Author's response to reviews

Title: Biomarkers of acute lung injury: worth their salt?

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Author's response to reviews: see over
Authors' response
Title: Biomarkers of acute lung injury: worth their salt?
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We would like to thank the reviewers for the close attention that they have given to our article. The modifications that they suggested have improved the quality and clarity of the manuscript hugely.

Reviewer 1
1. Sometimes emotional terms are used as 'frustrating', which is not very scientific.
The language has been “toned down”.

2. The figures are essentially the same and can be merged.
   Done.

3. Can the authors give directions for research into the biomarkers to become useful in clinical practise either as disease or outcome prognosticators? Any framework to be provided to rethink (what is to be predicted, how, when and why) and classify all this?
   Thank you, we have rewritten the Future Directions section (page 7).
Reviewer 2

1. Page 2, third paragraph, sentence that begins with “Similarly,” meaning of sentence is not clear. Which processes are being referred to and what does “similarly” refer to?
The paragraph has been rewritten to improve clarity.

2. Page 2, last paragraph, first sentence, do the authors mean that no pharmacologic treatments improve outcome in ALI? Low tidal volume ventilation and fluid conservative therapy improve clinical outcomes. Please clarify. In this same paragraph, the sentence that begins with “Hence half of ALI” is not clear. The way that the sentence is written it implies that the four reasons for mechanical ventilation were mechanical ventilation, transfusion etc. Please clarify. Also, please provide reference earlier in the paragraph for this study.
Thank you, this paragraph has been rewritten also and appropriate references have been added.

3. Page 4, first paragraph. Please provide more information about the results of the phase 3 studies. Most reader will not have inside knowledge that these studies were negative. It also might be helpful to expand this paragraph to discuss other problems with biomarkers as surrogate endpoints—improvement in P/F ratio is a good example that does not correlate with improved clinical outcomes in many clinical trials.
Agreed, we have included the results of the beta agonist trials and added some more detail about the use of EVLW(I) and P:F as surrogate end-points as suggested.

4. Page 4, second paragraph. A reference for the RAGE study should be provided here (ref 30?). If this is intended to refer to the Calfee study, then the study is misquoted. The study showed that RAGE levels were only associated with mortality in the high tidal volume group, not in the low tidal volume group. It did not show that the beneficial effect of tidal volume was only seen in patients with high plasma levels of RAGE. Quoting from the study, “In the highest quartile of baseline RAGE, the OR for death in subjects treated with lower tidal volume ventilation was 0.36 compared with those treated with higher tidal volumes (95% CI 0.19 to 0.67; p=0.001). In comparison, in the lowest quartile of baseline RAGE, the OR for death in subjects treated with lower tidal volumes was 0.52 (95% CI 0.26 to 1.00; p=0.05).”
You are right of course. This is very embarrassing and we are particularly grateful to you for pointing out this error. This section has been removed.

5. Page 4, second paragraph. The last point in this paragraph is a good one and could be expanded. Additionally a reference to the NHLBI workshop on this topic (Spragg et al. Am J Respir Crit Care Med. 2010 May 15;181(10):1121-7) would be helpful.
This reference has been included.

6. Page 4, last paragraph. Biomarkers of the established syndrome would also be useful for differentiating cardiogenic pulmonary edema from ALI/ARDS which can
sometimes be clinically challenging. Also, in the last sentence in this paragraph, it is not clear why “Similarly” is used and what it refers to.

The point about cardiogenic pulmonary oedema has been added and the offending “similarly” has been removed.

7. Page 5, first paragraph, the argument is presented that biomarkers are most likely to be useful when they are specific to a component or process that can be manipulated, suggesting that the biomarkers that are most effective are those that are related to pathogenesis. This seems to contradict what the authors say on the prior page, that biomarkers need not be related to pathogenesis.

Our opinion is that biomarkers that reflect individual processes that comprise ALI may be useful but that these biomarkers do not necessarily have to be part of the processes. We have attempted to clarify the text to make this point.

8. Page 5, second paragraph, last sentence. The meaning of this sentence is not clear to me. Do the authors intend to say that important contributors have not been accounted for by the model rather than what is currently stated? Please clarify.

Agreed thank you, sentence rewritten.

9. Page 6, paragraph 1, last sentence, meaning is unclear. What does the “it” in “it may hold promise” refer to? Please clarify. Also in this section, the argument for why OLV is a good model could be made more persuasively. If biomarkers are identified in the OLV model what would the next step be? Do the authors think that these biomarkers will translate to a more heterogeneous population?

Thank you the last part of this section has been rewritten to make it clearer and Figure 2 has been modified to help emphasise this point.

10. Page 6, section of Future directions. This section is quite vague, particularly the second paragraph and would benefit from rewriting/editing.

This section has been rewritten.

11. I did not find the figures to be very helpful and it was not clear to me what the point of the two figures is. I would consider leaving out the figures.

Figure 2 has been redrawn as one. The intention was to illustrate how complex coincident clinical processes can confuse the interpretation of biomarker data.