Author’s response to reviews

Title: Diagnostic performance of multi-organ ultrasound with pocket-sized device in the management of acute dyspnea.

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Version: 1 Date: 30 May 2017

Author’s response to reviews:

To Reviewer nr. 1:

We appreciate your thoughtful comments and valuable suggestions to improve impact our paper. For clarity in the manuscript draft we underlined additions in red and crossed out deletions in blue as you stated in editor’s letter. In this letter, we used red for our answers, italic red to report sentences of the paper and black for your comments.

We addressed your comments as follows:

1. The paper would improve if you could provide and compare also the accuracy values for other standard parameters that you have anyway recorded: clinical finding (you have Boston criteria), chest X-ray (by using a previously validated scheme for cardiogenic signs, or by a radiologist blind revision), natriuretic peptides (if it was part of your blood tests).

We thank the Reviewer for his/her comments. We have added the information regarding accuracy value of Boston Score (defined positive for a score 8-12) and chest X-ray (defined diagnostic of cardiogenic dyspnea if mention of pulmonary venous congestion and/or bilateral interstitial edema and/or alveolar edema was present). Evaluation of natriuretic peptides was not part of our routine blood tests.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>75</td>
<td>85.4</td>
<td>75</td>
<td>85.4</td>
<td>82</td>
</tr>
<tr>
<td>Boston score (8-12)</td>
<td>79.2</td>
<td>70.7</td>
<td>61.3</td>
<td>85.3</td>
<td>74</td>
</tr>
</tbody>
</table>

The above information have been added in table 3 and a comment in discussion section (Page 8 – Lines 3-7) has been added:

“In our study the diagnostic accuracy of chest X-ray and Boston clinical criteria risk score ≥ 8 was suboptimal for detection of patients with acute heart failure and was much lower compared to integrated ultrasound examination of Lung-Heart-IVC. As already demonstrated LUS performs better than Chest X-ray in identification of patients with acute heart failure, probably because of poor quality of X-ray in the setting of ED (18) (15).”.

2. Your definition of a positive exam is somehow arbitrary, because it is different i.e. from what indicated in the Consensus Document (your reference 10). I agree that this was necessary, given the simplified scanning scheme you used, but this should be highlighted in the text. In particular, one single scan with more than 3 B-lines and/or pleural effusion, would not be enough to define positivity in a more comprehensive chest evaluation. In my opinion, this is also the reason why your sensitivity for LUS alone is high, but not 100% as reported in other papers that used more comprehensive scanning schemes. Please, consider adding this consideration to the text.

We thank the Reviewer for his/her comments. We agree that a complete scanning examination of the thorax would have been useful to improve the diagnostic accuracy of the LUS but due to the emergency setting of our work and consequent time restrictions, we think that adopting a simplified protocol can match accuracy with efficiency. In the emergency setting a simplified protocol has already been used to assess the feasibility of LUS in the context of acute HF by Pivetta et al. using a six zone scanning protocol (1). Our sensitivity of 92.6% is comparable to that obtained by Pivetta et al (90.5%).

We have added in the discussion the following consideration (Page 8-9, Lines 22-3):

“One limitation of our approach in LUS should be highlighted: we decided to adopt a simplified protocol with only four zone scanning protocol to speed up the echo examination time. In the setting of ED this has already been done using a simplified six zone scanning protocol obtaining
a sensitivity for LUS alone comparable to what we have found (22). A more comprehensive scanning would have been optimal but also time consuming and so not feasible facing patients in critical condition.”

3. A drawing of your scanning scheme would also be useful.
A drawing of our scanning scheme has been done in Figure 1.

4. What do you exactly mean by “symmetrical”?
By symmetrical we mean the presence of abnormal finding at same level in both sides of the lungs. WE clarified this concept in the method section (Page 4, Lines 22-23).
“By symmetrical we mean the presence of IS and/or effusion in the same scans in both sides of the lungs”.

We have added the suggested paper and an accompanying sentence in the discussion section, (Page 9-10, Lines 23-5).
“In the diagnosis of acute heart failure the combination of reduced left ventricular EF and poor collapsibility of IVC has been demonstrated to have highest specificity and sensitivity for the diagnosis of HF (28), with an adjunctive specificity value for the LUS. In our paper we expand this finding demonstrating that a combination of positive LUS examination and reduced EF or IVC dilated and not collapsing demonstrates the best accuracy in the diagnosis of dyspnea of cardiac origin, mainly due to the ability of this combination to include a substantial proportion of patients with preserved EF-heart failure.”

The above reference has been added to the introduction section, (Page 3, Lines 15-17):

“Using pocket-size imaging device also the assessment of extravascular lung water with evaluation of B-lines and pleural effusion is feasible and reliable (8)”. 

Minor comments:

- I suggest using LUS as acronym for lung ultrasound for consistency with previous literature.
- Table 1, there is a typo: <cardiac> instead of <cardia>.
- In Table 3, I suggest to put the words <AND> and <OR> in capital letters, because the difference is very important and should be highlighted.
- Page 9, line 7: <is feasible and have reliable> should be <is feasible and has reliable>.
- Page 9, line 19: <ventricular> should be deleted.
- Page 9, line 41: <lines B> should be <B-lines>.

We thank the Reviewer for his/her careful editing. All the minor comments have been addressed.

We hope that our effort meets your expectations.

