Author’s response to reviews

Title: The VENUS prognostic model to predict disease recurrence following surgery for non-metastatic papillary renal cell carcinoma: development and evaluation using the ASSURE prospective clinical trial cohort

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Author’s response to reviews:

Diana Samuel, PhD
Associate Editor
BMC Medicine

RE: BMED-D-19-00474R1

Dear Dr Samuel,

Enclosed please find our revised manuscript entitled "The VENUSS prognostic model to predict disease recurrence following surgery for non-metastatic papillary renal cell carcinoma: development and evaluation using the ASSURE prospective clinical trial cohort" (Manuscript ID BMED-D-19-00474R1). We would like to thank you for considering our revised manuscript for publication in your journal. We are certain that the suggestions will improve the quality of our manuscript. We have carefully considered the points that have been raised, and detail our changes below. The changes in the manuscript are marked in yellow. Changes in figures and pdf files are not marked but described in detail.

Reviewer #3 - Kay See Tan

Please clarify the procedure of multiple imputation. After creating 5 imputed datasets by chained equations, "we used the median of the five imputed datasets for evaluation of ASSURE." (p8 lines 13-15). Please provide the appropriate reference to justify the use of the "median" values rather than data from all 5 imputed datasets. Conventionally, a model would be fit to each of the imputed datasets, and the model coefficients from each of the 5 imputed datasets would be "pooled" using Rubin's Rules (Rubin, 1987; Rubin & Schenker; 1986; and Little & Rubin, 1987).

We thank the reviewer for this comment. We apologise for the error and have now clarified the methods. Rubin’s rules were indeed followed to pool the model parameters from the imputed datasets. The pooling function is included in the mice library. We have updated the “Methods” (page 8), added a comment to the legend of “Supplementary Table 2” (last sentence) and included appropriate references (#28, #29).

Minor:

- Figure 1C: label the curves or provide figure legend

We thank the reviewer for this comment. Labels are now provided in “Figure 1C”.
- Figures 4 A-C: include numbers at risk at each time point

We thank the reviewer for this comment. The numbers at risk are now provided in "Supplementary Figure 4".

- Supplementary Table 1 (Validation cohort) should now state "Independent cohort" based on your edits.

The reviewer is correct. Supplementary Table 1 has been corrected.

- Figure 2A and Supplementary Figure 3 Calibration Plots: The y-axis can't possibly be "frequency" - It should be "observed event probability" - or better year, "observed 5-year cumulative incidence of recurrence"

We thank the reviewer for this comment. The y-axis labels in Figure 2A and Supplementary Figure 3 have been corrected.

We appreciate your favourable consideration of this manuscript for publication in BMC Medicine, and hope that these revisions address the reviewer’s recommendations in order to improve the quality of the manuscript.

Sincerely yours,

Tobias Klatte