Reviewer's report

Title: Validation of prediction models based on lasso regression with multiply imputed data

Version: 1 Date: 12 May 2014

Reviewer: Ewout Steyerberg

Reviewer's report:

This is a well-described and carefully done study. It addresses important issues in prognostic modeling: variable selection and estimation of regression coefficients, and issues of validation in the presence of imputed data.

Major comments:

1. One may debate the methodological approach.

   E.g. on page 4, model performance, Step 2: it seems a bit artificial to determine apparent performance for an averaged model in each of 10 imputed sets? The imputed sets each have a model that is optimal for their setting? Why not use these 10 apparent performances for step 3? This needs at least further motivation.

   On the other hand, if we aim for an averaged model, why not derive this directly from the 10 imputed sets? This was proposed by Chen and Wang, Stat Med 2013 <ref 31>. Their MI-Lasso would be expected to be evaluated in the current paper. The MI-Lasso prevents the situation that a variable is selected in e.g. 1 of the imputed sets, and not in 9 other sets; is a value of 0 assumed for the latter 9 sets? But then the aim of selection is not met anymore? And what if we increase the number of imputations to say 50 for more stability? No selection is achieved anymore?

   So, please consider replacing the current procedure by the MI-Lasso procedure. The discussion refers to the MI-Lasso approach as an alternative; to me it is a dominant procedure with better motivation than what is done in the current paper.

2. Re validation with MI, method 1 is theoretically the most plausible approach, as stated by the authors. It is also finally recommended if I understand correctly.

   This makes me wonder what the key scientific contribution of the paper is: the Lasso procedure is implemented for MI in a suboptimal way (but this can be corrected), and the validation results confirm that what seems most reasonable to do is indeed most reasonable?

   Is the main new research finding that the Lasso is optimistic when we assess MSE and other performance measures? But what has this to do with missing values and MI?

   Please consider sharpening the message of the paper.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests