Reviewer's report

Title: Association between Insertion/Deletion Polymorphism in Angiotensin-Converting Enzyme Gene and Acute Lung Injury/Acute Respiratory Distress Syndrome: A Meta-Analysis

Version: 1 Date: 14 March 2012

Reviewer: Andy Overall

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This manuscript outlines the results of a meta-analysis of published studies based upon the proposed association between the ACE I/D polymorphism and the risk of, and mortality due to, acute lung injury/acute respiratory distress syndrome. This study identified a limited number of published reports that appear to support a relationship between this polymorphisms and mortality from ALI/ARDS in Asian populations.

The aim of this analysis is sound, but I would like to see some minor, but essential revisions in this manuscript before I could recommend it for publication. Starting from the beginning and working through:

1. Abstract; as elsewhere throughout the manuscript, more care is required to avoid ambiguous meaning. The results section states that the ACE I/D polymorphism was not associated with the condition. Given the nature of this analysis, this statement cannot be justified. Without a careful consideration of the power of the analysis conducted, which is absent from this analysis, positive conclusions regards insignificant results cannot be made. All that can be stated is that no significant difference between the polymorphism and ALI/ARDS state was observed. Without any appreciation of the power of this analysis, type-II errors cannot be dismissed.

2. Abstract; Are the differences in percentage mortalities between genotypes significantly different? If not, then these are not noteworthy and shouldn’t be highlighted in the abstract.

3. Abstract; The conclusion that the ACE I/D polymorphism “may” be a predictor of mortality was the rationale for this study. It cannot also be a conclusion. I would strongly suggest avoiding such passive conclusions and stick with the basic format: hypothesise that the I/D polymorphism is not a predictor and conclude whether this is or isn’t supported by the new analysis. I would also advise against stating that more work is needed; this never needs to be stated. Also, that the sample size was too small should be known before analysis. It is rather lazy to suggest post-hoc that you conclude, post-analysis, that your sample size was too small. Having not conducted a power analysis you are not able to conclude this; it is mere speculation. Speculation can be fine, but it needs to be made clear that it is such. But again, it has no place in the abstract, which should highlight the salient points (not speculative points).
4. Page 4; A major criticism is that this manuscript does not lay down the rationale for conducting this study in the opening paragraphs. Oddly, the rationale appears in the discussion. I would advise bringing this forwards to the “Background” and informing the reader as to why it was ever considered sensible to assess an association between ACE polymorphisms and ALI/ARDS.

5. Page 4; It is stated that “Genetic variations between individuals likely explain at least some of this observed heterogeneity”, but not why.

6. Page 4; more care is needed with the written English. An example: “Recently, strong evidence[s] has been accumulated in not only the kidneys but also the lung...”. It needs to be made clear that the evidence is accumulating for a relationship between kidney and lung disorders/diseases and ACE polymorphisms.

7. Page 5; Again, avoid being too vague. “Several epidemiologic studies have shown that the ACE I/D polymorphism MIGHT take part...”. Make it clear if some studies show strong support for this relationship, but others fail to find an association; or whether all studies find nothing more than a weak relationship.

8. Page 5; The sample size issue predominates throughout his study, so I would like to see this aspect dealt with more robustly. It isn’t enough to simply assume that a failed association is likely due to small sample sizes. What is a small sample size? “Quite small for an association study” needs justification. The appropriate sample size depends, for one thing, on the effect size. Are you suggesting that the influence of ACE I/D polymorphisms on ALI/ARDS is very small, and therefore sample sizes in the thousands are required? This would explain why so few studies are available for a meta-analysis, but would also question the worth of looking for a contributing factor with such low predictive power. Or are you suggesting that the ACE polymorphism potentially has a large influence, such that sample sizes of only hundreds are required, but which then begs the question as to why so few studies are available. Either way, a comment on sample size must be within the context of effect size.

9. Page 6; I’m confused as to why you have an inclusion criteria of a case-control study and an exclusion of studies without controls. This exclusion criterion appears to be redundant.

10. Page 6; It is stated that studies were not to be restricted by language. Is this the case? Going into a meta-analysis where you were prepared to include a study regardless of the language strikes me as rather ambitious. Were potential translators of every language represented in publication at hand?

11. Page 7; Statistical analysis; clarify that the alleles being referred to are dominant DELETIONS (I/I vs I/D + D/D) and recessive DELETIONS (I/I vs I/D + D/D).

12. Page 7; what does “were recommended the genetic model” mean?

13. Explain what I^2 is.

14. Page 8; the separation of Caucasian from Asian studies was post-hoc and should be in the discussion. This was not something you had planned as part of your analysis.
15. Pages 9-12. The presentation of the results is confusing. For each analysis it is stated that “The pooled OR derived from ALL STUDIES…”, which is misleading. It needs to be clarified how each of these analyses differed. Clarify that, for example, that studies that include healthy controls, have 418 patients. Likewise, studies that included controls without ALI/ARDS, have 448 patients? And so on. As it currently stands, this isn’t completely clear.

16. Page 13; As pointed out above, much of this discussion presents the rationale for this study and should, therefore, be moved to the introduction/background. The discussion should only include an analysis of this study’s findings.

17. Page 14; There appear to be results here that should be in the RESULTS section. For example, the D/D frequencies amongst patients and controls.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests