Author’s response to reviews

Title: Multiple aneurysms in subarachnoid hemorrhage - Identification of the ruptured aneurysm, when the bleeding pattern is not self-explanatory. Development of a novel prediction score.

Authors:

Alexis Hadjiathanasiou (alexis.hadjiathanasiou@ukb.uni-bonn.de)
Patrick Schuss (patrick.schuss@ukb.uni-bonn.de)
Simon Brandecker (Simon.Brandecker@ukbonn.de)
Thomas Welchowski (welchow@imbie.meb.uni-bonn.de)
Matthias Schmid (matthias.schmid@imbie.uni-bonn.de)
Hartmut Vatter (hartmut.vatter@ukb.uni-bonn.de)
Erdem Güresir (erdem.gueresir@ukb.uni-bonn.de)

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Author’s response to reviews:

Author’s Revision Letter

Dear Reviewers, dear Editor,

We would like to thank you for your comments. We have addressed each of the concerns mentioned point-by-point below and hope that they are adequate in this regard. Please note that our responses are not marked in the manuscript, as advised. The corrections are mentioned below. We think that the quality of the manuscript is now improved and hope that it is suitable for publication in BMC Neurology.

Response to reviewer

Reviewer #1, Mr. James Burk, MD, MS:

Point 1

1. I only find the authors' argument in favor of their analytic technique partially persuasive. First, their argument that overfitting is unlikely to be a large problem is based on a rule-of-thumb that was derived from simulations using logistic regression. Yet, they have chosen a technique that
requires more data to fit a model and, thus, is more susceptible to overfitting. (Also, it is likely that the rule of thumb is itself somewhat suspect). Second, and more importantly, I discussed overfitting as part of a broader point — there is no justification for why the authors chose this model. Why choose a model that increases the risk for overfitting when the upside of that model is that it enables variable selection, when you have adequate prior data to inform variable selection? The authors implied argument is that the risk for overfitting is less than the gains from variable selection. Yet, they neither explicitly state this argument nor defend the reason why automated variable selection is important.

At the end of the day, it is unlikely to influence the conclusions one way or the other, but I would have like to have seen a justification for wy this

In addition to our previous arguments during the last revision of the manuscript we want to clarify that we wanted to develop a good prediction model and for that purpose the boosting model is theoretically more suitable. ‘We agree that a large external validation sample would allow for a much better evaluation of overfitting than the smaller sample considered for our analysis. On the other hand, we have used the best available methods to make model validation in our paper as fair as possible. In particular, we used nested cross-validation to determine the number of boosting iterations and the performance of our prediction model. It must be emphasized that the performance of logistic regression would have suffered from the small sample size as well, since the coefficients of this model would also have to be estimated from the small sample and would thus be subject to potential overfitting (even if all variables have been pre-specified correctly). Furthermore, based on our experience, we are confident that overfitting due to variable selection is not a severe problem, since the number of patients (n=252) was relatively large compared to the number of candidate variables (only 10).’

In the next two paragraphs we want to give more detailed reasons of our model choice:

Overfitting would occur, if the performance of the prediction model is much better on data used to fit the model than on their performance of an independent test set. We did not simulate new data but used the available data to estimate the predictive performance of our approach to check overfitting according to its definition, which we think is more appropriate than relying on subjective risks judgements without evidence. Second the boosting model in general does not require more observations for estimation than a logistic regression model. Instead the former is more flexible, because it does allow tuning of predictive performance by adaption of the regression coefficients, which usually yields a sparser representation. This results in a finer model adjustment between prediction bias and model uncertainty, while there is no such tuning available in logistic regression. Logistic regression can only be adapted by including prior knowledge into the regression formula and their coefficients are less flexible, because they are special cases of the adapted coefficients in the boosting context.

Note that relying too much on prior knowledge also has disadvantages: Expert opinions may differ for example due to experience biases and it is difficult to assess the reliability of expert opinions. Even if most experts agree on some theory there is always the danger of confirmation bias, e. g. that the statistical analysis just represents the subjective opinion of the expert and not
the complexity of the true underlying phenomena. We wanted to apply a less restricted explorative approach to reduce the risk of those mentioned biases. Furthermore, our approach allowed a straightforward extraction of simple scoring rules, which can be readily applied in practice.

Changes made on page 5, line 126-127: The coefficients of logistic regression are included in the search space as a special case of the more flexible gradient boosting model.

Editors comments:

Point 1

Please address the remaining reviewer comments.

We responded to the comment of reviewer Nr. 1 and as shown above. We hope with our response the statistical issues are now solved.

Point 2

In the "Ethic approvals and consent to participate" section, please clarify why consent for participation is not required. Please clarify if an ethics committee provided a waiver for informed consent and cite the appropriate legislation.

For retrospective analyses, the ethics committee provided a waiver for informed consent. For the prospective series, ethic approval was existing (No.: 331/12).

Changes made on Page 14, Lines 352-354: The appropriate permissions to access the patient database which provided the data for our study were granted by the Department of Neurosurgery, Rheinische Friedrich-Wilhelms-University, Bonn, Germany and approved by the local ethics committee (No.: 331/12).

Point 3

Please move the information provided in the "Disclosures" section to the Competing Interests section.

The information provided in the ‘Disclosures’ has been now moved to the Competing Interests section.

Point 4
Please state in the cover letter whether the model images of a person depicted in figure 5 are your own or taken from another source.

Figure 5 belongs to the corresponding author.

Again, we would like to thank you for thoroughly reading the manuscript after the revision and for the final suggestions for further improvement of our manuscript.

Yours sincerely,

Alexis Hadjiathanasiou, M.D.

(on behalf of the authors)