 ± 2.1 (41.3-49.5)	44.82 ± 2.81 (36-50.1)	0.465	−0.44	−1.64	0.76
Nasal FI	0.48 ± 0.02 (0.41-0.52)	0.46 ± 0.02 (0.39-0.51)	<0.001	−0.02	−0.03	−0.11
Inferior pPD	46.94 ± 1.42 (44.5-49.8)	46.16 ± 1.86 (41.7-51.2)	0.051	−0.78	−1.57	0.00
Inferior FI	0.46 ± 0.01 (0.42-0.48)	0.45 ± 0.02 (0.4-0.48)	<0.001	−0.01	−0.02	−0.00
Temporal pPD	48.73 ± 1.76 (44.9-53.4)	49.24 ± 2.47 (43.6-55.3)	0.319	0.51	−0.50	1.53
Temporal FI	0.50 ± 0.01 (0.45.0.53)	0.47 ± 0.02 (0.41-0.52)	<0.001	−0.02	−0.03	−0.01

CI, confidence interval; *COVID-19*, coronavirus disease; *FI*, flux Index; *OCTA*, optical coherence tomography angiography; *pPD*, peripapillary perfusion density.

cell signal detected by OCTA, consequently interpreted as a reduced OCTA parameter.

In the present study, recovered COVID-19 children seem to present a significantly increased macular VD and mPD and peripapillary FI compared with healthy children. The underlying mechanism for this age-related difference may lie in the different behavior of SARS-CoV-2 in children and adults. Yuan and colleagues[32] reported different immune responses between adults and children with COVID-19. There are also documented differences in the endothelium and clotting function in the pediatric population.[33,34] Furthermore, a lower expression of Angiotensin converting enzyme 2 (*ACE2*) gene, which is the main receptor for the entry of SARS-CoV-2 into human cells, has been shown in children relative to adults.[35] As a result, SARS-CoV-2 might have a different distribution across body sites, including the vascular endothelium.

Regarding the timing of ophthalmologic examination in adults and children with COVID-19, most of the studies in adults performed OCTA 2-12 weeks after infection, thus following a methodology similar to our study (4-8 weeks).

In our study, of FAZ metrics, only FAZ circularity showed significant differences between the two groups (greater in the COVID group). In COVID-19 adults, Turker and colleagues[22] found that FAZ area was greater in the COVID group than in the control group, but this did not reach statistical significance. FAZ may result in a low circularity for a number of reasons, including loss in capillaries immediately surrounding the FAZ, as has been observed in diabetic retinopathy.[36] Consequently, our results may be related to the fact that children recovered from COVID-19 presented an increased DV and mPV. As for peripapillary OCTA parameters, FI showed significant differences; however, pPD did not. OCTA studies in patients with glaucoma have suggested that structural damage may correlate more strongly with FI than pPD.[37] This may mean that FI may be more likely to detect changes in peripapillary OCTA than pPD.

This study has several limitations. First, our study included a relatively small sample size of subjects 6-18 years of age. Children <6 years of age were not recruited because of the difficulty of acquiring high-quality images in very young subjects. Second, the ophthalmological examination was performed 4-8 weeks after SARS-CoV-2 diagnoses. Strict infection prevention and control measures did not allow assessment during the acute phase of the disease. It would have been particularly interesting to assess findings during the symptomatic phase of the disease, although it is worth noting that some patients included were asymptomatic. In addition, the majority of the subjects included in our study presented mild COVID-19, not including severe and critical patients. Therefore, differences according to disease severity could not be analyzed. A recent study conducted in COVID-19 adults found that those with moderate-to-severe disease had lower central retinal VD than those with mild disease.[12] Hence, the differences observed in OCTA results in children and adults with COVID-19 might be partly attributable to the relatively milder course of the disease in children. Finally, the present study evaluated OCTA data in the superficial capillary plexus; however, neither the deep plexus, nor changes in the choroid, which might provide additional information, were analyzed.

This is the first study, to our knowledge, to report retinal vascular changes in children recovered from COVID-19. The retinal microvasculature may serve as an in vivo biomarker of vascular abnormalities in COVID-19 children in other organs. We found significant differences in OCTA-vascular indices in children recovered from COVID-19 and healthy children. However, these findings were opposite of those previously found in COVID-19 adults. We do not know the clinical relevance of these subclinical changes. Nonetheless, these findings might represent further evidence that highlights the different behavior and response to SARS-CoV-2 infection in children and adults. Larger prospective studies are warranted to elucidate the medium- and long-term consequences of these findings.

Literature Search

PubMed was searched on March 1, 2021, using the following terms in combination: *COVID-19*, *coronavirus; SARS-CoV-2*, *optical coherence tomography angiography*, and retina.

Acknowledgments

The authors thank Ana Gonzalez Alvarez-Nava, Helga Tallon Avila, Maria Isabel Sanchez Perea, and Maria Carmen Rivera Sequera for their collaboration in this study.

