Photodiagnosis and Photodynamic Therapy xxx (xxxx) 103965

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Short Communication

Portable color retinography findings in COVID-19 patients admitted to the ward☆

Antônio Augusto de Andrade Cunha Filho MD[a,b], Perseu Matheus Pugliese Neto MD[a,b], Gabriela Hamra Pereira MD[a,b], Neuder Gouveia de Lima Filho MD[a,b], Luis Antonio Sakakisbara MD[a,b], Cássia Fernanda Estofolete MD, PhD[a,b,**], Maurício Lacerda Nogueira MD, PhD[a], Luiz Carlos de Mattos PhD[a], Cinara Cássia Brandão PhD[a,*]

[a] *Medicine School of São José do Rio Preto (FAMERP), São José do Rio Preto, SP, Brazil*
[b] *Hospital de Base Regional Medical School Foundation (HB-FUNFARME), São José do Rio Preto, SP, Brazil*

ARTICLE INFO

Keywords:
Portable retinography
COVID-19
Eye infection
Color retinography
Retina
Intraretinal hemorrhages

ABSTRACT

Retinal lesions, including cotton-wool exudates, microbleeds, vascular occlusions and vasculitis, occur in a minority of Coronavirus Disease-19 (COVID-19) patients. Retinal assessments using retinography can help document these lesions. The objective of this work was to identify retinal changes in patients admitted to the ward with a positive Real Time Quantitative Polymerase Chain Reaction (RT-qPCR) exam for COVID-19. A cross-sectional, observational study was carried out of patients with mild and moderate symptoms admitted to the Hospital de Base in São José do Rio Preto. The Eyer® portable retinal camera (Phelcom® Technologies) was used to evaluate 30 male and 21 female patients. The ages ranged from 21 to 83 years (mean: 47 years). Systemic arterial hypertension was identified in 21 (41.2 %) and diabetes mellitus in 12 (23.5 %) patients. Six (11.7 %) reported worsening visual acuity, however, none of these patients had ocular findings to justify this complaint. Ten patients (19.6 %) had intraretinal hemorrhages; one (1.9 %) had cotton-wool exudates and seven (13.7 %) had dilations of veins. Thirteen patients (25.4 %) had vascular tortuosity and six (11.7 %) had pathological arteriovenous crossings. Portable retinography is useful to evaluate patients admitted to isolation wards due to COVID-19. It is important to remember that some of the patients investigated had comorbidities like diabetic maculopathy and systemic arterial hypertension. Hence, some care should be taken in attributing these observations uniquely to COVID-19 infection.

1. Introduction

The pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a new betacoronavirus that was first identified in China in December 2019, has spread throughout the world leading to millions of deaths with several challenging clinical manifestations, prolonged recovery time and post-recovery complications [1,2]. The SARS-CoV-2 infection, similar to other coronaviruses, mainly presents flu-like symptoms such as fever, cough, and asthenia. Furthermore, patients may evolve with severe lung injury, frequently causing critical interstitial pneumonia, Acute Respiratory Distress Syndrome (ARDS) and subsequent multiorgan failure, which are responsible for severe acute respiratory failure and high death rates [3,4].

Although the respiratory system is most commonly affected, SARS-CoV-2 presents neurotropism and endothelial tropism and can cause a systemic inflammatory reaction, known as a “cytokine storm” [5,6]. Due to this tropism, a significant proportion of patients affected by COVID-19 present neurological and vascular manifestations. [1,7–11]

The proposed routes by which the virus enters the Central Nervous System (CNS) are: via the bloodstream to the cerebral circulation –

☆ This study was awarded as Best Poster Presentation - Residents Category during the USP Ophthalmology Congress 2021.

