

## Peer Review File

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### Reviewer A

Most pitfalls of the study have already been addressed in the limitation section of the study.

1. Survival was defined as an outcome in COVID patients with and without barotrauma. Did you also consider the other confounding factors such as sepsis or underlying diseases?

**REPLY:** Yes, survival was defined as one of the secondary outcomes. In multivariable analysis we found that some factors were associated with survival. We did consider some other factors like those you mention in your comment. We agree that it would have been beneficial to see the effect of those factors on survival. However, due to limited data available to us, we were not able to perform such analysis.

2. The total of 1176 patients admitted to your ICU were all COVID patients. Make sure to state it properly in the first paragraph of the result section.

**REPLY:** Thank you for this observation. We have now corrected it. PAGE 8, LINE 181-182.

3. The word data is a plural noun so "data are".

**REPLY:** Thank you for your comment. We have corrected this throughout the manuscript.

4. A paragraph suggesting vigilance on the early diagnosis of barotrauma or tight precautionary measures might be useful to the readers.

**REPLY:** Thank you for your suggestion. The paragraph regarding importance of early diagnosis and tight precautionary measures is now added in Discussion section, PAGE 14, LINE 341-351.

### Reviewer B

Thank you for conducting this work. Many articles raised the point of barotrauma in COVID-19. The question remains how much it impacts the outcome and to which extent is it different than barotrauma in other ARDS?

1. The introduction can be shortened

**REPLY:** Thank you for your suggestion. The introduction is now shortened as suggested.

2. Line 63: I do not agree with 'Invasive ventilation is not the last step' as patients can be managed by ECMO.

**REPLY:** Thank you for your observation. We agree that this statement did not take into consideration use of ECMO. We have changed the statement in the revised manuscript as follows: "*Invasive methods of ventilation were considered to be as one of the last steps of treatment.*" PAGE 3, LINE 74-75.

3. Line 104: Should clarify if mechanical ventilation includes both invasive and non-invasive, any or both.

**REPLY:** Thank you for your comment. In the paragraph right before, we explained what was considered as non-invasive and what was considered as invasive respiratory support: *“For the purpose of this study, subjects on non-invasive respiratory support were defined as those who were treated with HFNC or CPAP masks. Invasive respiratory support was defined as intubation and mechanical ventilation”*. Therefore, term mechanical ventilation refers to invasive ventilation only.

4. Line 105: In my opinion it is not advisable to include Nasal cannula and face mask under non-invasive ventilation as this can be confusing for the readers and furthermore more systematic search and reviews. Terminology should remain the same across medical literature.

**REPLY:** Thank you for your comment. We agree with the reviewer that this terminology can be confusing. We have made changes to that paragraph as suggested: *“For the purpose of this study, subjects on non-invasive respiratory support were defined as those who were treated with HFNC or CPAP masks. Invasive respiratory support was defined as intubation and mechanical ventilation”*. PAGE 5, LINE 121-123.

5. Line 115: Exclusion criteria: Please do not repeat the opposite of inclusion criteria

**REPLY:** Thank you for your comment. We have modified the paragraph as suggested: *“Subjects who were readmitted to the ICU, subjects who spent less than 24 hours in the ICU and those who developed barotrauma before ICU admission were excluded from the study.”* PAGE 6, LINE 136-137.

6. Line 137: Do you mean PFR expressed as mmHg? Can you revise this point please?

**REPLY:** Thank you for your comment. We meant that PFR is expressed as mmHg. This is now revised in the manuscript as suggested: *“ $PaO_2/FiO_2$  ratio was calculated by dividing  $pO_2$  from arterial blood gas analysis with fraction (percent) of  $O_2$  that subject was receiving.  $PaO_2/FiO_2$  ratio is expressed in mmHg.”* PAGE 6, LINE 156-157.

7. I would expect the time of diagnosis of barotrauma was the first imaging/clinical exam on notes as this retrospective work. Are you doing daily X-ray? Do you think there may be a delay in diagnosing some barotraumas?

**REPLY:** The reviewer is right. Time of diagnosis of barotrauma was the first time it was observed on clinical exam or imaging study. X-ray was routinely done every 3-5 days but not on daily basis. Every patient was routinely checked couple of times a day and X-ray was done if the attending physician considered it of use. Of course, we cannot exclude the possibility that a delay in diagnosis of some cases of barotrauma occurred. However, since patients were checked on regularly, and in case of any suspicion about barotrauma occurrence an X-ray was done, we believe that this delay would not present in more than few cases. This is now added as one of the study limitations. PAGE 15, LINE 365-369.

8. Just to confirm my understanding that all included barotrauma took place after intubation (invasive mechanical ventilation). It is interesting to know there was 4 cases (flow chart) during non-invasive resp support but it seems this was not the objective of the study despite it can give support to P-SILI concept (probably you did not include more cases on NIV not escalated to ICU)

**REPLY:** The reviewer is correct, all barotrauma in our study took place after intubation while patients were on mechanical ventilation. We agree that analysis of barotrauma cases occurring on non-invasive respiratory support would be useful and interesting, especially taking P-SILI into consideration. COVID-19 department was organized in a way that patients who were on non-invasive respiratory support were treated on hospital wards, and only patients who needed invasive respiratory support were admitted to the ICU. Unfortunately, we did not have enough data on patients treated outside of ICU and we do not know if there were more than these four patients developing barotrauma while on non-invasive respiratory support. However, this would be an interesting topic for some future research.

9. In my opinion, what is sought by interested readers regarding barotrauma would be: How much barotrauma contributes to the outcome (association vs causation). In your work patients who developed barotrauma had worse outcomes but is this due to more severe disease requiring more aggressive treatment? Or barotrauma by itself worsens the outcome? In this context, propensity match score and analysis can be of help.

**REPLY:** Thank you for your comment. Incidence of barotrauma was the primary outcome of our study. Therefore, we primarily analyzed factors associated with its occurrence. It is possible that one of the reasons for worse outcomes, other than barotrauma, was more severe disease as patients in barotrauma group had lower PF ratio compared to control group. Furthermore, since all patients were treated according to principles of protective ventilation, we don't think that some of the patients were treated more aggressively than others. We performed a multiple logistic regression analysis and we found that barotrauma, as well as some other factors, was not associated with survival outcome. Results of this analysis is added to Results section. PAGE 9, LINE 217-225.

10. In case it is part of the pathophysiology of COVID, this can make another point how CARDS is different than other ARDS. You may be able to visit this point by comparing incidence of barotrauma with what is reported in the literature for other ARDS.

**REPLY:** Thank you for your comment. In the revised manuscript we compared incidence of pulmonary barotrauma between non-COVID ARDS with COVID ARDS. *“The reported incidence is higher than the incidence of barotrauma in patients with ARDS not related to COVID-19 (3% to 15%). When ARDS occurs due to other etiology, lung injury is proportional to severity of the illness, level of lung edema and the capacity of the lung for gas exchange. On the other hand, COVID-19 ARDS is a sum of several complex pathophysiological mechanisms such as excessive inflammatory response and changes on cellular level (dysregulation of ACE2 receptors).* PAGE 10-11, LINE 251-257.

11. If it is secondary to more aggressive treatment, this may mean those cases would need

stricter lung protective strategy and may be early escalation for ECMO when feasible. Unfortunately, ventilator settings are not available. It would be of benefit if available to know the impact of some treatment like neuro-muscular blockers and steroids on the incidence of barotrauma.

**REPLY:** Since all patients were subject to protective ventilation according to guidelines, we do not think that some of them were treated more aggressively. However, we agree that in certain cases a stricter protective strategy could have been beneficial as well as early use of ECMO. Unfortunately, as stated in study limitations, we do not have ventilator settings available. Regarding the impact of neuro-muscular blockers and steroids, since the great majority of patients were admitted to ICU due to severe ARDS, all of those cases were receiving corticosteroid therapy during their stay. Unfortunately, due to limited resources and availability of data, we are unable to analyze the impact of neuro-muscular blockers on barotrauma incidence.

12. The second paragraph of the conclusion ‘COVID-19 ARDS is a condition .....’ Is a general statement and does not reflect the work and I advise to remove it.

**REPLY:** This paragraph is removed from revised manuscript as suggested.

13. Table 1: do you mean that the incidence was significantly less in males? Any thoughts about that?

**REPLY:** There is difference in proportion of male patients in barotrauma compared to control group. However, in logistic regression analysis there was no correlation of gender and barotrauma incidence.

## Reviewer C

In this retrospective observational cohort study, the authors aimed to investigate the incidence of barotrauma among COVID-19 patients treated in the ICU and to examine different clinical outcomes among those subjects. They reported that overall incidence of barotrauma complications was 9.8%. Patients who developed barotrauma spent longer time on invasive ventilation and had longer ICU and hospital stay compared to control group. They also had significantly lower survival rate at hospital discharge.

