Author's response to reviews

Title: Prognostic survival model for people diagnosed with invasive cutaneous melanoma

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Author's response to reviews: see over
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Dafne Solera,
Executive Editor
BioMed Central

Dear Dr Solera,

Thank you for providing the reviewers' comments for our submission to BMC Cancer titled “Prognostic survival model for people diagnosed with invasive cutaneous melanoma”.

We have addressed each of the comments in turn, and provided details of our responses on the following pages.

We look forward to hearing from you regarding our submission.

Yours sincerely,

Peter Baade
[on behalf of the co-authors]
Reviewer: Branko Miladinovic

1. It would be useful if the authors commented on other (if any) survival models that have been proposed for melanoma patients in the past. This was not clear in the manuscript and from references 11-13. A thorough literature search may be in order.

Author response:
While there are many studies in the literature that have considered melanoma survival, we are aware of very few that have developed a prognostic model in a systematic way. We are not aware of any additional models for melanoma other than the ones already referenced. The prognostic models using the American Joint Committee on Cancer Melanoma Database have been the most widely reported, however these are limited in that the melanomas are sourced from specialist cancer centres, rather than being population-based as in our study.

2. Although the authors did not detect any significant time-dependent effects, it would be useful to the readers to mention in the Discussion that in the presence of (multiple) time-dependent effects, interpreting the time-dependent hazard ratios is difficult in the log cumulative hazard framework of the Royston-Parmar models. For alternatives, refer to Crowther and Lambert, "A general framework for parametric survival analysis," Stat in Medicine 2014, DOI: 10.1002/sim.6300

Author response:
One important characteristic of the probit (and logistic) models in the Royston-Parmar family is that ALL covariate effects have time dependent hazard ratios - an HR comparing any two values of a covariate moves towards 1 over follow-up time (see section 7.4 of reference #21). However, we found no (strong) evidence that the regression coefficients in our probit model were associated with time. We have added the following text to this section in the discussion. (Pages 15-16)
“We did not find any time-dependent regression coefficients of sufficient impact to include them in the final model. Proponents of other prognostic models using large epidemiological cancer datasets have observed time-varying coefficients[40-42] on the hazard scale. However, in our probit model, hazard ratios comparing any two values of a covariate can be shown to tend towards 1 as follow-up time increases. Thus, all hazard ratios are time-dependent. When there are multiple time-dependent regression coefficients, interpreting the time dependent hazard ratios can be difficult in the log cumulative hazard framework of the Royston-Parmar models.[21] The reason is that hazard ratios depend on the values of more than just one covariate. Alternatives, including modelling on the log excess hazard scale, may offer more interpretable options when time dependent coefficients are present. [43]”

3. I presume that the readers of BMC Cancer are clinicians and not statisticians. It would be useful if the authors elaborated on page 9 what “while there was some evidence that sub-site had a time-dependent association with survival...” means or implies clinically.

Author response: A brief elaboration of this association has been provided on pages 9-10. The revised paragraph now reads as follows:

“There was some evidence that sub-site had a time-dependent regression coefficient, so that the survival differential by subsite varied on the probit scale by follow up interval. However the effect was small and of no clinical relevance, and so was not included in the final model. Therefore, the selected model had no time-dependent regression coefficients.”

4. On page 14, the authors refer to the impact of competing risk within the flexible framework. Some work has been done recently in that area (see Hinchliffe and Lambert. "Flexible parametric modeling of cause-specific hazards
to estimate cumulative incidence functions” BMC Medical Research Methodology 2013, 13:13.

**Author response:** We added this reference to the text relating to competing risks. (Page 15, reference 40).

5. Finally, presuming the authors would want their model to be tested and used in other (heterogeneous) populations, it would be useful if they commented in the Discussion on how a researcher may do so in the context of the Royston-Parmar survival model, knowing the baseline function, scale used (probit), the knot positions and the prognostic indices the authors report in the manuscript.

**Author response:** We have added the following text to the discussion section (Page 14):

“Validation using an external dataset would entail calculating the prognostic index using the parameter estimates from this study cohort applied to the covariate values of the secondary dataset. Similarly, the baseline survival function is calculated in the external dataset using both the parameter vector from this study cohort, together with the (log) time values in the external dataset and the set of spline knots used in the current cohort.[36]”

**Minor**

1. Page 5, last sentence should read "The Royston-Parmar models were fitted using the stpm2 package (20, 28)."

**Author response:** This has been corrected in the text (Page 5)

2. The authors use "multivariate" instead of "multivariable" throughout the manuscript (page 6, page 9 heading "Multivariate analysis").
**Author response:** The word “multivariate” has been replaced with “multivariable” as noted throughout the text.

