

Peer Review File

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Reviewer A comments

This is a very well-written manuscript and is an important topic for the readers. However, my biggest critique of this manuscript is that it has redundancy (for example, LUS scores are mentioned multiple times throughout the manuscript) and needs to be focussed.

Q1. Title: “Use of Thoracic Ultrasound in ARDS” would be a more appropriate title as no novel techniques or new avenues have been discussed in this paper

A1. We thank the reviewer for this suggestion. We think the title that you have provided is very appropriate and we have rewritten it as suggested. (Page 1, line 1 of tracked version).

Q2. I suggest a systematic approach by defining ARDS, stating the prevalence and issues with gold-standard diagnostic modalities (radiation, moving patients, lack of availability in resource-poor settings), and then introducing how LUS is a valuable skill to learn to diagnose and management of ARDS.

A2. We agree with the reviewer’s advice and have, therefore, deepened the definition of ARDS and the limitations of chest-X-ray and CT scan in ARDS diagnosis, as well as the advantages that LUS may provide (Page 3, lines 50-65).

Q3. Probe selection and patient position are appropriate sub-headings

A3. We thank the reviewer for this suggestion. We have changed the sub-heading accordingly under the section entitled “Basic ultrasound examination” (Page 4 line 88).

Q4. I suggest defining LUS in ARDS patients and omitting LUS findings as redundant information. Diaphragmatic US should come next, and all the data should be under one heading. Echocardiography findings should be detailed in the end. Since VTI has a lot of recent literature published, it will be a good idea to define the technique and give reference values for fluid responsiveness and current evidence. Since TEE is not well described in your manuscript, please mention this in your limitations.

A4. We thank the reviewer for the advice. We have summarized LUS in ARDS in order to avoid redundant information under “ARDS diagnosis” (Page 6, line 162) and grouped lung, diaphragm, and echocardiography findings under “Basic ultrasound examination”. (Page 4, line 88). We have also defined VTI and fluid responsiveness in more detail in the “Circulatory failure and resuscitation” section. (Page 9, line 259). Finally, we have added the fact that the echocardiography technique is not well described in the manuscript due to its complexity and the amount of information that can be obtained, which is beyond the aim of this review (Page 6, lines 151-153).

Reviewer B comments

General comments

I commend the authors for their thorough work on ultrasound in ARDS, I agree that ultrasound is a highly feasible diagnostic, prognostic and decision making tool on the ICU. There are some aspects that need attention in my opinion:

Q1. Throughout the manuscript grammatical and syntactical errors which do its overall quality injustice. I think this point is easily addressed by consulting with a native speaker. This will greatly improve on general readability.

A1. We apologize for these errors. The current version has been carefully reviewed by a native speaker, and grammatical and syntactical errors have been corrected.

Q2. The structure needs some attention. It is now grouped by organ (heart) and clinical entity (weaning). I think structuring by either organ eg: lungs, heart, diaphragm or by clinical problem eg: mechanical ventilation, extravascular lung water, weaning might be beneficial.

A2. We agree with the reviewer's comment and have re-structured it according to the clinical problem (basics of ultrasound examination, initial approach, mechanical ventilation, and weaning).

Q3. The basics of lung and diaphragm ultrasound can be a bit shortened in my opinion. The review focuses on "new avenues" and as such should compile the largest body of the manuscript.

A3. We thank the reviewer for this advice. The section about the basic concepts of LUS and the diaphragm has been shortened under the section “Basic ultrasound examination” (Page 4, line 88 of tracked version).

Q4. I think the holistic approach may deserve more in depth view. ARDS is a highly complex disease not only involving the lungs, which the authors already highlight.

A4. We thank the reviewer for bringing up this point. We have included the idea of the holistic approach throughout the manuscript. We have discussed how LUS could be used in the diagnosis of ARDS and the etiological diagnosis of ARF (Page 7, lines 177-185). We have also extended the discussion about fluid resuscitation, which is an important part in the overall management of ARDS patients (as suggested by Reviewer A in Q4) (Page 9, line 259). Moreover, we added a general explanation about how ultrasound assessment (not only LUS, but also diaphragm ultrasound and assessment of cardiac function) could help us to set mechanical ventilation in a more appropriate way. Finally, in the last part of the manuscript, we focused on how ultrasound could be used during the weaning process of mechanical ventilation.

Q5. The conclusion lacks a clear message in my opinion. Based on the manuscript, to me it would seem the authors are convinced by the use of ultrasound in ARDS. This can be communicated in an opinionated yet scientifically sound conclusion.

A5. We thank the reviewer for this suggestion. We have rephrased the conclusion to emphasize the benefits of LUS, while noting that clinical decisions based on ultrasound assessment requires further research. (Page 16, line 457).

Specific comments:

S1. Lines 19-20: I think this sentence needs restructuring. It now reads as if the edema leads to shunting which in turn leads to impaired gas exchange, whereas the edema leads to shuntingç.

S1A. We thank the reviewer for pointing this out. We have rephrased the sentence and now it reads as follows: “Acute respiratory distress syndrome (ARDS) is defined as noncardiogenic pulmonary edema that leads to alveolar shunt and gas-exchange impairment”. (Page 3, lines 50-51).

S2. Lines 22-24: I would add “lung” protective ventilation, as “diaphragm” protective ventilation is an topic of growing interest and attention. PMID: 32516052, PMID: 36038890.

S2A. We agree with the reviewer’s suggestion and have added “lung” to the sentence. (Page 3, line 53).

