

## Peer review file

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### Reviewer A

**Comment 1:** The last portion of the abstract needs editing as does the discussion which seems overly long.

**Reply:** The abstract is within the word limits.

The discussion is long because we felt that there were many issues to need to be enlightened. The lack of evidence obliges us to extend the discussion towards different topics in order to try extrapolating some more robust data to the COVID-19 induced spontaneous pneumothorax.

### Reviewer B

The systematic review of pneumothorax in the otherwise healthy, non-intubated patients with COVID pneumonia is interesting, and might be suitable for publication but requires supplementations.

Authors presented a group of patients collected from many studies. There is lack of information regarding cannabis smoking and environmental exposure. If you do not have such information please discuss this problem in discussion section

How many of these patients had coinfections with other pathogens?

Three patients died. What was the cause of death?

In discussion section, please present data regarding pneumothorax in otherwise healthy patients with other viral pneumonia such as influenza.

**Comment 1:** Authors presented a group of patients collected from many studies. There is lack of information regarding cannabis smoking and environmental exposure. If you do not have such information, please discuss this problem in discussion section

**Reply 1:** A comment is added in the last part of the Discussion section (study limitations) concerning lacking data about cannabis use and/or environmental or occupational exposure

**Changes in the text:** Lines 314-315

**Comment 2:** How many of these patients had coinfections with other pathogens?

**Reply 2:** Data is lacking and a comment is added

**Changes in the text:** Line 319

**Comment 3:** Three patients died. What was the cause of death?

**Reply 3:** The available information from the case reports is added on the Results section

**Changes in the text:** Lines 141-144

**Comment 4:** In discussion section, please present data regarding pneumothorax in otherwise healthy patients with other viral pneumonia such as influenza.

**Reply 4:**

Only a few publications discuss pneumothorax as radiologic sign in Influenzae A (H1N1)-pneumonia. These reviews teach us that the incidence is very low. As in Covid19-associated pneumothorax, confounders such as mechanical ventilation, ARDS, and pre-existing lung disease play a role in the development of pneumothorax in Influenza A-infection. Other reviews such as the one from Chen et al. found no reports of chest CT comparisons between SARS-CoV-2, SARS-CoV and MERS-CoV. As authors, we estimated that influenza-associated pneumothorax has not been well described in the current literature. For this reason, making comparisons between Influenza A- and Covid19-associated pneumothorax seemed not essential due to lack of data. It would have been useful to have a good review article about Influenza A (H1N1)-associated pneumothorax, with reflections about diagnostic approaches or the influence of given treatments. This underlines the importance of reviewing data and case reports about rare presentations of a certain disease, as is done in our review about Covid19-associated pneumothorax.

Valente T, Lassandro F, Marino M, Squillante F, Aliperta M, Muto R. H1N1 pneumonia: our experience in 50 patients with a severe clinical course of novel swine-origin influenza A (H1N1) virus (S-OIV). *Radiol Med.* 2012 Mar;117(2):165-84. doi: 10.1007/s11547-011-0734-1. Epub 2011 Oct 21. PMID: 22020427; PMCID: PMC7088783.

Onigbinde SO, Ojo AS, Fleary L, Hage R. Chest Computed Tomography Findings in COVID-19 and Influenza: A Narrative Review. *Biomed Res Int.* 2020 Jun 5;2020:6928368. doi: 10.1155/2020/6928368. PMID: 32596354; PMCID: PMC7275219.

Chen X, Zhang G, Hao SY, Bai L, Lu JJ. Similarities and Differences of Early Pulmonary CT Features of Pneumonia Caused by SARS-CoV-2, SARS-CoV and MERS-CoV: Comparison Based on a Systemic Review. *Chin Med Sci J.* 2020;35(3):254-261. doi:10.24920/003727

## **Reviewer C**

A systematic review submitted by Apostolos and colleagues describing secondary spontaneous pneumothoraces (SSPs) in non-intubated patients suffering from COVID-19 was meticulously reviewed. Generally speaking, this systematic review was written well. The authors concluded that pathogenetic mechanism of these SSPs seems to be different from primary spontaneous pneumothorax (PSP), and recommended that de novo SSPs should be part of the different diagnosis in COVID-19 patients suffering from acute respiratory deterioration. They also mentioned that imaging techniques especially CT scans should be repeated throughout the clinical course, and after the SSP's diagnosis surgical treatment is feasible and should be offered according to the existing guideline regarding spontaneous pneumothorax. The paper provides interesting data but it still needs a considerable revision to be acceptable for the JTD. I hope that you can share my arguments below.