1. This retrospective study has some shortcomings. What is the power of the study? It would be better if the sample size was calculated according to the primary endpoint.

**REPLY:** Since this was a retrospective study with defined sample size and very little, we could do about that, we did not do sample size calculations before. In post-hoc power analysis, we calculated that expected incidence of barotrauma would be 15% based on previous published literature on similar population. We calculated the probability of type I error to be 0.05, and calculated post-hoc study power was 99.8%.

2. It would be better if the causes of the development of barotrauma, its relationship with mechanical ventilation settings, and recommendations for its prevention were also discussed. This topic has been covered in some publications. For example: Eroglu A. Barotrauma in mechanically ventilated patients with COVID-19. *Minerva Anestesiol* 2021;

87:144-6. Doi: 10.23736/s0375-9393.20.15378-1. (Barotrauma causes prolonged stay in the ICU and the risk of morbidity and mortality in the mechanically ventilated patients with covid-19. If high tidal volumes and the ventilator setting pressures of peak, plateau, driving and PEEP are avoided, the risk of barotrauma in the mechanically ventilated patients can be markedly reduced, and barotrauma may be dependent on the underlying medical condition of the patients rather than the setting of ventilator parameters for COVID-19. ARDS, pulmonary embolism, pulmonary infarctions, the necrosis of pneumocytes and pulmonary fibrosis may facilitate the development of barotrauma with pulmonary parenchymal damage in the covid-19 patients. In order to reduce the risk of barotrauma in mechanically ventilated COVID-19 patients, peak inspiratory pressure, positive end-expiratory pressure, tidal volume, plateau pressure and driving pressure slightly lower than our current practice may be recommended.)

**REPLY:** Thank you for your comment and suggestion. Unfortunately, since we do not have data on ventilator settings available, we are unable to discuss the impact of those settings on barotrauma occurrence. All of our patients were treated according to guidelines for protective ventilation. Despite that, in some cases barotrauma did occur. It is possible that COVID-19 does damage to the lungs which makes those patients more susceptible to barotrauma despite protective ventilation. We have added this to the Discussion as suggested. PAGE 13-14, LINE 329-340.

#### **Reviewer D**

I have carefully reviewed the authors manuscript titled "Barotrauma in patients with severe Coronavirus disease 2019 – retrospective observational study" and would like to provide my feedback. Overall, I find that the study is a pure descriptive study.

However, I have several concerns that I believe should be addressed in order to enhance the impact and relevance of the work. My comments are outlined below:

##### **Study Design and Nature:**

1. It is evident from your manuscript that the study is purely descriptive and retrospective in nature. While retrospective studies can provide valuable insights, it is important to ensure that they offer novel perspectives, innovative methodologies, or significant contributions to the existing literature. Unfortunately, based on my assessment, the study does not bring forward any new knowledge or findings that would substantially add to the published literature on this topic.

**REPLY:** Thank you for your comment. We believe that this study is a contribution to the field of research regarding the impact of COVID-19 on pulmonary complications in patients with severe forms of this disease who were treated in ICU. We have treated and included in this study relatively high number of patients and we analyzed association of certain factors and incidence of barotrauma, as well as factors associated with survival at hospital discharge. Shrestha et al. wrote systematic review and meta-analysis of pulmonary barotrauma in COVID 19. As a part of their meta-analysis they compared 15 observational studies related to COVID 19 and the development of pulmonary barotrauma. Highest number of study subjects was in the study conducted by McGuinness et al. (601). Other studies were conducted on much lower number of subjects (from 20 to 343). *Shrestha DB,*

*Sedhai YR, Budhathoki P, et al. Pulmonary barotrauma in COVID-19: A systematic review and meta-analysis. Ann Med Surg (Lond). 2022;73:103221.*

**Originality and Contribution:**

2. The reader cannot find any substantial addition to the existing literature in the given manuscript. It would greatly benefit the study if the authors could emphasize the novel aspects of their research or present unique interpretations that can advance the field.

**REPLY:** We have modified the Discussion section and put more emphasis on interpretation of results in terms of need for more protective ventilation protocols or earlier application of ECMO as suggested. PAGE 14, LINE 345-351.

**Practical Implications and Implementation:**

3. While it is commendable that the authors have transparently reported some limitations, it raises concerns about the practical implementation of their study's findings. It would be valuable if they could further discuss the potential implications of these limitations and offer suggestions for future studies that could address these issues and lead to actionable changes in clinical practice.

