Rethinking the efficacy of awake prone positioning in COVID-19-related acute hypoxaemic respiratory failure

Authors' reply

We read the comments from Qinyuan Li and colleagues on our published systematic review and meta-analysis on awake prone positioning in patients with COVID-19-related acute hypoxaemic respiratory failure.[1] We appreciate their interest in our study, and welcome the opportunity to further explain some of the finer details of our study.

Qinyuan Li and colleagues challenge our methods on the basis of the two small cluster randomised controlled trials (RCTs)[2,3] included in our meta-analysis. As shown in figure 2 of our paper,[1] no intubation or death occurred in either group in these two trials. Therefore, they could not contribute any information to the meta-analysis of intubation and mortality. As recommended by the Cochrane Handbook,[4] we performed a sensitivity analysis to establish the robustness of our results after removing these two cluster RCTs (appendix). These findings are supported by the helpful analysis presented by Qinyuan Li and colleagues, given that their adjusted forest plots also show no difference between awake prone positioning and standard care for these three secondary outcomes.

We agree with Qinyuan Li and colleagues that unlike individual RCTs, the potential for bias in cluster RCTs might arise from how individual participants were identified and recruited within clusters. In fact, this issue is why we carefully evaluated recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individual RCTs, in accordance with chapter 23 of the Cochrane handbook.[4] We incorporated the identification and recruitment bias from cluster RCTs in allocation concealment, which were classified as unclear.

Finally, Qinyuan Li and colleagues argue that blinding was not considered in the Grading of Recommendations Assessment, Development and Evaluation assessment. This statement is incorrect. In fact, we do mention the absence of blinding in the first footnote to supplementary table 5 (appendix p 22).[1] Blinding a behavioural intervention such as awake prone positioning is impossible and is irrelevant for an objective outcome such as death. We assume that the absence of blinding is unlikely to induce a strong bias in assessing the cumulative incidence of intubation, which is, again, an objectively measured outcome. Of note, Qinyuan Li and colleagues claim that no blinding exaggerates the intervention effects by 13%. However, they cite a paper[5] that reported a combination of subjective and objective outcomes, and "evidence was weak for an influence of double-blinding in trials with objectively assessed or all-cause mortality outcomes", according to that same paper.[5] More precisely, outcomes such as intubation are considered to be "objectively measured but potentially influenced by clinician judgment", which is associated with a low risk of bias according to Savović and colleagues.[5] Accordingly, we evaluated the risk of bias as being not serious (appendix p 22).[1]

In short, we maintain that our conclusions remain accurate, and we appreciate this opportunity to clarify our methods.

Competing interests remain the same as in the original Article.

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1 Li J, Luo J, Pavlov I, et al. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. *Lancet Respir Med* 2022; **10:** 573–583.

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3 Kharat A, Dupuis-Lozeron E, Cantero C, et al. Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. *ERJ Open Res* 2021; **7:** 00692–02020.

4 Higgins JPT, Eldridge S, Li T. Cochrane handbook for systematic reviews of interventions version 6·3. Cochrane, 2022.

5 Savović J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med* 2012; **157:** 429–38.

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