Reviewer’s report

Title: Predictors for independent external validation of cardiovascular risk clinical prediction rules: Cox proportional hazards regression analyses

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Reviewer: Kuanrong Li

Reviewer’s report:

Many risk prediction rules (mathematical models) have already been developed for diagnosis and prognosis of chronic diseases, including cancer and cardiovascular disease. Instead of developing new models from scratch, researchers should focus more on validating, modifying, and updating the existing models. Before clinical adoption, risk prediction rules should be carefully validated in independent populations. However, a large majority of risk prediction rules have never been revisited by other researchers for external validation since their debut. This article aims to explain this phenomenon in a quantitative way. The authors’ objective seemingly can be understood as building a risk prediction rule to predict the possibility for a prediction rule to be externally validated (if this is the case, shall we assess its own reliability?). From a methodological perspective, one major concern is the study's univariate survival analyses due to the small sample size and the low number of events. However, a multivariable analysis is equally challenging because the selected features of the prediction rules are correlated. For example, it is not difficult to imagine that studies from the United States usually have a large study population and therefore are more likely to be accepted by high-ranking journals. The authors therefore should consider refining their selection of the features. A number of issues need to be clarified as well (see below).

Abstract

p2, line 29-30: it is not clear how the authors calculated the time variable for the CPRs that have never been externally validated (i.e. the definition of the time at censoring, or the survival time as the authors referred to in the next paragraph).

p2, line 32: the 12 characteristics should be listed here. The authors should also clearly state that the Cox regression was actually univariate.

p2, line 37-38: Is it a coincidence that the 25 percentile of the event time is equal to the 75th percentile of the survival time? Since there are only 29 event times, consider reporting the range (as well).

p2, line 45-47: consider replacing "incidence" with "likelihood", or simply use "xxx times more likely…".
p2, line 49-50: consider deleting this sentence, since a similar sentence has already appeared in the Background paragraph.

So far some concerns regarding the Cox model:

1. Among the 125 CPRs, some might be the modified version of the others and they are not independent. It is unclear whether and how the authors handled this situation (at least it should be discussed).

2. Consider adjusting for the "age" of the CPRs.

Methods

Please add the number of studies excluded according to each of the criteria (e.g. p7 line 124-127, p8 line 156-159, etc.).

p8 line 150-151: please list in this paragraph the predictor variables and their definitions. This information is important and should be presented in the main text.

p11 line 225-226: Figure 3 and 4 are not the results of Cox univariate analyses, please correct. Please explain why KM analyses are necessary in addition to Cox regression. The authors mentioned that the proportional hazards assumption was not violated. However, there are obviously some crossing curves in the KM plots.

p11 line 226-227, p12 line 233-235: please report the direction and the effect size of the associations.

p13 line 256-261: it should be kept in mind that some studies are more likely to be accepted by high-IF journals, for example those with a large sample size or from certain countries.

p14 289-291: again the censoring mechanism remains unclear: for CPRs received external validation, the follow-up ends at the date of validation, then when did the follow-up end for CPRs that have not been externally validated?

Page 12 line 248 to page 14 line 285: this part to some degree is a repetition to the Result section, consider deleting some words.

Table 2 last row: replace median(IQR) with one unit increase

**Level of interest**

Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests
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