Alfonso Sforza,  
Costantino Mancusi

To Reviewer nr. 2:

We appreciate your thoughtful comments and valuable suggestions to improve impact our paper. For clarity in the manuscript draft we underlined additions in red and crossed out deletions in blue as you stated in editor’s letter. In this letter, we used red for our answers, italic red to report sentences of the paper and black for your comments.

We addressed your comments as follows:

1. The emergency physician is the "GOLD" standard for the diagnosis of dyspnea, this is a fundamental flaw in the approach. We cannot know that the patient had cardiac dyspnea or
non-cardiac dyspnea based solely on the emergency physicians diagnosis at the initial presentation. Furthermore the authors state routine blood tests were taken. What was included in them? "Routine" blood tests may vary significantly from health care provider to health care provider. Did they include troponin, Pro-BNP, D-dimer etc? Although the authors briefly mention they were unable to follow the patients clinical course and therefore final diagnosis at discharge. This is a significant limitation as we have no data on what the actual discharge diagnosis was. How many patients have there initial diagnosis changed at time of discharge from hospital? What are the p-values and confidence intervals of the listed results in table 3? Was there a power estimate performed before the study.

We agree that our paper has limitations. Our routine blood test investigations included all standard biochemical lab investigation, Troponin and D-dimer when clinically indicated. BNP and NT–pro-BNP where not standard part of our routine laboratory test in the setting of the emergency department where the study has been performed. However, we agree that these are limitations and we generated a paragraph of limitations at the end of discussion, where we listed a number of potential flaws of our observational study. Nevertheless, we think that our observation is relevant to design focused clinical trial on the issue of discrimination of cardiac from non-cardiac dyspnea.

After a full re-examination of all clinical folders, we have found that of the 68 patients enrolled 44 were admitted to Bufalini Hospital and 17 were temporary admitted in the ED ward. Seven patients were referred to other community hospitals and lost to follow-up. Among the 61 patients with discharge diagnosis, the Emergency Physician’s diagnosis was confirmed in 57 (93.4%).

We have added the following sentence in the discussion, limitation section (Page 10 -11 Lines 20-1)

“It was not possible to follow the clinical course of all enrolled patients because 7 of them were admitted to a different hospital after the ED evaluation. In the remaining 61 patients the EP diagnosis has been confirmed in 93.4% of the cases at the final hospital discharge. Since our aim was to evaluate the diagnostic accuracy of ultrasound in the ED we decided to adopt as diagnostic gold standard the EP diagnosis.”

Regarding the questions of p-values and confidence intervals of the listed results in table 3 we have added the CI in the tables. To answer about the p values we have built Receiving Operating characteristic (ROC) curve, comparing accuracy of the each different ultrasound modality (Lung, Heart, IVC) and the combination between bilateral IS/effusion and only 1 of the cardiovascular abnormalities (EF ≤40% or dilated and not collapsing IVC). Results are listed in Figure 2.

Figure 2.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area under curve (AUC)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS/ effusion AND EF ≤ 40% OR IVC dilated and not collapsing</td>
<td>0.894</td>
<td>0.787-0.958</td>
<td>-</td>
</tr>
<tr>
<td>IS/ effusion</td>
<td>0.859</td>
<td>0.744-0.935</td>
<td>0.39</td>
</tr>
<tr>
<td>IVC dilated and not collapsing</td>
<td>0.768</td>
<td>0.641-0.867</td>
<td>0.03</td>
</tr>
<tr>
<td>EF ≤ 40%</td>
<td>0.787</td>
<td>0.662-0.882</td>
<td>0.02</td>
</tr>
</tbody>
</table>

p vs IS/ effusion AND EF ≤ 40% OR IVC dilated and not collapsing

Legend: IS Interstitial syndrome; EF Ejection Fraction; IVC Inferior Vena Cava

The table above clearly demonstrate that the combined presence of bilateral IS/effusion AND only 1 other cardiovascular abnormalities (EF ≤40% OR dilated and not collapsing IVC) give the best accuracy to detect patients with dyspnea of cardiac origin

We have added in the method section the following sentence (Page 6 - Lines 7-10):

“Receiver operating characteristic (ROC) curves (AUC) are used to describe and compare the performance of each different ultrasound modality (Lung, Heart, IVC) and the combination between bilateral IS/effusion and only 1 of the cardiovascular abnormalities (EF ≤40% OR dilated and not collapsing IVC) versus the final ED diagnosis (16).”

We have added in the results section the following sentence (Page 7 - Lines 4-7):

“Figure 2 shows receiving operating characteristics (ROC) curves (AUC) of the different ultrasound diagnostic approaches evaluated. The combined presence of bilateral IS/effusion AND only 1 other cardiovascular abnormalities (EF ≤40% OR dilated and not collapsing IVC) has the highest AUC for the identification of patients with dyspnea of cardiac origin. Although the difference is not statistically significant from the LUS alone. Specificity is maximized”.  

There was no calculation of the power estimate before the study, but the patients have been enrolled consecutively when the responsible EP (AS) was available and not responsible of the care of the patient to ensure the blind process.
2. There are also a lot of acronyms used throughout the article which I find pointless and make reading the article arduous. I suggest that several of these be written out instead (such as EP, HF, CD, IUE, to name but a few).

We thank the Reviewer for his/her comments. The number of acronyms have been reduced.

We hope that our effort meets your expectations.

Alfonso Sforza,

Costantino Mancusi