Peer review file
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Reviewer A

Comment 1:

The article is too broad and this leads to shallowness in certain areas. I would recommend the authors only focus only on the topic of pleural disease in COVID 19. The authors attempt to cover all viruses, MERS SARS, and others, and what occurs is too much information which dilutes the message. I would avoid all the discussion on parenchymal findings, this again dilutes on the topic. It is useful to have the other virus for reference or comparison, yet maintaining the focus on COVID.

Reply 1:

We agree and thank the reviewer for the suggestions. According to the reviewer's suggestions, we have modified the entire manuscript. The manuscript has been reorganized. The section on SARS and MERS has been reduced significantly. The discussion regarding parenchymal disease has been removed completely from the text.

Changes in the text:

1. The comparison among different viruses has been provided predominantly in table 5.

Comment 2:

I would recommend reorganization of the article. The tables are very good and complete, and these have the majority of the key statements. So I would suggest start by outlining what has been reported. Then the findings on CT, CXR, USG, MRI. Then the pleural fluid characteristics.

Reply 2:

We thank the reviewer for the excellent suggestions. We have outlined the known aspects of the disease in Table 1 and reorganized the manuscript according to the recommendations and consolidated certain sections of the manuscript together.

Changes in the text:

1. Section 3.1 and 3.2 were removed. They are now reported in 3.6, combining both sections. The discussion of pulmonary parenchymal disease has been removed.
2. Section 3.5 and 3.6 has been modified and now presented as one section, 3.3

Comment 3:

Pneumothorax is part of pleural space, yet, it seems it is barely superficially touched on this article. So is pneumomediastinum. I would suggest that you decide if you want to keep or remove. If you keep, please address more clearly. Spontaneous pneumothorax in presence or absence of positive pressure ventilation are very different entities. One may be a primary manifestation of the disease, the other a manifestation of ventilator induced lung injury. This needs to be differentiated.

Reply 3:

We agree and thank the reviewer for the suggestions. We have expanded the section on pneumothorax according to the reviewer's suggestions. We have also provided more detailed data regarding the incidence, pathogenesis, outcomes among patients with pneumothorax and pneumomediastinum. The differentiation between ventilated and nonventilated patients have been added.

Changes in the text:

1. We have removed Table 5 and added Table 4 that includes recently reported observational studies reporting patients with pneumothorax and or pneumomediastinum
2. The revised manuscript describes the section on pneumothorax as 3.5

Comment 4:

The references on the tables need to be reviewed, as the numbers do not match.

Reply 4:

We thank the reviewer for the keen observation. We have made all necessary modifications.

Changes in the text:

1. References have been added to tables 1, 2,3, 4 and 5.

Comment 5:

A figure with a timeline of the pleural abnormalities (if there is such) may be useful.

Reply 5:
We thank the reviewer for the suggestion. Unfortunately, based on the available data, no definitive timeline exists regarding the development of pleural abnormalities. Sometimes the changes are overlapping as well. We, therefore, could not provide an additional figure.

Comment 6:

Figures outlining the pleural findings would be very useful to understand what the authors are describing

Reply 6:

We thank the reviewer for the suggestion.

Changes in the text:

1. We have added new figures to the revised manuscript.

Comment 7:

Page 7, line 166, need to clarify, cant understand what it means.

Reply 7:

This section has been removed with the parenchymal changes.

Comment 8:

SARS COV2 pathological findings are not pathologically distinguishable from other ARDS (correct on line 169)

Reply 8:

This section has been removed with the parenchymal changes.

Comment 9:

Line 204: White Lung, perhaps complete consolidation?

Reply 9:

This section has been removed with the parenchymal changes.

Comment 10:

The pleural fluid section should only focus on the findings in COVID, rather than revisiting the criteria for diagnosis and causes for exudative effusions

Reply 10:

We thank the reviewer for the suggestions. We have made the suggested changes.

Changes in the text:

1. The section on diagnostic criteria has been removed.
2. Section 3.4 now describes pleural fluid characteristics.

Comment 11:

Line 353, clarify what is Macklin effect

Reply 11:

We have made the suggested changes.

Changes in the text:

1. Page 15, line 3-5

Reviewer B

Comment 1:

Very clear and well-structured work, full of theories to better understand the lung damage mechanism of the sars-covid-2019. In the our experience, did you have the treated pleural empyema in covid+ patients and what was the clinical development of the disease? How did you treat this complication? Did open surgery or VATS play a role?

Reply 1:

We thank the reviewer for the encouraging comments.
In our practice, we had patients with both pleural effusion and pneumothorax (primarily ICU patients). The microbiologic studies on the pleural fluid sample had always been negative, and therefore we did not require any intrapleural tPA, dornase or surgical intervention for decortication.
The literature review also revealed that these patients were typically managed following traditional recommendations. However, there had been concerns for aerosolization of SARS-CoV-2 due to air leak in patients undergoing chest tube drainage. We have discussed this in the revised manuscript.

Changes in the text:

1. Page 15 line 14-24

Reviewer C

Comment 1:

Dear authors, thank you for letting me review this article. I think it is well written and of course it is flattering when you cite my own work. However, I do not think it adds anything to the available literature on Covid-19, and its pleural characteristics. As Jose Porcel writes, (https://erj.ersjournals.com/content/56/5/2003308), where there is fire, there is smoke and vice versa. I have also noted that one cannot be clear that Covid-19 causes pleural effusions as other causes are not always studied. You do mention this, and the mere presence of Covid in pleural fluid does not imply causation. (https://pubs.rsna.org/doi/10.1148/ryct.2020200330)Whislt not technically the pleural space, a discussion of pneunomediastinum would also be appropriate. There is also a fair bit of work by Kevin Blyth who has looked at whether a bubbling chest drains are AGPs and I think any aspect of pleural issues with Covid-19 should also incorporate that as well as pre-operative swabs for patients undergoing advanced procedures such as medical thoracoscopy: such practice is now widespread.

Reply 2:

We thank the reviewer for the insightful suggestions and we have modified the manuscript accordingly. We agree that there have been confounding factors for the occurrence of pleural effusion in patients with COVID-19. We have clarified this aspect in the revised manuscript.

We have included a more detailed discussion of pneumomediastinum in the revised manuscript.

A new paragraph regarding the risk of aerosolization through the chest tube and water seal drainage system (including the work by Kevin Blyth) has been added.

Changes in the text:

Page 10 line 14 to 17 reports the difficulty in the determination of true causation of pleural effusion by SARS-CoV-2

Page 14 line 20 to and Page 15 line 9 reports more detailed information on pneumomediastinum.

Page 15 line 14-24 describes the risk of aerosolization with chest tube drainage in the setting of air leak.

Reviewer D

Comment 1:

It would be good to include the SARS and MERS search terms in the methods, as per the Covid-19 search terms.

Reply 1:

We agree and thank the reviewer for the suggestions. We have included the search terms in the method section.

Changes in the text:

1. Page 6, line 5 to 9

Comment 2:

The description of the changes in other viruses only adds value if this is clearly compared/contrasted with Covid-19, so these sections either need to be rewritten with this in mind or taken out, I would suggest the former.

Reply 2:

We thank the reviewer for the suggestions. As the manuscript was already lengthy, we have decided to focus primarily on the pleural diseases in COVID-19 and shorten the section on SARS, MERS and other viral infections.

Changes in the text:

1. Section 3.1 and 3.2 were removed and are now reported in 3.6 combining both sections.
2. The comparison among different viruses has been provided predominantly by table 5.

Comment 3:

In fact the whole piece feels a little like a collection of copy and paste statements and needs pulling together a bit more.

Reply 3:

We thank the reviewer for the suggestions. As stated earlier, we have reorganized the manuscript completely and focuses only on the pleural pathology.

Comment 4:

Lines 113-117 – Did Chan et al give any detail about how long “longer” is? E.g. more common in patients surviving x days or mean survival of those with pleural involvement?

Reply 4:

We thank the reviewer for pointing out this crucial aspect. Although the authors did not specifically point this out, the review of Figure 1 and Table 1 in their paper demonstrated that these findings developed beyond two weeks.

Changes in the text:

1. Page 16, line 13-15 specifies the time frame now.

Comment 5:

Line 116- 11% of the 26% or of the total cohort i.e. 37% had one or both?

