



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

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 paper⁵ 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.

Jian Luo†, Ivan Pavlov†, Elsa Tavernier†, John G Laffey, Claude Guerin, David Vines, Yonatan Perez, Oriol Roca, Aileen Kharat, Bairbre McNicholas, Miguel Ibarra-Estrada, Wei Tan, Stephan Ehrmann, *Jie Li
jie_li@rush.edu

†Contributed equally.

Respiratory Medicine Unit and Oxford National Institute for Health and Care Research Biomedical Research Centre, Nuffield Department of Medicine, Experimental Medicine, University of Oxford, Oxford, UK (JLu); Department of Emergency Medicine, Hôpital de Verdun, Montréal, QC, Canada (IP); Clinical Investigation Centre, INSERM 1415, CHRU Tours, Tours, France and Methods in Patients-Centred Outcomes and Health Research, INSERM UMR 1246, Nantes, France (ET); Department of Anesthesia and Intensive Care Medicine, Galway University Hospitals and School of Medicine, National University of Ireland, Galway, Ireland (JGL, BM); Médecine Intensive Réanimation, Hôpital Édouard Herriot, Lyon, France, and Université de Lyon, France, and Institut Mondor de Recherches Biomédicales, Créteil, France (CG); Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, IL 60612, USA (DV, JLi); CHRU Tours, Médecine Intensive Réanimation, CIC INSERM 1415, Tours, France (YP, SE); Servei de Medicina Intensiva, Hospital Universitari Vall d'Hebron, Barcelona, Spain (OR); Department of Respiratory Medicine, Geneva University Hospital, Geneva, Switzerland (AK); Unidad de terapia Intensiva, Hospital Civil Fray Antonio Alcalde Guadalajara, Jalisco, México (MI-E); Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital, China Medical University, Shenyang, China (WT); INSERM, Centre d'étude des pathologies respiratoires, Université de Tours, Tours, France (SE)

- 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.
- 2 Taylor SP, Bundy H, Smith WM, Skavronck S, Taylor B, Kowalkowski MA. Awake prone positioning strategy for nonintubated patients with COVID-19: a pilot trial with embedded implementation evaluation. *Ann Am Thorac Soc* 2021; **18**: 1360–68.
- 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.



If you would like to respond to an article published in *The Lancet Respiratory Medicine*, please submit your correspondence online at: <https://www.editorialmanager.com/THELANCETRM>

See Online for appendix