Author's response to reviews

Title: Standard b-Value Versus Low b-Value Diffusion-Weighted MRI in Renal Cell Carcinoma: a Systematic Review and Meta-Analysis

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Author's response to reviews: see over
Dear Editor(s):

Thank you for your interest in our manuscript entitled “Standard b-Value Versus Low b-Value Diffusion-Weighted MRI in Renal Cell Carcinoma: a Systematic Review and Meta-Analysis.” We have addressed both referees’ comments on a point-by-point basis below and have made the appropriate revisions to the manuscript. We look forward to your feedback.

Best regards,

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Referee 1

**Major Compulsory Revisions:**

None

**Minor Essential Revisions:**

1. *In the Methods, make all the heading consistent in terms of capitalization style.*
   
   We have reviewed all the headings and made them consistent.

2. *In the Methods, please rewrite the "Ethics Statement" subsection - it is grammatically flawed.*
   
   We have corrected the English grammar in this section.

3. *In the Methods, some text uses future tense (e.g., lines 74-75). Please make the tense consistent.*
   
   We have reviewed the entire Methods section and corrected all tense errors.

4. *In the Author Contributions, some contributions do not make sense for a meta-analysis. For example, "clinical studies" and "experimental studies" are not relevant to a meta-analysis. Please revise the contributions to describe the exact role(s) of each co-author.*
   
   We have revised the author roles in the Author contributions.

**Discretionary Revisions:**

1. *In the Introduction (lines 37-39), I would describe the concept of b-value in a little more depth so a reader not versed in DW-MRI technology grasp it better.*
   
   We have explained the concept of b-value in DW-MRI in more detailed terms in the revised Introduction section.
Referee 2

General Comments:

This is a systematic review and meta-analysis of the literature, comparing intermediate and high b-value diffusion weighted imaging (DWI) for the diagnosis of renal cell carcinoma. The authors included four manuscripts for review and found a pooled sensitivity of 59% and specificity of 50% for high b-value DWI compared to a sensitivity of 58% and specificity of 23% for intermediate b-value DWI. Based on receiver operator characteristics analysis, the calculated area under the curve was 0.61 for high b-value and 0.68 for intermediate b-value DWI. The authors conclude that high b-value DWI has superior specificity, but equivalent sensitivity for renal cell carcinoma, but that intermediate b-value DWI has superior overall accuracy.

A previous meta-analysis has suggested that apparent diffusion coefficient (ADC) analysis from DWI could differentiate malignant from benign renal masses, but did not evaluate the strength of diffusion imaging (European Radiology 2014; 24:241-49). Another recent manuscript has suggested that in-phase signal loss, likely related to hemosiderin deposition, is present in nearly 21% of renal masses and up to 42% of papillary renal cell carcinomas (AJR Am J Roentgenol 2014;203: W421-28). The presence of hemosiderin within renal masses has the potential to affect DWI, which is sensitive to local magnetic susceptibility-induced intravoxel dephasing, and may in part explain the limited sensitivity of DWI for the diagnosis of malignant renal masses seen in this meta-analysis. Also, one cannot rely on a single MRI sequence to differentiate benign from malignant masses, and when intravenous contrast cannot be administered, such as in patients with end-stage renal disease, T1 and T2 heterogeneity can be very important.

Major comments that need to be addressed in a revision:

1. Please comment on recent literature that describes hemosiderin within many renal masses and how hemosiderin may affect DWI in the discussion section.

   We have added commentary on this issue to the third paragraph of the Discussion section as requested.

Other comments that should be addressed:

1. Page 3, line 56: Should read "as follows".

   We have changed the language as requested.