Author’s response to reviews

Title: Validity of the CR-POSSUM model in surgery for colorectal cancer in Spain (CCR-CARESS Study) and comparison with other models to predict operative mortality

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Version: 2 Date: 29 Mar 2017

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Please see our point-by-point responses to the editor or the reviewers here below.

Editor Comments:

1) Methods, Line 139 “All the hospitals provided services…” perhaps you should include location into the end of the sentence so that it reads “and their size, location and level of technology varied”

Included in page 7, methods, Line 147

2) Declarations: Please include a Consent to publish section, even if this is not applicable to your study. (see below for further guidelines)
3) Please upload English language versions of all interview questions developed specifically for use in this study as supplementary files. If the questionnaires are not yours or are already published by you, please supply references and/or links to them.

Dear Editor, there are no interview questions in data analyzed for this manuscript; clinical data was gathered from clinical records. We have made a small change in the sentence that you'll find in the 'variables and data collection' section, page 8, line 163.

Reviewer reports:

Kate Walker (Reviewer 2): I still recommend this paper for publication, subject to corrections. Most but not all of the specific comments that I made have been addressed very well. I made 4 major comments about the paper. The authors have responded to me clearly about these 4 issues but haven't made enough changes to the manuscript in response to these. I will address these 4 comments in order and state what I think needs changing within the manuscript to deal with them.

Dear reviewer, we apologize if every question was not clearly addressed, we have tried to be more explicit in the manuscript.

1. Justification needs to be made within the manuscript for the choice of the 4 models that are included, as they do not include all relevant models. The authors justified this in their response to me but not in the manuscript.

In the Background section, pages 5-8, you'll find in yellow a clear justification about the selection of the 4 models included in our analyses (line 96, 113, 127-134). He hope these sentences improve the explanation.

2. Justification needs to be made within the manuscript for the need to externally validate these models when external validations have already been published. The authors explained to me in their response that the intention is to re-calibrate these models for use in Spain, and to validate these for use in Spain. Therefore (i) this aim needs to be made clear in the introduction, and (ii) the re-calibrated model equations need to be presented.
In the Background section, pages 6-7, you'll find in yellow some sentences (line 128-131) as well as a more detailed aim (line 137). Also, the Appendix D and E, show the recalibrated equations of the different models.

3. The authors are not clear within the manuscript whether they are comparing a model for risk adjustment in order to make comparisons between healthcare providers or a prognostic model to guide clinical decision making. The introduction implies they are interested in risk adjustment but the discussion implies they are interested in clinical decision making. This needs to be clarified.

Some modifications have been included in the Background section: In page 6, line 96, the sentence avoids any issue about comparisons between healthcare providers.

4. This relates back to point 2. If the intention is to validate the models for use in Spain then this aim needs to be made clear in the introduction.

The specific comments that I made that I do not feel have been adequately addressed within the manuscript are points 3 and 6 which relate to the methods used for missing data, and efforts made to investigate the impact of missing data. It needs to be stated in the methods section that a complete case analysis was used for each model (i.e. patients missing on any risk factor were excluded). It then needs to be stated in the results section that the number of patients included in validating each risk model differs and the numbers included need to be stated for each model. This is important because up to half of patients are excluded due to missing data in some of the analyses. In addition, some explorations of the impact of the missing data needs to be explored. It is not enough to explain why the values were missing; the likely bias from excluding incomplete cases needs to be explored. To do this there needs to be a comparison of the characteristics of the patients excluded versus those included, in particular comparing the mortality in the complete and incomplete cases.

We completely agree that missing cases can lead to a possible bias. For this reason, in the limitations section we took into consideration this possibility. We considered that 'limitation is due to the models’ incompatibility with the available clinical information and/or routine clinical practice in our context'. See for example the missing cases in 'weight loss' variable. According to the reviewer's suggestions, in page 10, line 211, we have added the sentence "For these purposes, patients missing on any risk factor were excluded".

Also, in the results section, page 11, line 240-241, we state that the number of patients included in every model is different. In fact, the number was detailed in table 3 but, now, we have also
added the number of deaths included in the model, both for in-hospital mortality and for 30-day mortality estimation.

We think that for our purposes, and following the reviewer's suggestion, showing the number of patients and outcomes available in each analysis allows the reader to gain an idea of two aspects: first, the possible feasibility of using these models in the Spanish context based on absences of information and, secondly, if the mortality of the sample analyzed has been affected by these absences. In order not to overload the manuscript, and since the objective was to validate the models in the Spanish context and under usual clinical practice conditions, a comparative analysis of variables in the included patients with respect to those not included is not shown.