

## Peer Review File

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### Reviewer A

This is an observational study in which the authors describe pneumothoraces in 60 patients out of a cohort of 138 consecutive patients with PCR-confirmed COVID-19 infection. Underlying lung pathology was graded into stages and pneumothorax was graded into stages. The authors conclude that underlying lung pathology was not associated with an increased risk of pneumothorax.

**Comment 1: Title could be better described to focus on the severity of lung disease, mechanical ventilation, or incidence of pneumothorax, instead of focusing on "visceral pleura". Does not seem pertinent to the manuscript.**

**Reply 1:** Thank you for your observation, recommendation accepted, title adjusted according to your suggestion. Choosing a title was indeed not easy to capture the essence of the article as well as grab the attention of potential readers. Our goal for the title was not to focus on the connection between ventilation and barotrauma since that is evident and not of primary importance from the point of view of the article. Rather our goal was to focus on the possibility of developing pneumothorax and pneumomediastinum (which in light of the results did not meet the preliminary expectations based on previous literature reports, namely that patients with pre-existing lung pathology have a higher chance of barotrauma).

**Changes in text:** In accordance with the suggestion, the title was changed to Pneumothorax/pneumomediastinum and pre-existing lung pathology in ventilated COVID-19 patients: a cohort study. (see page 1, line 2-3)

**Comment 2: Methodology needs to be described better. It is unclear how the data was collected and stratified into groups.**

**Reply 2:** Thank you very much for your comment, methodology was amended. The medical history of all patients included in the study was checked for previously diagnosed and treated chronic lung disease and pulmonary medical care medication type and duration. The most relevant data was the pre-existing pathological lung parenchyma confirmed by CT as we assumed that among patients who have suffered from barotrauma, there would also be cases of chronic lung disease that have not been treated but are positive based on the CT image. The assessment of the severity and stage of the lung disease was based on specifically the extent of the pathological lung area and not on the respiratory function or gas exchange.

**Change in text:** We modified the text as follows in accordance with your suggestion:

All records of the patients included were evaluated with the Hungarian patient-specific (Health Insurance Number coded) electronic database. The analysis was secured by full anonymization protocol. As far as the CT images are concerned, ... (see page 4, line 20-23)

**Comment 3: The grading of pneumothoraces also appears immaterial to the study – simply focusing on the presence of absence of pneumothorax may be sufficient.**

**Reply 3:** Thank you for pointing this out. From a thoracic surgical point of view, it is particularly important to differentiate between the type, the extent, and the completeness of the given pneumothorax. We found that in “Grade 1 and 2” pneumothorax cases - which developed along the chest wall - the formation of pneumothorax did not significantly impair gas exchange, its drainage did not significantly improve the gas exchange and the lungs did not expand even on active chest suction. In the discussion, we also described this observation in connection with the surgical management of pneumothorax. From this point of view, the differentiated approach to the pneumothorax phenomenon is an important contribution and a possible question to investigate in subsequent studies. Therefore, we would prefer to keep the text as it is, without alteration.

**Change in text:** none

**Comment 4: Conclusions: The authors conclude that air leaks may be related to underlying lung disease rather than barotrauma - the evidence provided in results is not enough to support the conclusion.**

**Reply 4:** Thank you for your comment. This is a report on a highly unusual phenomenon: pre-existing lung pathology did not predict pneumothorax, it is not a multiplier risk factor in this group of patients. In our study, we tried to find an acceptable explanation. Barotrauma due to high end-inspiratory pressure is part of the canon. The same hypothetical barotrauma was exposed to both groups of patients (with or without pre-existing lung pathology) and the pre-existing lung pathology did not make their tissue more fragile resulting in pneumothorax. Hopefully, our observation will generate further research, which could improve the validity of our observation. Our parallel review of the medical history and CT images of ventilated patients treated in the non-COVID ICU during the same period (case number 156), did not reveal a particular case of pneumothorax. The problem is the heterogeneity of the two groups; therefore, no statistical analysis was involved. Extending our study in this direction with a third prong would make the research unmanageable without increasing the validity. Among the complications of modern respiratory therapy, barotrauma rarely occurs, and nowadays the primary aim of ventilation therapy is to avoid volutrauma rather than barotrauma.

**Change in text:** The following sentence was added for further clarification: The evidence provided needs further confirmation in the alveolar barotrauma versus visceral pleura vulnerability debate sparked by the authors (see page 9, line 19-21).