Reply 5:

We thank the reviewer for pointing this out. The pneumothorax of 11% was for the entire cohort. All patients with pneumothorax also had pneumomediastinum.

Changes in the text:

1. Page 16, line 15-17has been updated to better communicate the information.

Comment 6:

Line 120- 33-55% of patients who had it had it early or 33-55% of patients had it at any stage, but most had it early? If the latter sounds like it is more common in MERS than Covid-19, so should be circumspectly commented upon.

Reply 6:

We thank the reviewer for pointing this out. The overall incidence of pleural effusion in MERS ranges between 33-55% and often, the effusion appears in the first week of illness. The incidence seems to be higher than COVID 19.

Changes in the text:

1. Page 16, line 16-17 has been updated to better communicate the information at the reviewer's suggestion.

Comment 7:

Line 129 -Do you mean not well characterised? Or not frequently described or similar? This sentence needs a reference.

Reply 7:

We thank the reviewer for the keen observation. We have modified the sentence and added a new reference according to the reviewer's suggestion.

Changes in the text:

1. Page 17, line 1-2

Comment 8:

Line 139-140 That sentence presumably refers to influenza, but needs to be made clearer.

Reply 8:

We thank the reviewer for pointing this out. However, we have removed these lines to focus only on the pleural space abnormalities.

Comment 9:

Line 234-238, Reference 56 is from 1970, we do not see parapneumonic effusion anywhere near this frequently in the modern antibiotic era, this needs to contextualised and/or replaced with an up to date reference.

Reply 9:

We thank the reviewer for pointing this out. We agree that the incidence of parapneumonic effusion among hospitalized patients has reduced significantly with routine use of antibiotics. We have modified the manuscript and added new citation.

Changes in text:

1. Page 9, line 7-9

Comment 10:

243-244 "0.28ml/ml/hr, 20 times of normal" There is a typo, the second ml should be kg and I would lose the '20 times normal' it is either 28 times normal or if you want to round it then 30 times, but I would lose it altogether.

Reply 10:

This has been removed.

Comment 11:

240-245 needs referencing and "An adult weighing 70kg can remove 500cc of transudative pleural fluid." Adds nothing to the previous sentence, but more so shows a lack of understanding as parapneumonic effusions will be exudates by definition, is the rate different in exudates?

Reply 11:

This has been removed.

Comment 12:

Line 248, "lung water"!!

Reply 12:

The term 'extravascular lung water (EVLW)' is being increasing used in critical care to refer to the sum of intracellular, interstitial, intracellular, alveolar and lymphatic fluid present in the lungs. EVLW is increased in both hydrostatic as well as high permeability pulmonary edema and has been a focus of research for ARDS patients.

Changes in text:

1. Page 9, line 11-14

To remove ambiguity, we have used the term 'interstitial fluid' rather than extravascular lung water in the revised manuscript.

Comment 13:

269-273 I am not sure what conclusion you are trying to draw here? CKD = high incidence of effusion, but lower mortality than other Covid patients with pleural effusion. ESRF lower incidence of effusion than CKD. This section needs reconsidering.

Reply 13:

We thank the reviewer for pointing this out. We point we were trying to make was that in patients with comorbid conditions that could be responsible for pleural effusion, the mere presence of pleural effusion does not portend bad outcomes. This section has been modified significantly to convey the message to the reader.

Changes in text:

1. Section 3.3 has been modified significantly

Comment 14:

Line 280-284, This should probably be more circumspect and the first half of this conclusion comes a little out of the blue as the preceding section does not hint at late effusion inferring poor prognosis.

Reply 14:

We thank the reviewer for the suggestions. These sections have been modified to make the paper more coherent and easy to read.

Comment 15:

Section 3.7 needs heavily editing. The early paragraphs make a lot of inferences from very little evidence and it is unclear which statements are evidenced and which are the authors' opinions/inferences. The section in Light's criteria is unnecessary here, this is not a textbook/lecture notes. How you rewrite this then influences your Conclusions 379-381.

Reply 15:

We thank the reviewer for the suggestions. The discussion regarding Light's criteria has been completely removed. This section has been modified significantly to provide objective data. The conclusion section has also been modified.

