Author's response to reviews

Title: Rapid evaluation by lung-cardiac-inferior vena cava (LCI) integrated ultrasound for differentiating heart failure from pulmonary disease as the cause of acute dyspnea in the emergency setting

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Author's response to reviews: see over
Dear Prof. Eugenio Picano and Prof. Rosa Sicari,

Thank you for your comments and for providing us with the opportunity to submit a revised version of our manuscript entitled “Rapid evaluation by lung-cardiac-inferior vena cava (LCI) integrated ultrasound for differentiating heart failure from pulmonary disease as the cause of acute dyspnea in the emergency setting”.

We have now revised this manuscript according to the comments made by the referee. We have carefully considered their comments, and have provided point-by-point-responses (‘C’ indicates each comment and ‘R’ indicates our response). Neither the manuscript in whole nor any part of it has been published or is currently under consideration for publication by any other journal. All the authors have contributed significantly to this work. All the authors have read the manuscript and have approved this submission. The authors report no conflicts of interest. We hope that you will now find our paper suitable for publication in your journal, and we look forward to hearing from you.

Thank you for your kindness.

Sincerely yours,

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Replies to Reviewer

Major comments:


R1: We appreciate this comment regarding the definition of B-lines. According to the reviewer’s suggestion, we have cited the Volpicelli G’s paper (Intensive Care Med 2012;28:577, Ref 14) on Page 4, Line 13 and Page 6, Lines 10&16 in the revised manuscript.

C2: The definition of positivity for lung ultrasound (LUS) is questionable. Previous literature and the above mentioned Recommendation Paper suggest that a positive LUS exam for pulmonary interstitial syndrome consists of two or more positive regions bilaterally. A positive region is defined by the presence of three or more B-lines. Your definition of positivity as three or more zones bilaterally may have lowered the sensitivity of LUS. I would suggest to recalculate accuracy, taking into account this more established cut-off.

R2: We appreciate this comment regarding the definition of positivity for lung ultrasound. As the reviewer’s comment, ‘the presence of three or more B-lines’ is purely a mistake. Therefore, we have corrected the definition of positivity for lung ultrasound (on Page 6, Lines 16-17) in the revised manuscript as follows: lung ultrasound examination is positive if B-lines are found in two or more zones bilaterally of the eight zones assessed.

C3: The definition of positivity for cardiac examination is also questionable. I’m personally not convinced that a dyspnoic subject with a normal systolic function and a moderate tricuspid regurgitation must have a cardiogenic origin of the dyspnea. On the contrary, this is often the description of the echocardiogram of a patient with pulmonary disease. If the tricuspid regurgitation was not linked to any left-side alterations (unfortunately you cannot evaluate diastolic function, as you correctly state in the limitations), that regurgitation is more probably due to a pulmonary condition, if any. I would restrict cardiac positivity to left ventricular systolic dysfunction and at least moderate mitral regurgitation.
R3: We appreciate this comment regarding the definition of positively for cardiac examination. We agree with the reviewer. Therefore, we have modified the Method section (Page 7, Lines 6-9) of the revised manuscript as follows: A positive cardiac ultrasound examination meant that either a presence of moderate to severe mitral regurgitation (MR) in preserved EF subjects or a presence of moderate to severe MR or tricuspid regurgitation (TR) in reduced EF subjects was detected. Also, we have modified the Results section (Page 11, Lines 12-13) and added these findings in the revised Table 2.

C4: You state that it is impossible to differentiate AHFS from pulmonary fibrosis, ALI/ARDS or bilateral pneumonia by LUS. It is undoubtedly very difficult and often not possible, but sometimes there are some clear LUS signs that can significantly help (especially in ALI/ARDS, see Copetti et al. Cardiovascular Ultrasound 2008 Apr 29;6:16). I would replace the sentence “It is impossible” with “it can be very challenging”.

R4: We appreciate this comment regarding the differentiation of AHFS from pulmonary fibrosis, ALI/ARDS, or bilateral pneumonia. We agree with the reviewer. Therefore, according to the reviewer’s suggestion, we have modified the Introduction section (Page 4, Lines 13-16) of the revised manuscript as follows: However, it can be very challenging to differentiate AHFS from severe bilateral pneumonia, pulmonary fibrosis, acute lung injury, or ARDS. Also, we have cited the Copetti ‘s paper (Cardiovascular Ultrasound 2008;6:16-25, Ref 15) on Page 4, Line 16.