**REPLY:** Thank you for your comment. We have modified the Limitations section as suggested. PAGE 14-15, LINE 351-373.

**Reviewer E**

**METHODS**

1. Please better indicate the inclusion and exclusion criteria

**REPLY:** Thank you for your comment. Inclusion and exclusion criteria are now more clearly defined as suggested. PAGE 5-6, LINE 116-120, 136-137.

**RESULTS:**

2. line 177 in the description of the results, refer to the type of non-invasive support: I think the type of non-invasive ventilation and the ventilation methods should be specified very well in the two groups.

**REPLY:** Thank you for your suggestion. The results section is now modified as suggested: *“Sixty-four patients (72.7%) from barotrauma group received HFNC and 2 patients (2.3%) were on CPAP prior to ICU admission. In control group, 546 patients (67.2%) were on HFNC and 21 patients (2.6%) were on CPAP prior to ICU admission. There was no difference between two groups regarding the type of non-invasive respiratory support before mechanical ventilation”*. PAGE 8-9, LINE 201-208.

3. I also suggest you indicate your pronation protocol otherwise it remains a very generic indication

**REPLY:** Thank you for your comment. Pronation protocol is described in Methods section as suggested: *“In cases where ventilation targets could not be achieved during first hours after ICU admission despite the described measures, patients were ventilated in prone position for at least 12 h. Contraindications for prone positioning were recent cardiac,*

*abdominal or thoracic surgery, burns, pregnancy, unstable fractures and spinal instability*". PAGE 5, LINE 129-133.

#### DISCUSSION

4. line 224. I advise you to eliminate this conclusion regarding the explanation of the low incidence of barotrauma in your center: it is not supported by any data therefore it is not scientifically relevant

**REPLY:** Thank you for your comment. The explanation is now removed as suggested.

#### CONCLUSION:

5. I suggest you indicate in the conclusions the retrospective and single center nature of the study which does not allow for such "strong" conclusions

**REPLY:** The Conclusion section is now changed as suggested. PAGE 16, LINE 376.

6. Regarding the cause of the barotruma there is a lot of evidence (which I invite you to review) on the correlation between the Macklyn effect and the onset of barotruma in mechanically ventilated patients with COVID. I suggest you write a paragraph on this topic *Respir Med.* 2022 Jun;197:106853. doi: 10.1016/j.rmed.2022.106853. Epub 2022 Apr 20.

**REPLY:** Thank you for the suggestion. The paragraph is now added to Discussion section as suggested. PAGE 14, LINE 341-344.

7. I also suggest you to write a visual abstract of your manuscript; it makes reading your paper more captivating.

**REPLY:** Thank you for your comment. We wrote visual abstract for our manuscript.

#### Reviewer F

I read with attention the study entitled: Barotrauma in Patients with Severe Coronavirus Disease 2019 – a retrospective observational study.

1. Please move the following sentence to the end of the M&M after the ethics committee.
2. Line 94-95, page 5 - We present this article in accordance with the STROBE reporting checklist.

**REPLY:** Thank you for the suggestion. The sentence has been moved as suggested. PAGE 7, LINE 177.

3. Results page 10, line 193 please delete the word sex from the text and table and substitute it with Gender.

**REPLY:** Thank you for your suggestion. The word sex is now changed to gender as suggested.

4. Discussion: Please implement the debate with these references:

Cammarota G, et al. Advanced Point-of-care Bedside Monitoring for Acute Respiratory Failure. *Anesthesiology.* 2023 Mar 1;138(3):317-334. doi:

10.1097/ALN.0000000000004480. PMID: 36749422.

Vetrugno L, et al. Ventilatory associated barotrauma in COVID-19 patients: A multicenter observational case control study (COVI-MIX-study). *Pulmonology*. 2022 Nov 24:S2531-0437(22)00260-4. doi: 10.1016/j.pulmoe.2022.11.002. Epub ahead of print. PMID: 36669936; PMCID: PMC9684110.

Belletti A, et al. P-SILI in critically ill COVID-19 patients: Macklin effect and the choice of noninvasive ventilatory support type. *Crit Care*. 2023 Jan 24;27(1):38. doi: 10.1186/s13054-023-04313-z. PMID: 36694214; PMCID: PMC9873207.

**REPLY:** Thank you for your suggestion. The Discussion section is now changed and the references are added to the Discussion section PAGE 13-14, LINE 329-340.

5. An essential English revision is needed.

**REPLY:** Thank you for your comment. We did an English language revision as suggested.