Review 2: "Histopathological assessments reveal retinal vascular changes, inflammation, and gliosis in patients with lethal COVID-19"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

In the current document, Dr. Vijay K. Jidigam and colleagues (1) have evaluated a major concern about COVID-19, which is the risk for long-term consequences after infection. For this purpose, they have performed a comparative analysis of human eyes in an elegant ex-vivo evaluation of macroscopic (SLO and OCT imaging) and microscopic (epon-embedding and immunocytochemistry) case-control study. They have confirmed the presence of retinal changes described in several other reports in the macroscopic evaluation of the retina, and their document adds a microscopic description of COVID-19-related retinal derangement. Their findings justify with strong evidence their main conclusion and intention, which is to provide a rationale for evaluating the ocular physiology of patients that have recovered from COVID-19 to further understand the long-term effects caused by this virus. The retina is an accessible proxy for the central nervous system and Cotton wool exudates are a marker of vascular disease severity in other medical contexts, such as diabetes and hypertension, and are associated with an increased risk for acute vascular events not restricted to patients who complain of visual symptoms.

To date, COVID-19 has affected more than 120 million people worldwide (2), and universal screening for asymptomatic consequences seems unfeasible. An additional argument in favor of their approach is that not all COVID-19 infected subjects develop neurologic or visual symptoms, but among most severe cases, with pneumonia, the global pre-test probability (2 to 30%) might possibly be more accurately defined to about 20% (3), information that could be included in the manuscript. Whether COVID-19 acts synergistically with other diseases, such as diabetes, accelerating the neuro-ophthalmic vascular disease still requires further evaluation. The relevance of the in-vivo retinal evaluation is the possibility of identifying a population at risk that deserves a close follow-up. Most COVID-19 infected patients recover with no identifiable short-

term consequences, but the long-term repercussions of the infection are obviously unknown, especially considering the structural damage described in the current report. A non-invasive risk stratification might be a cost-effective strategy to select a subset of patients who deserve a close follow-up to promote preventive strategies (i.e. healthy lifestyle intervention) and/or early treatment of obesity and/or diabetes. Therefore, I recommend the acceptance of the document, with only the aforementioned minor suggestion, that is not even a concern.

References:

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2. COVID-19 Map - Johns Hopkins Coronavirus Resource Center [Internet]. [cited 2021 Mar 19]. Available from: <https://coronavirus.jhu.edu/map.html>
3. 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 [Internet]. 2021 Jan 1 [cited 2021 Mar 19];289(1):116–20. Available from: <https://pubmed.ncbi.nlm.nih.gov/32729633/>