



## Commentary

## Results from the SERPICO-19 study – the role of retinal evaluation and in vivo vascular assessment in COVID-19

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The results of the SERPICO-19 study [1] published in *EClinicalMedicine* suggest that regardless of comorbidities or treatments, patients exposed to the Sars-CoV-2 virus should have fundus evaluation, even though no visual complaints are described. In the SERPICO-19 study, 54 COVID-19 patients exhibited retinal findings, with retinal hemorrhages or cotton wool spots observed in 9,25% and 7,4%, respectively, of the subjects. As our previous publication in *The Lancet* [2] suggested, the retina may be a key place to study what happens to the rest of the body during and after the infectious course of COVID-19, as we are still trying to learn the extent of this new disease.

COVID-19 has been shown to cause significant microvascular alterations [3,4]. Fundus examination presents a unique opportunity to analyze microvasculature, specifically the retinal vessels, in a noninvasive way *in vivo*. Significant advances in the past decades have led to the development of technologies such as optical coherence tomography angiography (OCT-A), which allows an in-depth examination of the retinal layers, as well as the ability to reconstruct the vasculature without possible risks due to dye use [5]. However, one difficulty associated with this technique is how to perform these exams in an unresponsive patient, for example, in an intensive care setting. More recently, fundus pictures have been used to circumvent this issue, through the use of individual standardization measures according to the camera used and comparative measurement ratios [6]. However, the lack of a unique standard makes comparing different devices and results among different studies challenging.

Recent population-based studies have documented the subtle retinal vascular changes that occur in metabolic disorders such as

diabetic, hypertension, obesity and metabolic syndrome [7,8] providing a new understanding of the microvascular involvement in these disorders. It has now become evident that these retinal vascular changes might be markers of early, and even pre-clinical stages of metabolic disorders and may predict their clinical onset. Being predominantly automated and objective, these retinal structural analyses, can provide information regarding vascular changes, offering an exciting opportunity to study the potential to identify retinal microvascular abnormalities related to different pathologies.

In the context of the current pandemic, fundus pictures can be a way to assess patients whether an ophthalmologist is locally available or not, as most of the portable fundus cameras are focused on user experience irrespective of the operator's specialty, and data can be immediately available online. Although a correlation between the fundus manifestations and the systemic status has not been established, we know that cotton wool spots are considered sentinel lesions. These lesions are a sign of transient interruption of the axoplasmic flow, linked not only to mechanical etiologies but primarily to microvascular obstruction, a mechanism compatible with the hemorrhages described in fundus images and with other systemic findings, such as the higher prevalence of thromboembolic events, related to COVID-19. One question that arises is if we can somehow establish a parameter linking the augmented vessels diameter and the systemic severity; and, if so, could it be considered as a follow up routine relating to patient outcome? It is also important to mention that the SERPICO-19 study has shown that creatinine was the only variable that had a significant effect on arterial dilation, suggesting a possible link between renal microvascular lesions and ocular microvascular findings.

The use of retinal digital images analysis is becoming increasingly common and in association with artificial intelligence models offers newer and faster techniques to analyze different aspects of retinal vascular topography, including retinal vascular widths, geometrical attributes at vessel bifurcations and vessel tracking. We are currently witnessing those changes and the benefits of automation happening, but soon we will be able to track vascular parameters and use them to improve patient care. The SERPICO-19 study corroborates the importance of artificial intelligence and machine learning processes. The authors state that the software was able to detect vascular changes unseen by the human observer, providing a higher degree of sensitivity to the analysis.

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Overall the authors of the SERPICO-19 study should be praised on their successful efforts to establish preliminary parameters on retinal findings in a larger population than has been previously reported so far. The lack of correlation between the findings and comorbidities could be interpreted as a unique behavior of this still much unknown disease. Concerning the specific findings of the SERPICO-19 study, they are of major importance as openings for questions such as whether we can correlate vascular diameter as a phase marker. However, the study does not address whether those findings are a consequence of severe inflammatory pathology, as can be found in other diseases. Regardless, as more data is made available, we will be able to better understand the currently neglected role of fundus exam in diseases that are primarily non ophthalmological.

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The authors have nothing to declare.

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