Issues:

### **Comment1:**

#1: Lines 41 and 130-131: In 14 cases (31.8%) of all the covid-19 patients, air-filled lesions were reported to be detected on imaging. Please explain about the location, configuration, laterality, distribution, relationship between the lesion and de novo SSP, relationship between the lesion and corticosteroid usage.

**Reply 1:** Information about the localization of the lesions is added. The importance of the atypical localization is underlined. No causative relationship was established between corticosteroids and bullae development.

**Changes in the text:** Lines 135-138, 166-171, 267-269

### **Comment 2:**

#2: Bilateral SSPs including both sequential and concurrent happened in 10 patients (22.7%) during almost one month when the study was conducted. The 22.7% seems to be very high and the very interesting result. For example, SSPs resulted from BHD syndrome or LAM which has diffuse and multiple pulmonary cysts have been reported to show relatively higher percentage of bilateral and repeated pneumothoraces. If COVID-19 causes diffuse pulmonary damages, which may result in bilateral pneumothoraces. Please comment on this issue.

**Reply 2:** A comment is added about the high rate of bilateral pneumothoraces

**Changes in the text:** Lines 168-169

**Comment 3:**

#3: O<sub>2</sub> inhalation using high-flow nasal canula or non-invasive ventilation causes mild positive airway pressure which may be at between approximately 3 to 10 cmH<sub>2</sub>O. Please explain about relationship between these non-invasive positive airway pressure and the SSP's occurrence.

**Reply 3:** No causative relationship is established between the use of positive airway pressure and spontaneous pneumothorax as stressed in the discussion section

**Comment 4:**

#4: Regarding pneumothorax surgery under general anesthesia, American Society of Anesthesiology (ASA) and Anesthesia Patient Safety Foundation (APSF) made a joint statement on elective surgery and anesthesia for patients after COVID-19 Infection (1). Patients suffered from pneumothorax usually can wait until concomitant infectious diseases disappear using thoracic tube insertion. Accordingly, these pneumothorax surgeries seem to be elective. There are limited data now that address timing of surgery after COVID-19 infection (1). However, one study found a significantly higher risk of pulmonary complications within the first four weeks after diagnosis (2). An upper respiratory infection within the month preceding surgery has previously been found to be an independent risk factor for postoperative pulmonary complications (3). Since general anesthesia and lung surgery in patients with COVID-19 infection put medical stuffs in jeopardy of the infection, the joint statement concludes that elective surgeries should be performed for patients who have recovered from COVID-19 infection only when the anesthesiologist and surgeon or proceduralist agree jointly to proceed (1). The authors should mention these important issues.

(1) <https://www.asahq.org/about-asa/newsroom/news-releases/2020/12/asa-and-apsf-joint-statement-on-elective-surgery-and-anesthesia-for-patients-after-covid-19-infection>

(2) COVIDSurg Collaborative. Delaying surgery for patients with a previous SARS-CoV-2 infection. *BJS* 2020; 107: e601–e602.

(3) Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010;113:1338.

**Reply 4:** A comment has been added accordingly

**Changes in the text:** Lines 231-240

**Comment 5:**

#5: The authors mention that imaging techniques especially CT scans should be repeated throughout the clinical course. However repeated CT scans cause an irradiation damage to the patients, which may result in secondary malignant diseases. Generally, pneumothorax could be detected by an auscultation and/or ultrasonography. Please comment on this important issue. I hope my comments help you.

**Reply 5:** The fact that de novo air-filled lesions were discovered on sequential CT scans renders reasonable in our opinion this strategy. Repeated CT scans are of course not necessary in order to diagnose pneumothorax. The phrase is modified accordingly.

Concerning the comment about the use of lung auscultation and/or ultrasonography, we agree that lung auscultation should be part of the clinical examination of the Covid19-patient, however, a small or larger partial pneumothorax could easily be missed, and radiological imaging seems to have higher diagnostic value. When searching in PubMed, no articles were found describing pneumothorax in Covid19-patients diagnosed by the use of ultrasound. None of the case reports used for our review mentioned ultrasonography. We agree that ultrasonography is successfully being used to diagnose pneumothorax in non-Covid19-patients, with the limitation of being operator-dependent. Describing the use of ultrasonography would be an interesting topic for another review. One could for example reflect on the sensitivity and specificity of detecting Covid-associated pneumothorax versus bullae. Because of a lack of data in this specific patient population, and secondly because ultrasonography was not used in the case reports used for our review, we choose not to discuss this topic in our review.

