Review 1: "Histopathological assessments reveal retinal vascular changes, inflammation, and gliosis in patients with lethal COVID-19"

Alessandro Invernizzi¹

¹Assistant Professor, University of Milan, Department of Biomedical and Clinical Science "L. Sacco", Italy

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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:

I read with interest this paper which focuses on a debated point and adds novel information that could be of interest for ophthalmologists and shed more light on the impact of COVID-19 on the ocular structures. Most of the findings are reliable and supported by good scientific evidence. By contrast, I found some of the presented data to be less accurate and I'd suggest the authors remove them from the paper.

Please find my comments below.

- The introduction is too long and the first two paragraphs are beyond the focus of this paper. We have read so much about COVID that there is no need to spend more than 10 lines explaining to the readers that it is the virus responsible for a pandemic. Instead, the authors should spend more time describing the changes that have already been published on the posterior segment of the eye in COVID-19. (e.g. SARS-COV-2 has been found on the histological section of the retina, REF #27 of the paper)
- The authors state that evidence of posterior segment involvement is scarce, apart from OCTA studies. This is not correct. The study they cite in reference #13 was not performed using OCTA technology.
- The authors should also mention and cite previous reports on retinal vascular occlusions in patients with COVID-19: (e.g. Ocul Immunol Inflamm. 2020 Nov 16;28(8):1290-1292. and Am J Ophthalmol Case Rep. 2021 Jun;22:101046.)
- The end of the introduction anticipates the results of the study. This is unusual. If this is not a specific request of the journal, then it should be avoided.

- The authors compared COVID-19 patients with aged-matched controls. They found several alterations in COVID-19 eyes, most of which are signs of inflammation. Despite it is very likely that COVID-19 was the actual cause of these inflammatory changes, it is also true that COVID-19 patients often suffer from other underlying conditions like systemic hypertension, diabetes among others, which can induce retinal alterations by themselves. Since the controls were not matched by characteristics other than the age, the difference cannot be ascribed with no doubt to SARS-Cov-2 infection. This is a major limitation and should be stressed by the authors.
- I've performed imaging on post-mortem eyes myself in the past and I know that the retinal and choroidal tissue ex vivo undergo many changes related to the lack of blood flow. In particular, the choroidal thickness decreases, and the retinal layers often show swelling due to intracellular edema. For this reason, the authors should avoid comparing these measurements between the groups. There are too many confounding factors that could lead to wrong conclusions. Please exclude this analysis from the paper as it is misleading.
- The authors report that some of the COVID-19 patients had intraretinal cysts. They also report that some of the COVID-19 patients had signs of vein occlusions. Were these the same eyes? Please clarify. While it is important to stress the fact that COVID-19 patients can be at risk for retinal vein occlusions, it is also important to distinguish signs that could be specific of COVID-19 versus signs that are secondary to conditions consequent to COVID-19. Retinal vein occlusion may be a consequence of COVID-19 and the edema a consequence of the stasis induced by the vein occlusion.
- The authors mention the alterations reported by Marinho et al at the level of the IPL. Please note that these findings have been proven not reliable by the following paper: Eye (Lond). 2020 Dec;34(12):2153-2154. Please modify the discussion accordingly.
- Did the authors look at the histology of large retinal vessels? Invernizzi et al reported changes in the size of both main arteries and veins in acute COVID-19 (REF: #13) and they found the veins diameter to be directly correlated with disease severity. Were the authors able to investigate the changes that could be responsible for this dilation?