C5: You do not mention any other LUS sings other than B-lines. Did any of your patients have pleural effusion? Did you look for subpleural alterations or consolidations?

R5: We appreciate this comment regarding any other LUS signs. As the reviewer’s comment, we could detect pleural effusion and consolidation in any patients with AHFS, ARDS, or pneumonia. Therefore, we have added these findings and other ultrasound findings (LV systolic dysfunction, MR, TR, and IVC collapsibility) in the revised Table 1.

C6: You report in the Methods section that one cardiologist and one pulmonologist determined the final diagnosis. Was their agreement 100%? What happened in case of disagreement?
R6: We appreciate this comment regarding the determination of the final diagnosis. The ‘one’ cardiologist was not correct. The ‘two’ cardiologists and one pulmonologist were correct, indicating that the final diagnosis in our study was made by the majority rule. Therefore, we have modified the Method section (Page 8, Lines 11-12) of the revised manuscript as follows: To determine the final diagnosis, two cardiologists and one pneumologist, who were blinded to the results of the LCI integrated ultrasound at admission.

C7: It is rather unusual that in a consecutive population of 90 patients, nobody had an etiology of the dyspnea other than due to cardiac or pulmonary disease. It seems that you considered a dyspnea due to non-cardiac, non-pulmonary conditions as an exclusion criterion. This should be better clarified.

R7: We appreciate this comment. As the reviewer’s comment, 5 patients with acute dyspnea due to neither cardiac nor pulmonary causes were observed (2 hemodialysis patients and 3 patients with psychological stress). Therefore, we have added the exclusion criterion in the Methods section (Page 5, Lines 15-16) of the revised manuscript as follows: In addition, patients who had acute dyspnea due to neither cardiac nor pulmonary cause were excluded from this study.

C8: I suggest to include in the discussion a brief comparison with a previously published similar work (Kimura et al. Am J Cardiol. 2011 Aug 15;108(4):586-90).

R8: We appreciate this comment. We have modified the Discussion section (Page 14, Lines 3-10) of the revised manuscript as follows: Furthermore, Kimura et al. has reported the usefulness of cardiopulmonary-limited ultrasound examination consisting of only 4 ultrasound views, such as LV systolic dysfunction, left atrial enlargement, IVC, and B-lines, for the diagnostic accuracy and prognostic information, although they did not evaluate a diagnostic accuracy for differentiating acute dyspnea due to AHFS from that caused by primary pulmonary disease [45]. On the basis of these available reports and our findings, it is suggested that LCI integrated ultrasound assists with the rapid and accurate diagnosis and treatment of acute dyspnea in the emergency setting.

C9: Figure 1 is not clear, since you do not suggest a real algorithm. Please reshape this scheme indicating what to do in case you find a positive or negative evaluation. When you mention
cardiac ultrasound, why don’t you include systolic dysfunction? Moreover, I suggest to specify “multiple bilateral” B-lines and not only “B-lines”.

R9: We appreciate this comment regarding Figure 1. As the reviewer’s comment, Figure 1 was not clear. We agree with the reviewer. Therefore, according to the reviewer’s suggestion and the Volpicelli G’s paper (Intensive Care Med 2012;28:577, Ref 14), we have modified Figure 1 in the revised manuscript.

C10: It would be interesting to expand a bit on discordant cases, especially LUS/BNP discordant cases. Also LUS false negative cases (which are rare and I believe should decrease with the suggested different positivity definition) should be individually described. Previous literature report indeed a sensitivity of LUS close to 100%. Please, address.

R10: We appreciate this comment regarding LUS-BNP discordant cases and LUS false negative cases. In our study, the LUS in two patients with pure right-sided heart failure due to Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) or Tricuspid stenosis (TS) showed a false negative. Furthermore, these two cases showed LUS-BNP discordant, indicating that the LUS showed negative findings and BNP values were high. Thus the LUS may have limitation for patients with pure right-sided heart failure and not in association with left-sided heart failure. Therefore, we have added these cases in the Discussion section (Pages 13-14, Line 18-Line 1) of the revised manuscript as follows: However, in the present study, the lung ultrasound in two patients with pure right-sided heart failure, which was not in association with left-sided heart failure, showed a false negative, suggesting that B-lines may not be sensitive for pure right-sided heart failure.