* Corresponding author at: Faculdade de Medicina de São José do Rio Preto – FAMERP, Avenida Brigadeiro Faria Lima, 5416, Vila São Pedro. CEP: 15090-000 - São José do Rio Preto, São Paulo, Brazil.
** Corresponding author at: Faculdade de Medicina de São José do Rio Preto – FAMERP, Avenida Brigadeiro Faria Lima, 5416, Vila São Pedro. CEP: 15090-000 - São José do Rio Preto, São Paulo, Brazil.
E-mail addresses: cassiaestofolete@gmail.com (C.F. Estofolete), cinara.brandao@edu.famerp.br (C.C. Brandão).

https://doi.org/10.1016/j.pdpdt.2024.103965
Received 21 November 2023; Received in revised form 5 January 2024; Accepted 8 January 2024
1572-1000/© 20XX

where slower blood flow may be favorable for the virus to infect the capillary endothelium – and by dissemination through the olfactory bulb. An extensive study into the pathogenesis of vascular events has led researchers to suggest that COVID-19 is a respiratory and also a vascular disease that causes severe endothelial disruption, complement activation and widespread inflammation leading to a general procoagulant state. Along with the CNS, several cases since the start of the pandemic have shown involvement of the neurosensory retina and optic nerve. [2,9,10]

Retinal lesions, including cotton-wool exudates, microbleeds, vascular occlusions and vasculitis, occur in a minority of COVID-19 patients [12,13]. Assessment of the retina through imaging studies, including color retinography, help document these lesions [13–18]. The objective of this study was to use portable color retinography to identify retinal changes in patients admitted to the ward who tested positive for COVID-19 by Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR). The device used to capture the imagens in this study is the Eyer@ portable retinal camera, one of many handheld digital ophthalmoscopes. It is a portable device connected to a smart phone. [19] In many parts of the world where an ophthalmologist may not be directly available, general practitioners can be taught to use these rather cheap uncomplicated devices. The quality images, obtained without dilation of the pupil, can then be communicated to an ophthalmologist for remote diagnosis or the images from the smart phone's camera can be sent via internet to be analyzed by a trained AI system for a preliminary analysis. [13,19–27] Such procedures in many cases may save time and save eyes. This approach can provide valuable insights into the ocular manifestations of COVID-19 and contribute to the understanding of the virus's impact on the eyes.

2. Material and methods

This work was approved by the Research Ethics Committee of the Medicine School of São José do Rio Preto (FAMERP) (CAAE protocol number 31588920.0.000.54125, approved on 1 June 2021). All participants agreed to participate in the study by signing an informed consent form. During July 2021, this cross-sectional study enrolled patients in Hospital de Base of São José do Rio Preto hospitalized for COVID-19, as confirmed by RT-qPCR.

The viral RNA was extracted using the QIAmp Viral RNA Mini Kit (QIAGEN) for RT-qPCR according to the manufacturer's protocols. Viral RNA of SARS-COV-2 was detected by TaqMan®-based Real-Time PCR (Promega) using a Center for Disease Control (CDC) protocol with two primer/probe sets which amplify the virus nucleocapsid (N) gene (2019-nCoV_N1 and 2019-nCoV_N2). The Human RNase P (RP) primer/probe set was included to detect the gene in control samples. [8,28] The results were analyzed in QuantStudio 3 software v1.5.1 (Thermo Fisher Scientific, USA) and interpreted as a cycle quantification value (Ct) less than or equal to 40 as positive and Ct greater than 40 as negative. [8] After pupil dilation, the Eyer® portable fundus camera (Phelcom Technologies®) was used for color retinography of the posterior pole. Patients who did not agree to participate in the study and those for whom good images were not possible, either due to non-collaboration or because of opaque medium, were excluded. Facts about ocular complaints during COVID-19, ocular history and comorbidities of each patient were investigated. Patients admitted to the intensive care unit were not evaluated.

3. Results

During July 2021, 30 male and 21 female patients with ophthalmologic manifestations related to SARS-CoV-2 were enrolled and evaluated in this study. Patient ages ranged from 21 to 83 years (mean age: 47 years). Systemic Arterial Hypertension (SAH) was identified in 21 (41.2 %) and Diabetes Mellitus (DM) in 12 (23.5 %) patients. Around half of the patients (26/51; 50.9 %) had already presented with ophthalmologic complaints prior to COVID-19 infection including the necessity of wearing glasses, visual loss, glaucoma, presbyopia and myopia.

Of the 51 patients, 6 (11.7 %) presented ophthalmologic concerns. Thirty-four (66.6 %) had alterations in the retinography; ten (19.6 %) had Intraretinal Hemorrhages (IRH); one (1.9 %) Cotton-Wool Exudates (CWE) and seven (13.7 %) had Venous Dilatations (VeD), as shown in Fig. 1. Thirteen patients (25.4 %) had vascular tortuosity and six (11.7 %) had pathological arteriovenous crossings; other findings are described in Table 1. Among the patients with altered retinography, only three (8.8 %) had reported ophthalmologic complaints. All were taking 6 mg/day dexamethasone and were being treated with prophylactic anticoagulation and oxygen therapy.

