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## Deriving cut-off values for continuous predictors of severe outcomes in COVID-19 through meta-analysis of individual studies



Dear Editor,

We read the paper by Hariyanto et al. with great interest [1]. Meta-analysis has become increasingly popular during the COVID-19 pandemic and can provide pooled evidence on risk factors, diagnostic strategies, and treatment options for this disease. Whilst deriving cut-off values for laboratory variables related to higher risk of adverse outcomes in COVID-19 is of great clinical importance, it is not clear how the authors utilized studies' variability during the synthesis of data to generate the corresponding receiver operating characteristic (ROC) curves. It appears that the authors based the calculation of sensitivity, specificity, and ROC curves on study-level data which were then treated as individual data. However, this approach might introduce a degree of bias if equal weights are assigned to individual estimates. When meta-analysis is applied, each individual study is weighted according to sample size and its variance as well as random- or fixed-effects modeling assumptions. Another explanation would be that the authors have obtained the individual patient data (IPD) from eligible studies. In this case, we believe that submitting the raw data to an accessible repository will be helpful for future updated meta-analyses in this field. If IPD are not available, we propose a generic method to derive classification indices from summary-level estimates. In brief, IPD could be simulated for each eligible study using the corresponding mean and standard deviation alongside sample size for subgroups (number of patients with severe vs. non-severe COVID-19 outcomes). Subsequently, these reconstructed data would allow to perform an IPD meta-analysis and derive less biased ROC curves for variables of interest. Overall, we concur with the authors on the need of improving risk stratification in COVID-19 by accounting for increased levels of laboratory parameters and acknowledge their valuable effort in this direction.

## Reference

- [1] Hariyanto TI, Japar KV, Kwenandar F, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: a systematic review and meta-analysis. *Am J Emerg Med*. 2021;41:110–9. <https://doi.org/10.1016/j.ajem.2020.12.076>.

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