Comment 16:

337 is 1% rare? How does that compare to standard incidence of PTx?

Reply 16:

We thank the reviewer for the insight. Although initial reports showed an incidence of approximately 1%, a recent meta-analysis showed the overall incidence to be as low as 0.3% among all hospitalized patients. It is likely that the estimation of true incidence is lower than reported, due to selection bias.

Comment 17:

348-9 By "spectrum" do you mean severity, duration or something else? This needs considering and referencing, as does the rest of this section up to 356.

Reply 17:

We agree and thank the reviewer for the suggestions. We have made changes and updated the entire section on Pneumothorax. Appropriate references have been added throughout the section.

Comment 18:

360-361 reference perhaps https://doi.org/10.1007/s42399-020-00689-z

Reply 18:

We thank the reviewer for suggesting the paper. We have incorporated the paper in the revised manuscript.

Changes in text:

1. Page 15 line 8-9

Comment 19:

Table 1 I am not sure what the relevance of mediastinal lymphadenopathy is in a paper about pleural disease? Do not write "same" give a figure.

Reply 19:

We thank the reviewer for the insight. Since we had discussed pneumomediastinum in the manuscript, we had included the lymphadenopathy part as well. It has only been included in the tables in case the reader is interested without creating a distraction or lengthening the manuscript. We have also made the suggested changes in the table (now table 5)

Comment 20:

Table 2 This is a collection of meta-analyses not your meta-analysis. How have you defined "positive CT"?

Reply 20:

We thank the reviewer for pointing this out. We have modified the title of the table and well as the description of CT positivity in the table.

Comment 21:

Table 3 What is the source of this table? Typo "finings" should be findings. GGO needs defining in the table legend. Airways – Bronchiectasis or traction bronchiectasis? Pleura is pneumatocoele a pleural finding? Is subcutaneous emphysema mediastinal?

Reply 21:

We thank the reviewer for pointing out these mistakes. We have corrected them.

The table was prepared with the information gathered from multiple radiologic studies and has been added to the references.

Changes in text:

Now Table 1 has been modified

Comment 22:

I would not include Tables 4 & 5 as a series of individual case reports adds little.

Reply 22:

We thank the reviewer for the suggestions.
We have removed table 5 and this has been replaced by Table 4 which includes recently reported observational studies on pneumothorax and or pneumomediastinum.

Table 4 (now Table 3) will provide the reader quick access to the actual numbers and compare their own conclusions with the manuscript.

Comment 23:

Language should be a little more circumspect eg:
a. Line 56 – proved shown to be
b. 62 – is also may also be

Reply 23:

We thank the reviewer for the suggestions and we have made suggested changes.

Changes in the text:

1. Original line 56 had been removed
2. Changes have been made in Page 5 line 11

Comment 24:

Try to avoid emotive language in scientific writing e.g:
a. Line 60 – fearsome
b. 75 – life threatening – How often is pneumothorax life threatening, especially as your own conclusions disagree with this?
c. 76 – scrutinise review
d. 91 – thoroughly searched reviewed
e. 93 – scrutinized
f. 122 – dire
g. 372 – powerful

h. 384 – grim

Reply 24:

We thank the reviewer for the suggestions and have made all suggested changes.

Changes in text:

2. Page 5 line 10
3. Page 5 line 16-17
4. Page 5 line 17
5. Page 6 line 10
6. Page 6 line 11
7. Page 16 line 19
8. This line has been removed
9. This line has been removed

Comment 25:

Lines 105-108 is this all from reference 11? If so the sentence structure needs to make this clear, if not the statements between references 10 and 11 also need to be referenced.

Reply 25:

These lines have been removed in the revised manuscript

Comment 26:

Lines 108-111 "The autopsy…" it is unclear what autopsy is being referred to here? I assume, "in one autopsy study" or "in an autopsy series" similarly the second sentence of tis section needs work to clarify

Reply 26:

These lines have been removed.

Comment 27:

Lines 112 & 113 should be "Tsang et al and Lee et al"

Reply 27:

This line has been modified .

Changes in text:

1. Page 16, line 11-12

Comment 28:

Line 142, the comma should come after the 'and'. There are a lot of other examples of incorrect/unnecessary commas, especially before ands, but this one is strikingly grammatically incorrect.