**Changes in the text:** Line 342

**Reviewer D**

-although a very small small number of patients, it is very should be take into account for

thoracic surgeons such complication.

- there is no new information on this manuscript

- there is some important informations missing, such as type of chest tube, corticoids doses....

**Comment 1:** there is some important informations missing, such as type of chest tube, corticoids doses....

**Reply:** Comments are added about the missing data that were not always mentioned in the case reports

**Changes in the text:** Lines 194-195

## **Reviewer E**

The authors systematic review of “Pneumothorax in otherwise healthy non-intubated patients suffering from COVID-19 pneumonia” addresses an important topic that should be in general interest to the readership. However, there are several issues with the current manuscript that must be addressed before it is appropriate for publication.

A few general comments:

**Comment 1:** The results section should be expanded with more details; for example, the authors reported 3 deaths, but no cause of death or details thereof is reported.

**Reply 1:** The available information from the case reports is added on the Results section

**Changes in the text:** Lines 141-144

There are a number of statements without clarification/validation (see below).

**Comment 2:** The Discussion section is very long and could probably be condensed without sacrificing the points the authors are trying to make.

The section on NIPPV/HFNC in the Discussion should be condensed, clarified and the section on pediatrics should be removed as this population was not relevant to the systematic review.

### **Reply 2:**

The references to a pediatric population were made for 2 reasons. The first being the fact that there

is only 1 case report on this specific topic about an adult. This case report has been described in our review. Secondly, due to the influence of Covid19 on lung surfactant, it seemed interesting to us to compare the pathophysiology of Covid19 with other known conditions where lung surfactant is deficient. Therefore, it seems logic to see what happens in neonates with lung surfactant deficiency who develop or have pre-existing pneumothorax when being treated with HFNC. Currently there are no publications comparing HFNC and NIV in Covid-patients concerning the pneumothorax risk. Although we appreciate the comment about the pediatrics section, we prefer for the above-mentioned reason to keep this section in our review.

**Changes in the text: -**

Specific comments:

Page 2, line 34: replace “more” with “most” for clarity.

Page 2, line 45: remove “however” as it makes the sentence confusing.

**Reply:** The grammatical errors are corrected accordingly

**Comment 3:**

Page 2, line 46-47: “Imaging techniques should be repeated throughout the clinical course of the patients in order to detect newly developed pulmonary complications.” Please explain what data/reference validates this conclusion.

**Reply 3:** The fact that de novo air-filled lesions were discovered on sequential CT scans in some patients renders reasonable our opinion about this strategy.

**Changes in the text:** Line 342

**Comment 4:**

Page 3, line 54-57: The introductory sentence of the Introduction section is a run-on sentence, making it difficult to understand.

**Reply 4:** The sentence is simplified

**Changes in the text:** Lines 57-58

**Comment 5:**

Page 4, line 83: The word lecture is quite confusing. Do the authors mean, after “discussion” and analysis?

**Reply 5:** The phrase is modified accordingly

**Changes in the text:** Line 83

**Comment 6:**

Page 6, lines 130-131: “In 14 cases (31.8%) air-filled lesions were detected on imaging.” The authors present no data on the types or etiologies of such lesions. This is an important area where more data should be obtained from primary sources, if available, and incorporated into the results. For example, are these lesions caused by secondary bacterial/fungal infections or are the authors suggesting they are secondary to COVID-19 infection alone?

**Reply 6:** Arguments supporting the fact that development of air-filled lesions must be attributing to the COVID-19 infection (de novo air-filled lesions were discovered on repeated CT scans, patient with no respiratory comorbidities or smoking habit, lack of data about concomitant infections) are added to the Discussion section

**Changes in the text:** Lines 157-172

**Comment 7:**

Page 6, line 134: “Three patients died.” This is an important result and no further information is found in the manuscript. Please elaborate this section/result. For example, cause of death, time of death in disease course, any autopsy results, ect.

