

Statistical issues in the development of COVID-19 prediction models

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To the Editor,

Clinical prediction models to aid diagnosis, assess disease severity or prognosis have enormous potential to aid clinical decision making during the covid-19 pandemic. A living systematic review has, so far, identified 145 covid-19 prediction models published (or preprinted) between 03-January-2020 and 05-May-2020. Despite the considerable interest in developing covid-19 prediction models, the review concluded that all models to date, with no exception, are at high risk of bias with concerns related to data quality, flaws in the statistical analysis and poor reporting, and none are recommended for use¹. Disappointingly, the recent study by Yang and colleagues describing the development of a prediction model to identify covid-19 patients with severe disease, is no different. The study has failed to report important information needed to judge the study findings, but numerous methodological problems are apparent².

Our first point relates to sample size. The sample size requirements in a prediction model study are largely influenced by the number of individuals experiencing the event to be predicted (in Yang's study, those with mild covid-19 disease, as this is the smaller of the two outcome categories). Using published sample size formulae for developing prediction models³, based on information reported in the Yang study (40 predictors, outcome prevalence of 0.489), the minimum sample size in the most optimistic scenario would be 538 individuals (264 events). To precisely estimate the intercept alone requires 384 individuals (188 events). The study by Yang included 133 individuals, where 65 had the outcome of mild disease, substantially lower than required.

Developing a prediction model with a small sample size and large number of predictors will result in a model that is overfit, including unimportant or spurious predictors, and overestimating the regression coefficients. This means that the model will appear to fit the data (used in its development) too well – leading to a model that has poor predictive accuracy in new data. An important step in all model development studies is to carry out an internal validation of the model building process (using either bootstrapping or cross-validation), whereby the overestimation in regression coefficients can be determined and shrunk as well as estimating the optimism in model performance⁴. This important step is absent in the study of Yang, who reported an AUC of 0.8842 in the same data used to develop their model – this will almost certainly be substantially over-estimated.

Another concern is the actual model. The final model contains seven predictors and the authors have fully reported this permitting individualised prediction. However, an obvious and major concern is the regression coefficient reported for procalcitonin, with a value of 48.8309 and accompanying odds ratio with confidence interval of “>999.999 (>999.999, >999.999)” (sic). This is clearly nonsensical, and to put it bluntly, makes the model unusable. The reason for the large regression value (and standard error, confidence interval) is due to an issue called *separation*⁵. This occurred because there was little or no overlap in the procalcitonin values between individuals with mild and severe disease. The statistical software used by the authors, SAS, will report odds ratios as >999 when this occurs. Instead of retaining this in the model as is, one preferred approach would be to use Firth’s correction, available in both SAS and R⁴. The authors used the model to develop an early warning score – this score has not been presented by the authors – and we caution against such an approach with preference for alternative formats that permit estimation of absolute risk⁵.

Other concerns include the handling of missing data. Whilst the authors mention discarding observed values with more than 20% missing - it is unclear whether individuals were omitted, or whether entire predictors were omitted. Regardless, one can only assume a complete-case analysis was conducted in preference for more suitable approaches using multiple imputation⁶. Finally, we note the use of univariate screening, whereby predictors are omitted based on lack of statistical association. This approach is largely discredited, as predictors can be spuriously retained or omitted⁷.

We urge the authors and other investigators developing (covid-19) prediction models to read the TRIPOD Statement (www.tripod-statement.org) for key information to report when describing their study, so that readers have the minimal information required to judge the quality of the study⁸. The accompanying TRIPOD Explanation and Elaboration paper describes the rationale of the importance of transparent reporting, examples of good reporting, but also discusses methodological considerations⁹. Until improved methodological standards are adopted, we should not expect prediction models to benefit patients, and should consider the possibility that they might do more harm than good.

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