C11: When you combine different approaches (i.e. LUS and BNP) the accuracy should not decrease if you consider positive, a test where even only one of the two components is positive. In your results, sensitivity decreases when you add BNP to LUS, suggesting that you need both positive tests to define positivity. Please, clarify this issue.

R11: We appreciate this comment regarding the sensitivity of lung ultrasound combined with BNP ≥100 pg/ml. In this study, ‘lung ultrasound combined with BNP ≥100pg/ml ’ meant that ‘both lung ultrasound and BNP ≥100pg/ml’ were positive. Therefore, we have corrected this term in the Results section (Page 11, Line 11) and Table 2 of the revised manuscript as follows: ‘both lung ultrasound and
BNP $\geq 100$pg/ml.

Minor comments:

C1: Page 4: in the sentence “Recently, it was reported that detection of pulmonary interstitial edema (B-lines) by lung ultrasound“ should be changed in “Recently, it was reported that detection of pulmonary interstitial edema, by lung ultrasound evaluation of B-lines…“

R1: We appreciate this comment. According to the reviewer’s comment, we have modified the sentence (Page 4, Lines 10-13) of the revised manuscript as follows: Recently, it was reported that detection of pulmonary interstitial edema by lung ultrasound evaluation of B-lines has a high diagnostic accuracy for differentiating cardiac-related acute dyspnea from that due to chronic obstructive pulmonary disease (COPD) or bronchial asthma in the ED [3,10-14].

C2: Page 6: the sentence “The investigators attempted to detect a comet tail artifact” should be “The investigators attempted to detect comet tail artifacts” since AHFS is characterized by multiple B-lines.

R2: We also appreciate this comment. According to the reviewer’s comment, this has been corrected in the revised manuscript (Page 6, Line 14).

C3: When you refer to the collapsibility index, I suggest to cite the ASE/EAE Guidelines for the Echocardiographic Assessment of the Right Heart in Adults (Rudski LG et al. J Am Soc Echocardiogr. 2010 Jul;23(7):685-713). Did you measure IVC at end-expiration?

R3: We also appreciate this comment regarding the collapsibility. We always measured the IVC at both end-inspiration and end-expiration. Therefore we have cited the Rudski LG’s paper and modified the definition of collapsibility in the Methods section (Page 7, Lines 9-11) of the revised manuscript as follows: Finally, ultrasound evaluation of the IVC was examined within 2.0 cm of the IVC-RA junction. The maximum diameter (IVC max) was measured at the end-expiration and minimum diameter (IVC min) was measured at the end-inspiration [35].

C4: Page 11: when you list the ultrasound approaches (also shown in table 2) you do not include LV dysfunction. Is there a reason for that? In Table 2 “collapsibility” is misspelled.
R4: We appreciate these comments. First, we have added the ‘LV systolic dysfunction with moderate to severe mitral or tricuspid valve regurgitation’ in the Results section (Page 11, Lines 12-13) and in the revised Table 2. Second, the ‘collapsibility’ has been corrected in the revised Table 2.

C5: The employment of LUS for the evaluation of EVLW is also included in the EAE Position Paper on the use of pocket-size imaging devices. I suggest to mention it.

R5: We appreciate this comment regarding the extravascular lung water (EVLW). It is very important to evaluate the EVLW by the scoring of B-lines (Picano E, et al. J Am Soc Echocardiogr 2006;19:356-63). However, in this study, we could not evaluate the number of B-lines in all patients. Therefore, further investigation to evaluate the EVLW by a hand-held device for patients with acute dyspnea or AHFS in the emergency setting is needed. In the revised manuscript, we have added this comment in the limitation section (Page 14, Lines 14-17) as follows: Third, we could not evaluate the extravascular lung water in AHFS patients because we did not examine the number of B-lines. Therefore, further prospective investigation to evaluate the extravascular lung water by a hand-held device for patients with acute dyspnea in the emergency setting is needed.

C6: I suggest to add a few pictures of the US findings from your study population.

R6: We appreciate this comment. We have added the pictures of LCI integrated ultrasound findings in Figure 2 and the Methods section (Page 7, Lines 15-16) of the revised manuscript.