References

1. Öncül H, Öncül FY, Alakus MF, Çağlayan M, Dag U. Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. J Med Virol 2021;93:1126-32.
2. Loffredo L, Pacella F, Pacella E, Tiscione G, Oliva A, Violi F. Conjunctivitis and COVID-19: a meta-analysis. J Med Virol 2020; 92:1413-14.
3. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
4. Güemes-Villahoz N, Burgos-Blasco B, García-Feijoó J, et al. Conjunctivitis in COVID-19 patients: frequency and clinical presentation. Graefes Arch Clin Exp Ophthalmol 2020;258:2501-7.
5. Abrishami M, Emamverdian Z, Shoeibi N, et al. Optical coherence tomography angiography analysis of the retina in patients recovered from COVID-19: a case-control study. Can J Ophthalmol 2021;56: 24-30.
6. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: results from the SERPICO-19 study. EClinicalMedicine 2020 Oct;27:100550.
7. Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? J Intern Med 2021;289: 116-20.
8. Gascon P, Briantais A, Bertrand E, et al. COVID-19-associated retinopathy: a case report. Ocul Immunol Inflamm 2020;28: 1293-7.

9. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retin Vitr 2015; 1:5.
10. Aşıkgarip N, Temel E, Hızmalı L, Örnek K, Sezgin FM. Retinal vessel diameter changes in COVID-19 infected patients. Ocul Immunol Inflamm 2021;1-7.
11. Guemes-Villahoz N, Burgos-Blasco B, Vidal-Villegas B, et al. Reduced retinal vessel density in COVID-19 patients and elevated D-dimer levels during the acute phase of the infection. Med Clin (Engl Ed) 2021;156:541-6.
12. Zapata MÁ, Banderas García S, Sánchez-Moltalvá A, et al. Retinal microvascular abnormalities in patients after COVID-19 depending on disease severity. Br J Ophthalmol 2020 Dec 16. bjophthalmol-2020-317953.
13. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. Pediatr Pulmonol 2020;55:2565-75.
14. Castagnoli R, Votto M, Licari A, Brambilla I, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents. JAMA Pediatr 2020;174:882-9.
15. Patel NA. Pediatric COVID-19: systematic review of the literature. Am J Otolaryngol 2020;41:102573.
16. Masiá M, Telenti G, Fernández M, García JA, Agulló V, Padilla S, et al. SARS-CoV-2 seroconversion and viral clearance in patients hospitalized with COVID-19: viral load predicts antibody response. Open Forum Infect Dis 2021;8:ofab005.
17. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. Lancet 2020; 395(10237):1610.
18. Carl Zeiss Meditec. Cirrus HD-OCT User Manual – Models 500, 5000 [Internet]. 2017. Available at: https://www.zeiss.fr/content/dam/Meditec/international/ifu/documents/cirrus-hd-pct/current/2660021169012_a_cirrus_11_en_intl.pdf.
19. Guisado-Vasco P, Valderas-Ortega S, Carralón-González MM, et al. Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: a retrospective observational study (COQUIMA cohort). EClinicalMedicine 2020;28:100591.
20. Ashraf O, Young M, Malik KJ, Cheema T. Systemic complications of COVID-19. Crit Care Nurs Q 43:390-399.
21. Dutch COVID & Thrombosis Coalition. Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave. Thromb Res 2020;199:143-8.
22. Turker IC, Dogan CU, Guven D, Kutucu OK, Gul C. Optical coherence tomography angiography findings in patients with COVID-19. Can J Ophthalmol 2021;56:83-7.
23. Fernández-Vigo JI, Kudsieh B, Shi H, et al. Normative database and determinants of macular vessel density measured by optical coherence tomography angiography. Clin Experiment Ophthalmol 2020;48: 44-52.
24. Ahn H-C, Son H-W, Kim JS, Lee JH. Quantitative analysis of retinal nerve fiber layer thickness of normal children and adolescents. Korean J Ophthalmol 2005;19:195-200.
25. Sunita M, Manisha S, Sanjeev M, Ravi K, Aarzoo J, Ajai A. Anatomical and clinical characteristics of paediatric and adult eyes. Natl J Clin Anat 2021;10:5-9.
26. Li Y, Xia L. Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. Am J Roentgenol 2020;214:1280-86.
27. Spagnolo P, Cozzi A, Foà RA, et al. CT-derived pulmonary vascular metrics and clinical outcome in COVID-19 patients. Quant Imaging Med Surg 2020;10:1325-33.
28. Klein R, Klein BE, Knudtson MD, Wong TY. Tsai MY Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. Arch Ophthalmol 2006;124:87-94.
29. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-18.
30. Song W-C, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest 2020;130:3950-53.
31. Hathcock JJ. Flow effects on coagulation and thrombosis. Arterioscler Thromb Vasc Biol 2006;26:1729-37.
32. Yuan Y, Wang Q-P, Sun D, Wu Z-B, Peng H, Liu X-W, et al. Differences in immune responses between children and adults with COVID-19. Curr Med Sci 2021;41:58-61.
33. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child 2020 Dec 1. archdischild-2020-320338.
34. Ignjatovic V, Mertyn E, Monagle P. The coagulation system in children: developmental and pathophysiological considerations. Semin Thromb Hemost 2011;37:723-9.
35. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323:2427-9.
36. Krawitz BD, Mo S, Geyman LS, et al. Acircularity index and axis ratio of the foveal avascular zone in diabetic eyes and healthy controls measured by optical coherence tomography angiography. Vision Res 2017;139:177-86.
37. Schilt-Catafal M del M, Pérez-Torregrosa VT, Duch-Samper AM. Relationship between peripapillary perfusion density, peripapillary flow index and traditional glaucoma measurements in open-angle glaucoma and ocular hypertension: an optical coherence tomography angiography study. Acta Ophthalmol 2021;99(S265):j.1755-3768. 2020.0164.