Author’s response to reviews

Title: Hypertension Outcomes of Adrenalectomy in Patients with Primary Aldosteronism: a Systematic Review and Meta-analysis

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Hypertension Outcomes of Adrenalectomy in Patients with Primary Aldosteronism: a Systematic Review and Meta-analysis” (ID: BEND-D-16-00217). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Reviewer #1:

1. Response to comment: As the second meta-analysis to be performed on this topic, the authors should explain why a repeat meta-analysis is needed, how their meta-analysis differs and what new information their paper brings to the literature. This should be addressed in the introduction.

Response: We have made correction according to the Reviewer’s comments, in the Introduction section, line 21-22, page 4 and line 1-8, page 5, while Reference 10 and 11 were added. Furthermore, line 2-3, page 10 in the Discussion section, the statements of “To date, we believe this is the second systematic evaluation of published studies……” was corrected as “Thus we performed a systematic evaluation of published studies……”
2. Response to comment: The methodology/study selection of this analysis is nearly identical to
the JCH meta-analysis and yet there is quite a difference in the number of papers retrieved for
analysis. From my perusal of the references, it looks like the present meta-analysis includes 7
Chinese language papers that would not have been used in the JCH paper but that still leaves 11
more papers that were used in this analysis but excluded from the first meta-analysis - can the
authors explain why this might be?

Response: We thank the Reviewer for pointing this out. We set ‘hyperaldosteronism’ and
‘adrenalectomy’ as search terms. This is a looser literature search strategy and more potentially
relevant studies are identified from all databases. We also retrieve Chinese database compared
with the JCH meta-analysis, including China National Knowledge Internet (CNKI), WanFang,
SinoMed and Chongqing VIP. In the literature search process, we not only retrieve electronic
database but also retrieved the references from all relevant publications to obtain a part of
studies. At last, some studies are easy to be excluded by mistake because they don’t directly
reported the prevalence of hypertension resolution. However, these studies provide sufficient
data from figure and table for derivation of the pooled hypertension cure rate. Thus there are 7
Chinese language papers that would not have been used in the JCH paper but that still leaves 11
more papers that were used in this analysis but excluded from the first meta-analysis.

3. Response to comment: Why did the authors choose a 6 month cut-point for follow up? It
would be useful to perform a meta-regression analysis looking at more time-strata to see if cure
rates decline over longer periods of follow up time, as has been previously reported.

Response: Previous research has shown that 6 months was chosen as an adequate end point
because the effects of adrenalectomy should be certain within this time frame (Zarnegar R et al.
Annals of surgery 2008, 247(3):511-518). We choose a 6 month cut-point for follow up in order
to excluding the influence of the operation itself on blood pressure.

4. Response to comment: Tables 3 and 4 are unnecessary and more suited to a general review
article, not a primary research paper. The discussion of such data is good but the actual tables
should be deleted.

Response: Considering the Reviewer’s suggestion, we have deleted Tables 3, 4 and relevant
content in the Result and Discussion section.
5. Response to comment: The authors need to mention the limitation whereby most original studies do not report post-operative aldo-renin ratios and as such, biochemical cure cannot be ascertained. The authors should discuss the reasons why blood pressure alone is probably not a good outcome of interest in PA studies when viewed in isolation.

Response: We thank the reviewer for the kind comments. We have made correction according to the Reviewer’s comments in the Discussion section, line 9-17, page 10 and line 10-11, page 13.

6. Response to comment: Reference 47 is incomplete

Response: We have corrected Reference 49 (Reference 47 is updated as Reference 49) in the Reference section, line 11-15, page 24.

7. Response to comment: Table 1 should list the reference beside the study

Response: We have listed the reference beside the study in Table 1

Special thanks to you for your good comments again.

Reviewer #2

1. Response to comment: The difference between the 2 periods, 2001-2011 and 2011-2016 could be completed by:

- an analysis of the type of imaging method used for the diagnostic
- the use of catheterism for adrenal vein samplings

The results described in the manuscript have a real interest and can be published

Response: Considering the Reviewer’s suggestion, we have made correction in the Discussion section, line 16-18, page 11.
Special thanks to you for your good comments again.

Reviewer #3

1. Response to comment: I would like to see the inclusion of the method of diagnosis of unilateral disease if feasible, given that cure of hypertension is likely to depend at least in part on what is left in the remaining adrenal. Even if only at the level of imaging vs AVS, it would be interesting given the results of the recent Spartacus trial. If not possible it should be mentioned as a limitation.

Response: Considering the Reviewer’s suggestion, we have made correction in the Discussion section, line 4-9, page 13.

2. Response to comment: Although briefly mentioned in the discussion (page 10 line 31) I think this needs further stress - complete cure of hypertension as a binary benefit/no benefit variable is an oversimplification. Many patients would perceive achieving control of blood pressure and a large reduction in medications as worthwhile. Additional quality of life benefits have been reported, as have very recent metabolic effects.

Response: We thank the reviewer for the kind comments. We have made correction in the Discussion section, line 13-17, page 10.

3. Response to comment: Table 4 needs to be labelled better - I believe this is referring to the individuals studies (?) included in the meta-analysis but that is not clear from the legend, title or column headers.

Response: We agree with the reviewer’s comment concerning this issue. However, in respond to a comment raised by the other reviewer, we have deleted Tables 4.

Special thanks to you for your good comments again.
We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

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