Furthermore, six patients (11.7 %) reported worsening visual acuity however, none of these patients had ocular findings that justified their complaint.

4. Discussion

The course of the disease for most COVID-19 patients is mild, however, approximately 20 % develop severe disease often associated with advanced age, comorbidities and immunosuppression resulting in a high mortality rate [4,29] especially in unvaccinated people. The most important symptoms of COVID-19 infection are fever (87.9 %), cough (67.7 %), fatigue (38.1 %), diarrhea (3.7 %) and vomiting (5.0 %), all of which are similar to infections by other coronaviruses. [3] However, there is already evidence that COVID-19 can cause damage to tissues and organs other than those of the respiratory system, including ophthalmologic manifestations [16,18,30]. This study describes 34 cases of ophthalmologic manifestations in hospitalized COVID-19 patients, for whom involvement of the retina was significant.

The pathogenesis of ocular tropism and damage in unclear but it may involve the Angiotensin-Converting Enzyme 2 (ACE-2) receptor and protein Transmembrane Serine Protease 2 (TMPRSS2) as targets for recognition and the binding of SARS-CoV-2 as reported by Hu et al. [31]. All parts of eye can be injured, including the retina, where ACE-2 and TMPRSS2 are highly expressed. [32]

Examination of the retina offers a unique opportunity to analyze these cases with special attention being paid to retinal vessels. Retinal veins passively enlarge in caliber due to impaired drainage, whereas arteries actively dilate in response to decreased oxygen (O_2) or increased carbon dioxide (CO_2). Additionally, both types of vessels can dilate under the effect of inflammatory mediators. [11] A 2020 study, in which retinas of COVID-19 patients were examined within 30 days after the onset of systemic symptoms, reported that both retinal arteries and veins were significantly larger compared to those of unexposed individuals. Furthermore, the diameter of the veins were even larger in the most severe cases and showed an inverse correlation with the time of onset of symptoms.

Along with vascular changes in COVID-19 patients, IRH and CWE, both common signs of retinal microangiopathy, were also found. Similar changes have recently been reported in a small number of COVID-19 patients. The authors described lesions in the inner layers of the retina using optical coherence tomography, a more sophisticated imaging technique than the funduscopic examination. However, concerns have been expressed by a large number of experts about the possible misinterpretation of these findings attributed to COVID-19 [10,17] It is difficult to say whether IRH and CWE are secondary to COVID-19 or just incidental findings, given the high prevalence of hypertension and DM in the cohort. [8] In this study no clear correlation was found between the presence of these retinal signs and comorbidities, but it is possible that the virus itself, the inflammatory response or the treatment has a stronger effect on patients with an already fragile microvasculature due to their underlying conditions.

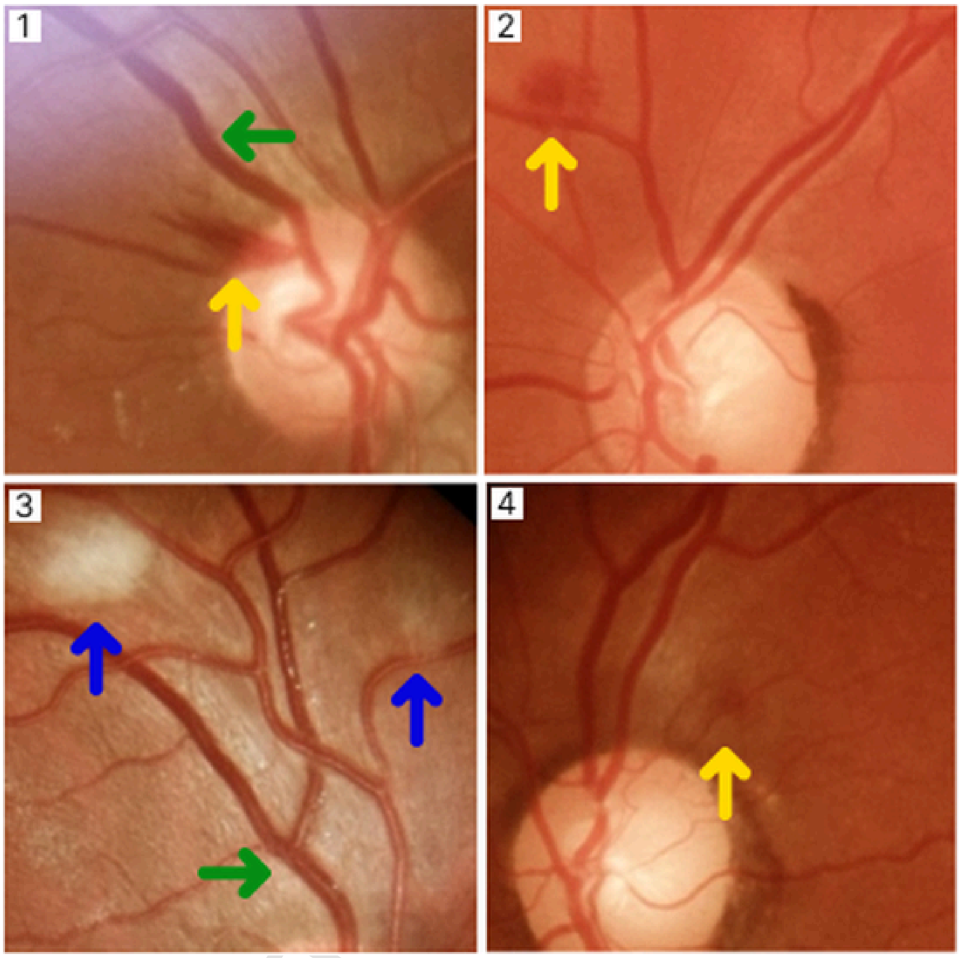

Fig. 1. Color fundus scans of eyes of patients with COVID-19 during their hospital stay. Yellow arrows: identify intraretinal hemorrhages; blue arrows: cotton-wool exudates; green arrows: venous dilations. According to the WHO COVID-19 severity classification, all patients presented as severe with Patients 2, 3 and 4 requiring supplemental oxygen therapy, while Patient 1 evolved with diabetic ketoacidosis, lung venous thrombosis and required support in the intensive care unit. These images were taken with the EYER@ portable retinal camera and were from different patients.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Main ophthalmological findings in COVID-19 patients in a teaching hospital ward, Brazil.

Findings	**n (%)**
Intraretinal hemorrhage	10 (19.6 %)
Cotton-wool exudate	1 (1.9 %)
Venous dilation	7 (13.7 %)
Vascular tortuosity	13 (25.4 %)
Pathological arteriovenous crossing	6 (11.7 %)

In the present study, of the 10 patients with IRH, eight (80 %) had SAH and/or DM. The patient with CWE had DM. Only one (14.2 %) of the seven patients with VeD had SAH and DM. A similar study reported 14.6 % of IRH and 3.1 % of CWE. [13] The limitation of these studies is that they are cross-sectional and cannot establish a cause and effect relationship between the findings and SARS-CoV-2 infection. Even so, they do not fail to present a detailed description of events of interest, including ophthalmological manifestations, in COVID-19 patients to the point of expanding knowledge of the health care team and developing a multidisciplinary nature to the clinical approach. Moreover, this study highlights the important role of portable retinography in detecting ophthalmological lesions at the bedside of patients with infectious diseases, as a cheaper and more practical exam than optical coherence tomography. An example of the use of a handheld fundus camera together with an in-built artificial intelligence algorithm has been published for use in Diabetic Retinopathy (DR), which is the main cause of vision loss in working persons. It was found that the Aurora fundus camera was effective in first-line screening of DR; it has been suggested that this could be used nicely in large screening efforts for DR. [21,23,26] Thus, exactly because of its portability and quality of images, the EYER@ is a good, cheap, hands-on option that can be used in the newborn intensive care unit, for children on wards and in any cases of isolation, as well as in field work, such as in campaigns to investigate eye diseases in the general population, among others.