**Comment 5: Discussion: the description of rationale for not seeing increased air leaks in underlying lung disease seems like a stretch. More evidence needs to be included to support the points raised, with references.**

**Reply 5:** Thank you for your observation, we absolutely agree with your comment. The COVID-19 pandemic resulted in a large number of homogeneous patient groups in health care systems which also multiplied the rarely occurring phenomenon of barotrauma in intensive care units. When we looked at only the studies confirming the relationship between existing lung disease and barotrauma associated with ventilation, then chronic lung disease was found to be a risk factor for barotrauma. We found that pneumothorax or pneumomediastinum occurred in a higher proportion among the COVID pneumonia patients who needed ventilation and who did not have chronic lung disease in the first place. This clinical observation was confirmed by highly sophisticated statistics. We found no literary data or research on the mechanism of pneumothorax formation in Covid-19 caused pneumonia. The two mutually not exclusive explanation shows only potential mechanisms of formation. Proof of these explanations would need further investigation, which was not the aim of this study.

**Change in text:** We have made the following clarification in the text: A similar pattern was recently identified in blunt liver trauma [22] (see page 8, line 11-12) ...and by our own biomechanical experiments [31,32] ]: resistance of resected pleural bullae walls up to 1938 cmH<sub>2</sub>O against pressure is another strong evidence against barotrauma caused PTX in ventilated patients [32]. (see page 9, line 5-7)

**Comment 6: The authors acknowledge some of the obvious limitations of this study – single center, small numbers, expert opinion-based management of the cases and change in management strategies over the course of the study period.**

**Reply 6:** Thank you. We agree that there are obvious limitations to this study. That is why we applied extensive biostatistical analysis. The extensively delivered statistical apparatus applied by us must safeguard against false generalization and other traps of bias. Hopefully, the reviewer is convinced by the quality of our calculations and the validity of the observations.

**Change in text:** none

**Comment 7: References appear inadequate and a more robust literature search is warranted.**

**Reply 7:** Thank you for your comment. Further references were included as requested.

**Change in text:** We have included the following references: Rajdev et al. 2021, Belletti et al. 2021, Shrestha et al. 2022, Zsoldos et al. 2017, Yang et al. 2020, Simon et al. 2020, (see References)

**Comment 8:** Some minor grammatical and typographical errors were noted. Please proof-read the manuscript for language corrections.

**Reply 8:** Thank you for your observation and we apologize.

**Change in text:** The grammatical and stylistic errors have been corrected in several places in the text.

## **Reviewer B**

The authors demonstrated that pre-existing lung pathology does not increase the risk of the onset of pneumothorax or pneumomediastinum in corporation with previously healthy lungs of ventilated COVID-19 patients. This study is an interesting observation. However, my main scientific concern is that the data are over-interpreted. The manuscript also would be improved by a thorough English language review before acceptance for publication. Thus, a major revision is needed before it can be accepted for publication.

Major comment>

**Comment 1: The authors evaluated pre-existing lung pathologies with only CT images. Could you show other data such as medical history and physical examination, ABG?**

**Reply 1:** Thank you very much for your comment. Data about medical history, physical examination, and ABG was and is readily available for us in the electronic patient dataset which we referred to on page 4 line 8. Should any of these data be necessary for better understanding and justifying our results, we could include further clarifications. Furthermore, we would like to emphasize that our goal – irrespective of patient history – was to detect pre-existing lung pathologies in patients before COVID-19 infection with CT scans. However, because for a number of patients, these pathologies or any lung diseases have not been diagnosed and thus treated and registered.

**Changes in text:** None. Upon request, further data will be included.

**Comment 2: As the authors also stated, the study's population is too small. Therefore, I am concerned that the analysis results may be misleading.**

**Reply 2:** Thank you for your comment! It always means a major problem in clinical studies how large sample does the study require. According to the latest literature, its number varies in a wide scale. Since we have designed a retrospective cohort study, we had the limitation of the number of cases attended in our medical facility and matched the previously set up criteria.

We have tested the desired sample size before the data collection and the statistical analysis to have the confidence to run the analyses. According to our results, the minimum sample size for the Cox-regression was 54 cases, the minimum sample size

for logistic regression was 53 cases. For the Spearman correlation, the minimum sample size was 52 cases.

**References:**

Abramowitz, M. and Stegun, I.A., eds. (1965). Handbook of Mathematical Functions. New York, NY: Dover.