Reply 28:

We appreciate the reviewer's suggestions. We have made appropriate changes throughout the manuscript.

Changes in the text:

1. Page 17 line 3-4

Comment 29:

Line 166-167 This sentence doesn't make sense.

Reply 29:

This line has been removed.

Comment 30:

Line 200, "The worst…" needs referencing and defining what is meant by worst. This certainly is not true of the many patients who have prolonged ventilation and develop fibrosis.

Reply 30:

We thank the reviewer for the suggestions. We have made appropriate changes to the revised manuscript. We have changed the word 'worst' to 'most severe'. We agree with the reviewer completely that patients requiring prolonged mechanical ventilation may demonstrate severe fibrosis. However, in this study, the authors reported patients early in the illness, which have been specified.

Changes in the text:

Page 7, line 13-14

Comment 31:

229 "much more sensitive" needs to be replaced with more professional/scientific language.

Reply 31:

We thank the reviewer for the suggestion. We have modified the language.

Changes in the text:

Page 9 line 2-3

Comment 32:

While this appears a long list, most are fairly minor suggestions and I would be happy to review the next version.

Reply 32:

We appreciate all the suggestions and looking forward to hearing from you.

Reviewer E

This is a nice review article for an important subject. Pleural changes related to COVID-19 have not been documented in such details. However, I suggest publication of this manuscript as a clinical note than a review article. In addition, the following minor issues have to be addressed:

Comment 1:

Line 53 needs references

Reply 1:

We thank the reviewer for the suggestion and references have been added in the revised manuscript.

Changes in the text:

1. Page 5 line 2-3

Comment 2:

Introduction section is unnecessarily long. I suggest that paragraphs at lines 53 to 56 and lines 66 to 72 need to be removed. Then introduction can be summarized and shorten with focus on pleural changes and radiological findings especially ultrasound.

Reply 2:

We agree and thank the reviewer for the suggestions.
We have made significant changes to the introduction section , including deletion of the suggested part. We believe now the introduction is more concise and focused on the current review.

Comment 3:

I would suggest adding the following reference: Sultan LR, Chen YT, Cary TW, Ashi K, Sehgal CM. Quantitative pleural line characterization outperforms traditional lung texture ultrasound features in detection of COVID-19. J Am Coll Emerg Physicians Open. 2021 Apr 2;2(2): e12418. doi: 10.1002/emp2.12418. PMID: 33842925; PMCID: PMC8018308.

Reply 3:

We thank the reviewer for suggesting the paper. We have updated the ultrasound section in the revised manuscript and included the citation provided by the reviewer.

Changes in the text:

1. Page 8 line 20 to Page 9 line 3

Comment 4:

In discussion, sections 3.5, 3.6 and 3.7 can be condensed together and rewritten in one section.

Reply 4:

We thank the reviewer for the suggestion. We have made significant modifications and restructuring of the discussion section. We have condensed 3.5 and 3.6 together and left pleural fluid characteristics separate, as this section provides a detailed discussion.

Changes in the text:

1. Sections 3.5 and 3.6 have been condensed together and now 3.3

Reviewer F

Comment 1:

I think that the review requires 1 major change: it is a very long, blunt text, which from the one side summarizes nicely and in a well written way the data from the included studies. On the other side, it is almost impossible to stay concentrated and read around 18 pages review without it containing any statistic or new information.
My first recommendation is to drastically reduce the content of the review so it becomes readable. The second recommendation has more to do with the comparability of the COVID-19 with the other two diseases of the past. They certainly have common features but COVID-19 has probably led to the most serious pandemic of the last 50 years while the other viral infections clearly had a significantly more benign profile.

Reply 1:

We thank the reviewer for the suggestions.

We have removed all discussions other than pleural space disease in COVID-19 in the revised manuscript. We have consolidated that information in table 1.

The section of SARS and MERS have also been reduced significantly with only focus on the pleural disease aspect. We completely agree with he reviewer that COVID-19 had been responsible for the worst pandemic compared to the other viruses and we have stated that in the revised manuscript in the very first paragraph of the introduction section.

Changes in the text:

1. Page 5, lines 2-5