5. Conclusion

Portable color retinography is useful in evaluating hospitalized patients isolated on wards due to COVID-19 infection. The findings found should not be directly attributed to the disease without further evidence, as they may be due to comorbidities, the medications used during treatment, the immunological response against the infection or be incidental findings. More studies are needed to better understand the results and should include larger sample sizes, longitudinal patient follow-up and multimodal assessment with the addition of methods, when it is possible, such as fluorescent retinography, fluorescein angiography, optical coherence tomography and optical coherence tomography angiography. On the other hand, using these last four technologies, in addition to the high cost, requires that the patient is healthy enough to be able to move around and be examined in a clinic where the equipment is installed, since they are not portable. Therefore, any assistive technology that is developed to provide portable, quality healthcare to patients in isolated situations, such as riverside populations, isolated native populations and populations without access to medical care, is always very welcome.

CRediT authorship contribution statement

Antônio Augusto de Andrade Cunha Filho: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Perseu Matheus Pugliese Neto:** Visualization, Methodology, Investigation, Formal analysis. **Gabriela Hamra Pereira:** Visualization, Methodology, Investigation, Formal analysis. **Neuder Gouveia de Lima Filho:** Visualization, Methodology, Investigation, Formal analysis. **Luis Antonio Sakakisbara:** Validation, Methodology, Data curation. **Cássia Fernanda Estofolete:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis. **Maurício Lacerda Nogueira:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition. **Luiz Carlos de Mattos:** Writing – review & editing, Validation, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Cinara Cássia Brandão:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest. The authors are solely responsible for the content of this work.

Data availability

No additional data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

This study was supported by São Paulo Research Foundation research grants (FAPESP 2020/04836-0 to MLN and 2020/06471-9 to LCM). The opinions, assumptions, and conclusions or recommendations expressed in this material are the responsibility of the authors and do not necessarily reflect the views of FAPESP.

Acknowledgements

The authors wish to thank Phelcom Technologies® for providing the Eyer® portable retinography.

References

[1] C. Brandão-de-Resende, A. Diniz-Filho, F. de Almeida Brito, D.V. Vasconcelos-Santos, SARS-CoV-2 and COVID-19 for the ophthalmologist, Clin. Exp. Ophthalmol. 49 (2021) 70–80, https://doi.org/10.1111/ceo.13877.

[2] M. Sen, S.G. Honavar, N. Sharma, M.S. Sachdev, COVID-19 and eye: a review of ophthalmic manifestations of COVID-19, Indian J. Ophthalmol. 69 (2021) 488–509, https://doi.org/10.4103/ijo.IJO_297_21.

[3] Z. Qi, Y. Yu, Epidemiological features of the 2019 novel coronavirus outbreak in China, Curr. Top. Med. Chem. 20 (2020) 1137–1140, https://doi.org/10.2174/1568026620999200511094117.

[4] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061, https://doi.org/10.1001/jama.2020.1585.

[5] R. de la Rica, M. Borges, M. Gonzalez-Freire, COVID-19: in the eye of the cytokine storm, Front. Immunol. 11 (2020) 558898, https://doi.org/10.3389/fimmu.2020.558898.

[6] R.K. Mehlotra, Chemokine receptor gene polymorphisms and COVID-19: could knowledge gained from HIV/AIDS be important? Infect. Genet. Evol. 85 (2020) 104512, https://doi.org/10.1016/j.meegid.2020.104512.

[7] F. Pichi, A. Invernizzi, W.R. Tucker, M.R. Munk, Optical coherence tomography diagnostic signs in posterior uveitis, Prog. Retinal. Eye Res. 75 (2020) 100797, https://doi.org/10.1016/j.preteyeres.2019.100797.

[8] C.C. Pacca, N. Zini, A.F. Versiani, E.E.de O. Lobl, B.H.G.A. Milhim, G.R.F. Campos, M.M. Moraes, T.M.I.L. dos Santos, F.S. Dourado, B.C. Marques, L.C. da Rocha, A.L. dos Santos, G.C.D. da Silva, L.G.P. Ruiz, R. Nicesio, F. Queiroz, A.F.N. Reis, N.S. da Silva, M.L. Nogueira, C.F. Estofolete, Follow-up of a hospital cohort during the first 3530 suspected cases of COVID-19 in Sao Jose do Rio Preto, Sao Paulo, Brazil, BioRxiv (2021), https://doi.org/10.1101/2021.02.04.429711.

[9] S. Sen, N.B. Kannan, J. Kumar, R.P. Rajan, K. Kumar, G. Baliga, H. Reddy, A. Upadhyay, K. Ramasamy, Retinal manifestations in patients with SARS-CoV-2 infection and pathogenetic implications: a systematic review, Int. Ophthalmol. 42 (2022) 323–336, https://doi.org/10.1007/s10792-021-01996-7.

