Letter to the Editor: More Efforts for Detecting the Elevated Liver Biochemistries in Patients With Severe COVID-19

TO THE EDITOR:

We read with great interest the recent study by Kovalic et al.[1] showing that patients with severe/critical COVID-19 may have elevated liver biochemistries. We found that there are some potential methodological pitfalls.

First, the authors searched only three databases, which may not be enough to collect all the eligible studies. Since the outbreak of COVID-19, many studies have been uploaded to preprint websites, such as the Social Science Research Network, bioRxiv, and medRxiv. Omitting these important grey literature publications may lead to exaggerated estimates of pooled effects.[2] Additionally, although the meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the protocol was not preregistered in any platforms, such as the Cochrane Library and the International Prospective Register of Systematic Reviews, which may affect its transparency and reproducibility.

Second, the authors analyzed publication bias and concluded that there was not significant publication bias in the included studies. It may be inappropriate, however, to use funnel plots or Egger's test to assess publication bias when there are fewer than 10 studies.[3] In the Methods section, the authors stated that the fixed-effects model was used when no significant heterogeneity was found ($I^2 < 50\%$). However, we are confused because some of the pooled results ($I^2 < 50\%$) shown in figures 2A and 3 were calculated using the random-effects model.

Third, accumulating evidence indicated that chronic liver diseases (CLDs) were independent prognostic factors for patients with COVID-19.[4] Therefore, it would be better to evaluate the influence of different stages of CLDs on liver biochemistries in subgroup analysis, which may contribute to risk stratification and individualized treatments for patients with COVID-19. Additionally, the pooled results of the current meta-analysis were based on 6 studies with a total of 586 patients, so the potential "small-sample effect" or "false-positive effect" cannot be excluded. Consequently, the conclusions should be interpreted with caution, and this limitation should be stated in the Discussion section.

We respectfully thank Kovalic et al for providing us with valuable work. Considering the potential methodological flaws, further studies with better scientific designs are warranted to elucidate this problem.

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