**Reply 7:** The available information from the case reports is added on the Results section, however there is limited data

**Changes in the text:** Line 141-144

**Comment 8:**

Page 6/Results: Although there is no line to reference, the authors goal to systematically review pneumothorax in COVID-19 “otherwise healthy” patients should be supported by an analysis of the co-morbidities of the patients included. In particular, for case reports it seems likely that co-morbidities would be reported and if the reports specifically reported “no co-morbidities” then this should be included as a data point.

**Reply 8:** The study population was carefully selected based on the absence of underlying respiratory pathology. The case reports did not always mention other comorbidities than respiratory ones. Sometimes it was clearly stated that the patients had no remarkable medical history.



**Changes in the text: -**

**Comment 9:**

Page 7, line 146: “however it is advocated that it rather is underestimated” is a very awkward phrase. Perhaps, “however, it has been suggested that it is underreported” might clarify the point.

**Reply 9:** The phrase is modified accordingly

**Changes in the text:** Line 156

**Comment 10:**

Page 7, line 153-160: Again, the authors discuss “air-filled cavities” in “healthy” patients. This requires clarification. Are the authors suggesting the these “healthy” patients have pre-existing cavitory lesions that may rupture when COVID-19 pneumonia is superimposed? Or are cavitory lesions a part of the COVID-19 pneumonia process and, if so, what is the mechanism?

**Reply 10:** Arguments supporting the fact that development of air-filled lesions must be attributing to the COVID-19 infection (de novo air-filled lesions were discovered on repeated CT scans, patient with no respiratory comorbidities or smoking habit, lack of data about concomitant infections) are added to the Discussion section

**Changes in the text:** Lines 157-172

**Comment 11:**

Page 7, line 155-158: The transition to the sentence “On the other hand, these cavities can disappear spontaneously with time, as demonstrated in the case reported by Fan et al (15).” is a non sequitur. Do the authors mean to convey that these cavities may potentially lead to pneumothorax, but may also spontaneously regress?

**Reply 11:** This is exactly what this case report illustrates. More specifically, the authors mention “At the 92-day follow-up, the pneumothorax and subpleural bullae had completely resolved, which indicated that these complications had self-limiting features.”

**Changes in the text: -**

**Comment 12:**

Page 8, line 196: Would remove the anthropomorphism: “the lung has lost his compliance.”

**Reply 12:** The phrase is modified accordingly

**Changes in the text:** Line 212

**Comment 13:**

Page 9, lines 213-215: The authors state that the BTS and AAST proposed recommendations for tube thoracostomy, but fail to place these in the context of the current manuscript. Please clarify.

**Reply 13:** We would like to highlight that a COVID-19 induced spontaneous pneumothorax must be treated initially as any other ordinary pneumothorax. The same rules apply but some precautions need to be taken

**Changes in the text:** Line 227

**Comment 14:**

Page 10, line 253-255: Please clarify/validate how hyperglycemia from corticosteroid treatment could lead to increased pneumothorax risk.

**Reply 14:**

As mentioned in reference 64 of our review (and if needed more information can be found in the reference below of Baker EH et al.), hyperglycemia is associated with higher incidences of respiratory infections with pathogens such as *Pseudomonas aeruginosa*, MRSA,...

Certain pathogens can be associated with necrotizing pneumonia which could lead to secondary pneumothorax.

We modified the text in order to clarify.

Baker EH, Wood DM, Brennan AL, Clark N, Baines DL, Philips BJ. Hyperglycaemia and pulmonary infection. *Proc Nutr Soc.* 2006 Aug;65(3):227-35. doi: 10.1079/pns2006499. PMID: 16923307.

Baker EH, Baines DL. Airway Glucose Homeostasis: A New Target in the Prevention and Treatment of Pulmonary Infection. *Chest.* 2018 Feb;153(2):507-514. doi: 10.1016/j.chest.2017.05.031. Epub 2017 Jun 10. PMID: 28610911.

**Changes in the text:** Lines 281-285

**Comment 15:**

Page 12, lines 310-312: Again, would expand on details of the mortalities.

**Reply 15:** The available information from the case reports is added on the Results section

**Changes in the text:** Lines 141-144

**Comment 16:**

Grammatical comments:

Page 4, line 97: form is a typo, correct to “from.”

Page 5, line 107: replace more with most.

Page 4, line 92: replace “intubation and invasive” with “intubation or invasive.”

Page 6, line 119: replace “smoke” with “smoked.”

Page 6, line 121: type “et” should be “and”

**Reply 16:** All grammatical errors are corrected accordingly