

LETTER

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Prone positioning in acute respiratory distress syndrome during venovenous extracorporeal membrane oxygenation

Shiping Zhu^{1*}

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Dear Editor,

We read with respect the recent study by Dr. Poon [1], which investigated the potential benefit of prone positioning (PP) during venovenous extracorporeal membrane oxygenation (ECMO) in patients with acute respiratory distress syndrome (ARDS). Total of 11 studies were included and the pooled result showed a non-significant increasing trend of survival rate in patients receiving PP during ECMO (RR 1.2, 95% CI 0.9–1.5). We would like to add some comments.

First, in the forest plot, we noted that the result from Garcia-2020's study was significantly different from others. We performed a sensitivity analysis by excluding Garcia-2020's study (Fig. 1), and the pooled result became statistically significant (RR 1.28, 95% CI 1.08–1.52). We believe several reasons may help to explain this finding. 1 > In Garcia-2020's study, the overall mortality rate was significantly higher than others (85% vs. 30–60%), which suggested potential heterogeneity within these ARDS cohorts. Therefore, whether PP during ECMO presented different efficacy in different ARDS phenotypes needs to be further investigated. 2 > PP during ECMO is still not routinely applied to patients during ECMO, due to risk

of life-threatening complications, such as cannula dislodgement. In all these included studies, the indications for PP differed significantly. In Garcia-2020's study, PP was only used in case of severe hypoxemia or extensive lung consolidation, which generated an inter-relationship between PP and disease severity due to selection bias. However, in Giani-2020's and Schmidt's studies, PP is routinely performed or encouraged during ECMO. The indications in Chaplin-2020, Guervilly-2020, Yang-2021 and Rilinge-2020's studies were unclear. Therefore, we suggest that these conditions should be considered when interpreting the pooled result of the current study.

Second, a meta-analysis aims to pool studies with similar design, cohort, intervention, and outcomes. This also one reason for the debate that whether observational studies and randomized controlled studies should be included in one meta-analysis [2, 3]. In the current study, both the unadjusted findings from four studies and results after propensity score matching (PSM) from three studies were included in one forest plot. We suggest that the unadjusted findings and adjusted result (PSM or regression) should be separated [4].

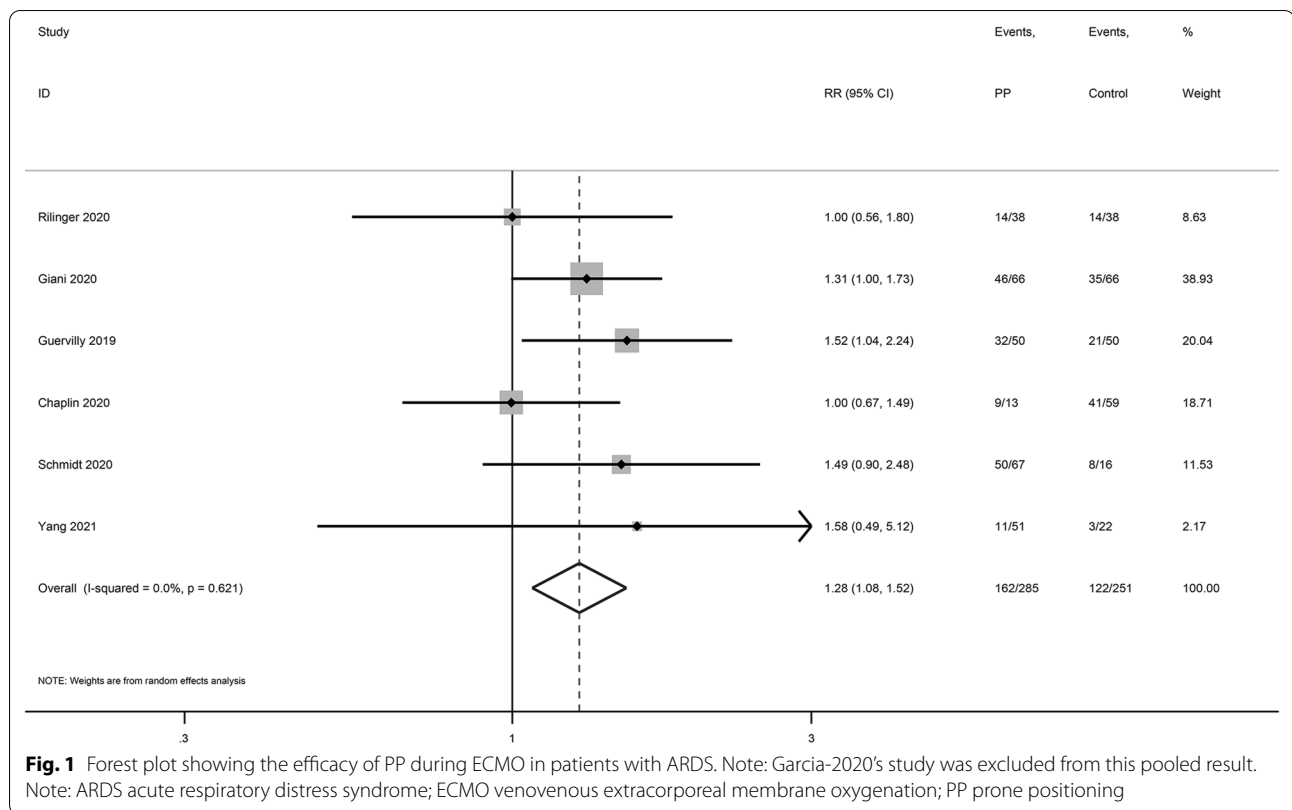
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*Correspondence: zsping0908@163.com