**Reviewer:** Therese Andersson

1. It is stated in the methods section that anyone with more than one diagnosis of melanoma is excluded. Is this correct or is it anyone with a known diagnosis before start of the study? When selecting a cohort, members of the cohort should not be excluded based on what happens during follow-up, only based on information at baseline. So, the best approach here would be to only consider first diagnosed melanoma, leading to exclusions of everyone with a diagnosis prior to 1995. And for all diagnosis during 1995-2008, only the first diagnosis for each individual is considered.

**Author response:**

The investigator team discussed this issue in detail during the planning of the study. Our focus for this study was to develop a prognostic model based on the characteristics of the melanoma. Where there are multiple melanomas involved, we had no way of knowing which melanoma caused the death of the patient. We acknowledge that should a subsequent melanoma be diagnosed, the predicted survival probabilities from the MSI would no longer be relevant. We have added the following sentence in the discussion (Page 14).

“Finally, since we included only patients with one diagnosed melanoma to ensure a greater link between the melanoma characteristics and survival outcome, the predicted survival outcomes would no longer be relevant if a subsequent melanoma was diagnosed.”

2. I lack a discussion about the assumptions underlying the multiple imputation. What are the likely reasons for missingness and are the
assumptions fulfilled?

Author response: We have added the following text to the discussion section (Page 14).

“The use of multiple imputation for missing data assumed that the data are missing at random (MAR). We were not able to rule out that the data are missing not at random (MNAR), and it remains possible that there is some unmeasured characteristic of the treating clinician or pathology laboratory that impacted on the completeness of the registry data.”

3. I would like some more description on how the proportional hazards assumption was tested? How many degrees of freedom?

Author response: We initially assessed the suitability, according to goodness of fit (BIC statistic), of the three different scales available in the Royston-Parmar model class: cumulative hazards, cumulative odds and probit. The last of these was found to be superior and was therefore adopted. We did no formal testing of non-proportional hazards since there was no need to do so. We have included additional text in the following paragraph in the methods section to describe the testing of time dependent covariate effects (Page 7).

“Finally, we used a forward selection process to investigate whether the regression coefficients for any variables depended on follow-up time using the approach described by Royston & Parmar.[21],[22] with one degree of freedom for the time dependent covariate effects. This approach modifies the spline function of time used to model the baseline distribution function and is implemented using the stpm2t command in Stata. Covariates without time dependence were included in the model in standard fashion.”

4. Related to the comment above, I was surprised that no covariates needed
time-dependent effects, since that is often needed when modeling cancer mortality. Age is for example a covariate with time-dependent effect. Could the authors perhaps add a comment on this in the discussion?

Author response:
We found no evidence of age having a time varying covariate effect. We have added the following comment to the discussion (Page 15). Please also see our response to Reviewer #1, point #2.

“We did not find any time-dependent regression coefficients of sufficient impact to include them in the final model.”

5. In the last paragraph of the results, there is no mentioning of how the survival estimates compare to MPOPT. Consider adding this.

Author response: We have added the following text to the last paragraph of the results section (Page 12):

“When comparing the MSI and the MPOPT (Table 5), the predicted 10-year survival percentages for MSI were generally higher than for the MPOPT, with the exception of the two most advanced cases of melanoma.”

6. Concerning the final covariates chosen for the MSI, there is not much discussion about how this compares to covariates in other prognostic models, or other studies.

Author response: We have added the following text to the discussion section (Page 14):

“Importantly, we did include variables that were demonstrated by others to be significant predictors of melanoma survival by other studies, notably
7. Related to the comments above, did the authors consider including gender in the MSI? Gender has been shown to be an important predictor of melanoma patient survival in many studies, and since gender should always be known to the primary care physician it might as well be included even though a parsimonious model is preferred.

Author response:
We did consider including gender in the MSI. However as we have stated in the manuscript, we were interested in building the most parsimonious model for use in primary care practices. We found strong evidence that while gender had a significant association with melanoma survival, it provided very little prognostic value over and above that provided by the other variables in the model. In addition, the MPOPT melanoma prediction tool did not include gender in their final model.

8. In the last sentence on page 5 the references seem to be incorrect.

Author response: These references have been corrected. (Page 5)

9. In the description of the Royston-Parmar model it states that 3 degrees of freedom was used, but 2 knots. Should this be 2 internal knots and 2 boundary knots?

Author response: This sentence has been expanded to know read as follows: (Page 7)

“For our data, the probit scale with 3 degrees of freedom (or 2 “knots”) provided the best fit. These 3 degrees of freedom equate to 2 interior knots along with the 2 boundary knots.”

[END]