[10] A. Invernizzi, A. Torre, S. Parrulli, F. Zicarelli, M. Schiuma, V. Colombo, A. Giacomelli, M. Cigada, L. Milazzo, A. Ridolfo, I. Faggion, L. Cordier, M. Oldani, S. Marini, P. Villa, G. Rizzardini, M. Galli, S. Antinori, G. Staurenghi, L. Meroni, Retinal findings in patients with COVID-19: results from the SERPICO-19 study, EClinicalMedicine 27 (2020) 100550, https://doi.org/10.1016/j.eclinm.2020.100550.

[11] R.S. Alonso, F.O.M. Alonso, B.F. Fernandes, V.O. Ecard, M.P. Ventura, COVID-19-related ocular hypertension secondary to anterior uveitis as part of a multisystemic inflammatory syndrome, J. Glaucoma 30 (2021) E256–E258, https://doi.org/10.1097/IJG.0000000000001835.

[12] F. Bertoli, D. Veritti, C. Danese, F. Samassa, V. Sarao, N. Rassu, T. Gambato, P. Lanzetta, Ocular findings in COVID-19 patients: a review of direct manifestations and indirect effects on the eye, J. Ophthalmol. 2020 (2020) 4827304, https://doi.org/10.1155/2020/4827304.

[13] P.M. Marinho, A.A.A. Marcos, A.M.C. Branco, A.C. Romano, V. Sakamoto, M.L. Matuoka, N.F. Moraes, A. Roque, P.F.G.M.M. Tierno, P.R.A. Ferreira, W.M. Mourad, P. Schor, M. Farah, R.B. Rosen, R. Belfort, H. Moraes Do Nascimento, COVID-19 retinal findings in patients admitted to intensive care units and wards, Ocul. Immunol. Inflamm. 29 (2021) 705–708, https://doi.org/10.1080/09273948.2021.1912362.

[14] A. Lecler, F. Cotton, F. Lersy, S. Kremer, F. Héran, Abnormal MRI findings of the orbital or visual pathways in patients with severe COVID-19: observations from the French multicenter COVID-19 cohort, J. Neuroradiol. 48 (2021) 331–336, https://doi.org/10.1016/j.neurad.2021.07.004.

[15] A. Lecler, F. Cotton, F. Lersy, S. Kremer, F. Heran, Ocular MRI findings in patients with severe COVID-19: a retrospective multicenter observational study, Radiology 299 (2021) E226–E229, https://doi.org/10.1148/RADIOL.2021204394.

[16] S. Abdolrahimzadeh, M. Lodesani, D. Rullo, A. Mariani, G. Scuderi, Overview of the retina and imaging in patients with severe acute respiratory syndrome coronavirus 2, Int. Ophthalmol. (2022) 3601–3610, https://doi.org/10.1007/s10792-022-02338-x.

[17] O.E. McGrath, T.M. Aslam, Use of imaging technology to assess the effect of COVID-19 on retinal tissues: a systematic review, Ophthalmol. Ther. 11 (2022) 1017–1030, https://doi.org/10.1007/s40123-022-00509-8.

[18] E. D'Alessandro, A. Kawasaki, C.M. Eandi, Pathogenesis of vascular retinal manifestations in COVID-19 patients: a review, Biomedicines 10 (2022) 2710, https://doi.org/10.3390/biomedicines10112710.

[19] F.K. Malerbi, R.E. Andrade, P.H. Morales, J.A. Stuchi, D. Lencione, J.V. de Paulo, M.P. Carvalho, F.S. Nunes, R.M. Rocha, D.A. Ferraz, R. Belfort, Diabetic retinopathy screening using artificial intelligence and handheld smartphone-based retinal camera, J. Diabetes Sci. Technol. 16 (2022) 716–723, https://doi.org/10.1177/1932296820985567.