Caharan, J. and Biswas, T., 2013. How to Calculate Sample Size for Different Study Designs in Medical Research? Indian Journal of Psychological Medicine Volume 35(2); Apr-Jun 2013.

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd Edition). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cohen, J., Cohen, P., West, S.G., and Aiken, L.S. (2003). Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences (3rd edition). Mahwah, NJ: Lawrence Earlbaum Associates.

Soper, D.S. (2022). A-priori Sample Size Calculator for Multiple Regression [Software]. Available from <https://www.danielsoper.com/statcalc>

**Changes in text:** The following sentence was added to the manuscript for further clarification: Therefore, higher case number or data from more centres would be beneficial. (see page 9, line 9-10)

**Comment 3: The authors should describe in detail the parameters of ventilation.**

**Reply 3:** Thank you very much for your comment. You have raised an important point here. The ventilation strategy is indeed of fundamental importance when examining the incidence of barotrauma. Since the method and parameters of ventilation can be changed from hour to hour depending on changes in gas exchange, the parameters of ventilation were fixed, but not analysed. In accordance with the request, we would like to integrate this into the text.

**Change in text:** We have added the following clarification to the manuscript as requested: Based on the currently valid evidence in ARDS ventilation strategy, we tried not to exceed the maximum end-inspiratory pressure of 30-35 mbar. Depending on lung compliance, allowing permissive hypercapnia, we set a tidal volume of 6 mL/kg. Basically, we used pressure-controlled ventilation or airway pressure release ventilation [17]. (see page 4, line 13-17)

**Minor comment>**

**Comment 4: P4, L14-16. Please replace “1, 2, 3” with “I, II, III”.**

**A**

**Reply 4:** Thank you for your observation. Indeed, there is a mistake there. However, it is not concerning the use of numbers. The text on page 4 line 14-16 was supposed to refer to the severity of the PTX indicated by “Grade 1,2,3” as shown in table 2, but by mistake, we referred to it as “Stage 1,2,3,”.

**Changes in text:** “stage” was replaced by “Grade” to indicate the severity of PTX (see page 5, line 3-6)

**Comment 5: P5, L24. Please replace “,” with “.”.**

**Reply 5:** Thank you for your comment, changes applied.

**Changes in text:** 16.16 vs 23.25 % (see page 6, line 16-17)

## **Reviewer C**

**Comment 1: Abstract Page 2 Line 2- is to be replaced by are**

**Reply 1:** Thank you, however, I disagree with the suggested correction since the subject of the sentence (number) and the predicate (is increasing) correspond with each other so we assume, the sentence is therefore correct.

**Changes in text:** none

**Comment 2: 4- increases**

**Reply 2:** I agree, thank you very much for your observation. It has been corrected.

**Changes in text:** increase replaced by increases (see page 2 line 6)

**Comment 3: Page 3 Introduction line 2- 150 year old can possibly be omitted**

**Reply 3:** Thank you very much. I completely agree. Changes have been made.

**Changes in text:** “150-year-old diagnosis” was omitted from the text (see page 3, line 4)

**Comment 4: Line 5- or else seems an abrupt conclusion of the sentence please modify**

**Reply 4:** Thank you. Indeed, the ending is abrupt. We have made the necessary corrections.

**Changes in text:** The sentence has been rewritten as follows: “...by some underlying chronic pathology such as bullous emphysema.” (see page 3, line 7)

**Comment 5: Page 4- line 1- gave permission can be replaced with approved**

**Reply 5:** Thank you. I agree, it is much more concise.

**Changes in text:** “Gave permission to” was replaced with approved: “The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Regional Science and Research Ethics Committee of Petz Aladar University Teaching Hospital (NO.: 76-1-8/2021.) and individual consent for this retrospective analysis was waived.” (see page 4, line 4-10)

**Comment 6: Line 4- matching images, please elaborate**

**Reply 6:** Thank you very much, “matching images” was removed from the text. The

admission criteria to ICU was respiratory failure independently from the radiologic image.

**Changes in text:** “with matching images” was removed (see page 4, line 13)

**Comment 7: Page 7 Line 6- second pandemic?**

**Reply 7:** Thank you, I agree that the expression “second pandemic” was too vague.

**Changes in text:** wave, between March 2020 and March 2021 in Hungary (see page 7, line 23)

**Comment 8: Line 15-by two**

**Reply 8:** I agree with the correction. Thank you very much for pointing it out.

**Changes in text:** An additional “by” was added to the sentence for grammatical correction (see page 8, line 9)