S3. Line 25-26: consider rewording “maneuvers and framework”. I would call them treatment strategies/goals etc.

S3A. We agree with the reviewer. The sentence has been reworded. Now it reads as follows: “However, the response to these therapeutic strategies may vary, and it is poorly predictable”. (Page 3, lines 55-56).

S4. Line 31: I would be more precise, technically ultrasound can traverse air, but the impedance difference between tissue and air is what was thought to be the limiting factor for thoracic ultrasound.

S4A. We agree with the reviewer's comment and have changed the sentence accordingly. Now it reads as follows: "Since its first description in 1968 (11), the clinical utility of LUS has been questioned for many years because the impedance difference between tissue and air was considered a limiting factor for ultrasound examination". (Page 3, lines 72-74).

S5. Line 49: what is the parietal wall ?

S5A: We have reworded parietal wall as "chest wall". (Page 4, line 93).

S6. Line 52: I think saying that consolidation is a deeper pathology is a misnomer. By definition, all pathology that can be examined by ultrasound has to reach the pleura. As such, calling it deep pathology seems illogical to me.

S6A: We agree with the reviewer and have rephrased the sentence. (Page 4, line 96).

S7. Line 58: this is assuming hospitalized patients. Ambulant patients will h be upright before presentation and as such pathology will present at the most caudal part of the thoracic cavity.

S7A. We thank the reviewer for this comment. Nevertheless, we have shortened this section of the manuscript, and it has been removed.

S8. Line 67: the twelve region protocol and BLUE protocol are philosophically distinct protocols, not differing based on department. The blue is a diagnostic protocol while the 12 region a quantitative protocol.

S8A. We agree with the reviewer's comment. We have clearly stated this difference on the manuscript. We have specified that the BLUE protocol was developed for the

diagnosis of ARF in the Emergency setting, whereas the 12-region approach allows for a quantitative approach. (Page 4, line 97).

S9. Line 75: ultrasounds is a grammatical error. Ultrasound waves would be appropriate.

S9A: The paragraph containing this grammatical error has been removed to shorten the section.

S10. Line 96: I would consider that there is discussion on the quantification of B-lines, see PMID: 32236940, PMID: 31996959

S10A: We agree with the reviewer and have included a more detailed discussion about B-lines, including both abovementioned references (in the “Evaluation of lung aeration” section). (Page 8, line 205).

S11. Line 115: this is based on a recent consensus statement, prior to this there was variability in measurement of diaphragm thickness. PMID: 35395861.

S11A: We thank the reviewer for his comment. We have updated the information accordingly. (Page 5, line 142).

S12. Line 163: if I recall correctly the study by Bouhemad was performed with transversal transducer orientation. With that, the width of the intercostal space should not be relevant.

S12A: We agree with the reviewer’s comment, and we have specified it in the manuscript. (Page 5, line 108).

S13. Line 164: *coalescent

S13A. We have corrected the misspelling mistake.

S14. Line 166: subpleural consolidation is a misnomer in my opinion. By definition, each lung consolidation is subpleural.

S14A. We have removed the word “subpleural” to avoid misunderstanding.

S15. Line 172: *Mongodi

S15A. The surname has been corrected.

S16. Line 182: in contrast ? on the contrary ?

S16A. We have rewritten the sentence according to the reviewer’s suggestion

S17. Line 236: consider PMID: 33969350

S17A. We have added this data to the manuscript (Page 7, lines 198-203).

S18. Line 238: consider PMID: 33257915

S18A. We have added this reference to the paragraph on “COVID-19 US possible findings” (Page 7, lines 198-203).

S19. Line 291: I think there is scarce evidence for this statement. In the study by Vivier et al a wide range of thickening fraction could be correlated with any given pressure generated.

S19A. We agree with the reviewer’s comment. We have reworded the sentence to emphasize the fact that there is still controversy regarding TF cut-off values that may

correlate with respiratory effort and the effect of positive pressure ventilation on it.
(Page 12, line 332).

**S20. Line 294: 15-30% is not per se similar to a healthy range with goes up to 260%
PMID: 34778304.**

S20A. We have removed this statement according to the reviewer's comment. Now it reads as follows: "It has been suggested that a diaphragm thickening fraction in the range of 15–30% may be associated with the shortest duration of mechanical ventilation compared to lower or higher thickening fraction values". (page 12, line 338).

S21. Line 357: I think this sentence deserves nuance. I am not convinced by the current body of evidence, as the authors state themselves in the following sentence. In this regard, consider the recently published articles: PMID: 35989352 PMID: 33850048.

We thank the reviewer for this suggestion. We have added recent evidence to highlight US limitations on predicting successful weaning. Now it reads as follows: "Recently, the predictive value of diaphragm ultrasound was also tested in mechanically ventilated COVID-19 patients, but TFDi was not predictive of weaning failure." ... "A multimodal approach, integrating LUS, diaphragm ultrasound, and echocardiography findings, may help identify patients at risk and predict SBT failure (89, 100). Although a holistic ultrasound approach has previously been determined to be a weak predictor for extubation failure (101), understanding the pathophysiology of weaning failure can help physicians to optimize the clinical status and physiological function before proceeding to mechanical ventilation discontinuation." (Page 14, line 398).

S22. Line 368: I think this is nicely summarized by PMID: 31938825 and merits mention.

S22A: We agree with the reviewer's opinion and have expanded the discussion on the holistic approach for weaning (Page 14, line 403).