Peer Review File

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Reviewer A

A very well-written review looking at histopathology features of severe COVID-19 patients based on whether they underwent mechanical ventilation. The authors identified a clear association between mechanical ventilation and certain histopathologies consistent with ventilator-associated lung injury in these patients. Though no conclusion can be drawn, I think the review will offer useful information which will aid further research into this topic. I only have some minor suggestions.

Comment 1. Line 184 "MV significantly increased the risk of fibrosis". The evidence presented may not be enough to draw a conclusion regarding causality. Association may be a better description.

Reply 1: The reviewer is right in stating that this regression analysis only provides an association between the examined variables and not a causal link. We accordingly changed this sentence and the other sentences in this paragraph.

Changes in the text:

- Page 9, Line 202: Besides, the multivariate analysis confirmed this association between MV and fibrosis (Table 4).
- Page 9, Line 207: After adjusting for age and gender, there still was a clear association of DAD or interstitial or intra-alveolar fibrosis and MV (Table 4).
- Page 10, Line 210: This pattern was significantly more frequent in MV patients (n=26) than in controls (n=12) (Table 3) with an odds ratio of 3.27 after multivariate analysis (Table 4).
- Page 10, Line 216: In MV patients, these vascular patterns were significantly more frequent than in controls (Table 3), with a 4 to 5-fold higher odds ratio when compared to the not-MV group (Table 4).

- Page 10, Line 220 (now page 10, line 222): Finally, multivariate analysis showed a significant association between MV and the combination of DAD and fibrosis and VD (Table 4).

Comment 2. As severe COVID-19 pneumonia, cytokine storm and other possible etiologies may cause some of these histopathologic features, this should be clearly stated

Reply 2: We agree with the reviewer that there are other possible explanations for the histopathological lung damage described. In order to stress this, we added this once more in the conclusion of the manuscript.

Changes in the text:

Page 14, Line 304: In this review, DAD was a predominant finding among patients suffering from severe COVID-19 pneumonia, with histopathological features in above 50% of cases. We identified that patients ventilated >24 hours had a significantly higher rate of pulmonary injury on histopathology independently of age and gender. Although Different mechanisms such as hyperinflammation, cytokine storm, massive SARS-CoV-2 replication, tissue invasion and vascular injury may also play a role in the histopathological patterns observed. Our findings suggest the importance of maintaining a protective ventilator strategy when treating subjects with COVID-19 pneumonia.

Reviewer B

Comment 1. In abstract (line 54). This is a retrospective observation, i.e. whether mechanical ventilation was playing a role in tissue and vascular injury, or vice versa the tissue and vascular injury from COVID-19 pneumonia was the cause leading to the use of mechanical ventilation, cannot be concluded in the study. Suggest to rewrite the abstract conclusion.

Reply 1: Thank you for raising this concern about the conclusion in the abstract. We

adapted the conclusion in order to be coherent with the conclusion in the manuscript and taking the comment of reviewer 1 into account.

Changes in the text:

Page 3, Line 624: We identified that patients mechanically ventilated >24 hours had a significantly higher rate of pulmonary injury on histopathology independently of age and gender. Our findings emphasize the importance of maintaining a protective ventilator strategy when subjects with COVID-19 pneumonia undergo intubation.

Comment 2 line 92. PAP with high TV. How high were the TV relative to IBW? Protective lung strategy has been the standard for decade, the authors could explain and discuss why high TV approach was prevailing in the study centers.

Reply 2: Several of the manuscripts included in this retrospective review did not indicate the specifications of the ventilation parameters. Therefore, we adapted the description of the ventilation in the materials and methods section, and we added this lack of knowledge regarding tidal volume and lung compliance as a limitation of the study. The conclusion still remains though that focus should be kept on a protective ventilation strategy.

Changes in the text:

- Page 6, Line: 106: A retrospective case-control literature review study was performed comparing histopathological patterns among COVID-19 patients with acute respiratory failure requiring positive airway pressure (PAP) ventilation (MV) 24 hrs or more vs a control group without MV (or for less than 24 hours).
- Page 13, Line 289 : Our study had some limitations. It did not identify peripheral biomarkers nor assessed specific immunological profiles in the lung. No correlation was done with the degree of hypoxemia, therapeutic interventions, ventilator settings such as tidal volume, lung compliance at intubation, steroids administration, viral load or sequencing SARS-CoV-2 variants.

Comment 3. DAD and fibrosis are common pathways among the diseased with ARDS

of other causes. It is multi-factorial and may or may not be associated with ventilator settings. The higher prevalence of DAD/fibrosis among MV patients cannot be directly linked to implication on ventilator settings.

Reply 3: Indeed, other mechanisms also play a role in the development of DAD and fibrosis. We therefore added these alternative explanations for these HP findings in the conclusion section.

Changes in the text:

Page 14, line 313: We identified that patients ventilated >24 hours had a significantly higher rate of pulmonary injury on histopathology independently of age and gender. Different mechanisms, such as hyperinflammation, cytokine storm, massive SARS-CoV-2 replication, tissue invasion and vascular injury may also play a role in the histopathological patterns observed. Our findings suggest the importance of maintaining a protective ventilator strategy when treating subjects with COVID-19 pneumonia.