¹ Department of Respiratory Medicine, Hangzhou Hospital of Traditional Chinese Medicine, No. 453, Tiyuchang Road, Hangzhou 310000, Zhejiang, China



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Authors' response
Prone Positioning During Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: Reply

Wynne Hsing Poon², Kollengode Ramanathan^{2,3,9}, Ryan Ruiyang Ling², Matthieu Schmidt^{4,5} and Kiran Shekar^{6,7,8,9}

²Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
³Cardiothoracic Intensive Care Unit, National University Heart Centre, National University Hospital, Singapore, Singapore.
⁴Service de Médecine Intensive-Réanimation, Institut de Cardiologie, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France.
⁵Sorbonne Université, GRC 30, Réanimation Et Soins Intensifs du Patient en Insuffisance Respiratoire aigüe, AP-HP, Hôpital de La Pitié Salpêtrière, 75013 Paris, France.
⁶Adult Intensive Care Services, Prince Charles Hospital, Brisbane, QLD, Australia.
⁷Queensland University of Technology, Brisbane, Australia.
⁸University of Queensland, Brisbane, Australia.
⁹Bond University, Gold Coast, QLD, Australia.

Wynne Hsing Poon and Kollengode Ramanathan have contributed equally to this work

We thank Dr Zhu for the attention and valuable comments provided regarding our article. The indications for prone positioning (PP) during extracorporeal membrane oxygenation (ECMO) were indeed variable across studies, as outlined in our Supplementary Table 2 of our

original manuscript [1]. Based on our a priori criteria for sensitivity analyses (Joanna Briggs Institute score <8), the exclusion of study by Garcia et al., which primarily focused on COVID-19 patients, was not indicated. While we note that the sensitivity analysis suggested found significant survival benefits, this would be an unplanned post-hoc analysis, which should be considered exploratory and interpreted carefully [5].

Despite varied indications for PP, the baseline PF ratio reported by Garcia et al. (82.3 ± 22.5) was relatively similar to Giani et al. (73 ± 29) and Schmidt et al. (all patients, 60 [54–68]), suggesting a similar degree of refractory hypoxemia despite ECMO support. Additionally, metaregression analysis found that PF ratio did not independently influence patient survival. Though establishing an inter-relationship between disease severity or ARDS phenotypes and concurrent PP during ECMO goes beyond the scope of our meta-analysis, we wholly agree with Dr. Zhu that further studies should be conducted to shed light on these thought-provoking insights.

A plausible reason for the increased mortality reported by Garcia et al. could be related to the planning and provision of ECMO services during the COVID-19 pandemic [6]. With a pandemic-stricken and overwhelmed healthcare system, it is possible that patient outcomes are affected. Our subgroup analysis, albeit insignificant, also

Table 1 Subgroup analysis based on study data type for chance of cumulative survival

Data type	No. of studies	RR (95% confidence interval)	P value	P value for interaction
Non-PSM	4	0.98 [0.54–1.79]	0.95	0.354
PSM	3	1.33 [1.07–1.64]	0.0086	

PSM Propensity score matched

found a trend towards decreased survival in patients with COVID-19 (37%) compared to those without (64%).

This meta-analysis of observational studies aimed to summarize all available information on the application of PP with ECMO. The Cochrane recommendations suggest that in a meta-analysis of non-randomized data, adjusted results should be collected where possible [7]. However, we appreciate the suggestion to separate adjusted and unadjusted data, for which an additional analysis found no significant difference between groups (Table 1).

While the adjusted data suggest significant survival benefit, this should be interpreted with caution as the conclusions are based on observational study-level data from three studies. As we understand ARDS and its therapeutic interventions better, the clinical outcomes of patients are likely to improve. Clinical decisions for these patients should evolve with time, while being evidence based. Better evidence should be obtained from well-conducted clinical trials to elucidate whether PP during ECMO demonstrates a survival benefit and identify patients who are most likely to benefit.

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SZ came up with the question and was responsible for writing.

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Consent for publication

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Competing interests

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