[20] J.M. Nunez do Rio, P. Nderitu, R. Raman, R. Rajalakshmi, R. Kim, P.K. Rani, S. Sivaprasad, C. Bergeles, R. Raman, P. Bhende, J. Surya, L. Gopal, R. Ramakrishnan, R. Roy, S. Das, G. Manayath, T.P. Vignesh, G. Anantharaman, M. Gopalakrishnan, S. Natarajan, R. Krishnan, S.L. Mani, M. Agarwal, U. Behera, H. Bhattacharjee, M. Barman, A. Sen, M. Saxena, A.K. Sil, S. Chakabarty, T. Cherian, R. Jitesh, R. Naigaonkar, A. Desai, S. Kulkarni, Using deep learning to detect diabetic retinopathy on handheld non-mydriatic retinal images acquired by field workers in community settings, Sci. Rep. 13 (2023) 1392, https://doi.org/10.1038/s41598-023-28347-z.

[21] E. Midena, L. Zennaro, C. Lapo, T. Torresin, G. Midena, E. Pilotto, L. Frizziero, Handheld fundus camera for diabetic retinopathy screening: a comparison study with table-top fundus camera in real-life setting, J. Clin. Med. 11 (2022) 2352, https://doi.org/10.3390/jcm11092352.

[22] M.E. Martinez-Perez, A.D. Hughes, S.A.McG. Thom, K.H. Parker, N.W. Witt, Evaluation of a portable retinal imaging device: towards a comparative quantitative analysis for morphological measurements of retinal blood vessels, R. Soc. Open Sci. 10 (2023) 230065, https://doi.org/10.1098/rsos.230065.

[23] M. Lupidi, L. Danieli, D. Fruttini, M. Nicolai, N. Lassandro, J. Chhablani, C. Mariotti, Artificial intelligence in diabetic retinopathy screening: clinical assessment using handheld fundus camera in a real-life setting, Acta Diabetol. 60 (2023) 1083, https://doi.org/10.1007/S00592-023-02104-0.

[24] M.A.P. Vilela, A. Arrigo, M.B. Parodi, C.da S. Mengue, Smartphone eye examination: artificial intelligence and telemedicine, telemedicine and E-health. (2023). https://doi.org/10.1089/tmj.2023.0041.

[25] R.F.T. Gomes, L.F. Schuch, M.D. Martins, E.F. Honório, R.M. de Figueiredo, J. Schmith, G.N. Machado, V.C. Carrard, Use of deep neural networks in the detection and automated classification of lesions using clinical images in ophthalmology, dermatology, and oral medicine—a systematic review, J. Digit. Imaging 36 (2023) 1060–1070, https://doi.org/10.1007/s10278-023-00775-3.

[26] R. Robles, N. Patel, E. Neag, A. Mittal, Z. Markatia, K. Ameli, B. Lin, A systematic

review of digital ophthalmoscopes in medicine, Clin. Ophthalmol. 17 (2023) 2957–2965, https://doi.org/10.2147/OPTH.S423845.

[27] A. Pujari, G. Saluja, D. Agarwal, A. Sinha, A. P R, A. Kumar, N. Sharma, Clinical role of smartphone fundus imaging in diabetic retinopathy and other neuro-retinal diseases, Curr. Eye Res. 46 (2021) 1605–1613, https://doi.org/10.1080/02713683.2021.1958347.

[28] X. Lu, L. Wang, S.K. Sakthivel, B. Whitaker, J. Murray, S. Kamili, B. Lynch, L. Malapati, S.A. Burke, J. Harcourt, A. Tamin, N.J. Thornburg, J.M. Villanueva, S. Lindstrom, US CDC real-time reverse transcription PCR panel for detection of severe acute respiratory syndrome coronavirus 2, Emerg. Infect. Dis. 26 (2020) 1654–1665, https://doi.org/10.3201/eid2608.201246.

[29] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, The Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[30] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun, L. Xia, Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases, Radiology 296 (2020) E32–E40, https://doi.org/10.1148/radiol.2020200642.

[31] K. Hu, J. Patel, B.C. Patel, Ophthalmic Manifestations Of Coronavirus (COVID-19), (2022) In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32310553. http://www.ncbi.nlm.nih.gov/pubmed/32310553. (Accessed 18 July 2022).

[32] L. Zhou, Z. Xu, J. Guerra, A.Z. Rosenberg, P. Fenaroli, C.G. Eberhart, E.J. Duh, Expression of the SARS-CoV-2 receptor ACE2 in human retina and diabetes—implications for retinopathy, Investig. Ophthalmol. Vis. Sci. 62 (2021) 6, https://doi.org/10.1167/iovs.62.7.6.