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CORRESPONDENCE

The need to define "who" rather than "if" for ECMO in COVID-19

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We thank Watanabe [1] and Wendel-Garcia et al. [2] for the interest they have taken in our article [3]. Both raise valid points regarding the characteristics of patients selected for matching, the potential for unmeasured confounding, and the method of extracorporeal membrane oxygenation (ECMO) delivery.

Patients with a decision of "perceived futility" were excluded from matching. As originally published, the last three lines of Table 1 were incorrect. This has been fixed in a correction [4] and we sincerely apologise for the error. We confirm that patients with "perceived futility" died more frequently than those included for matching (73% vs 43.2%, $p < 0.001$) and none received ECMO. These patients were excluded from matching, as once assigned this decision, there was no possibility of receiving ECMO. Whilst in most cases, "perceived futility" was determined using the physiological data utilised for matching, decision-making may have been influenced by nuanced information not recorded in the referral (e.g. phone conversations between the centres). "Perceived futility" can, therefore, be seen as a fallible, human-assigned label, and finding matches amongst this group of patients would likely have resulted in a greater treatment effect. However, exclusion of these patients aimed to reduce other unmeasured confounding that might result in overestimation of a treatment effect.

Unmeasured confounding remains a threat to the validity of our results, and indeed any retrospective cohort study. The decision for ECMO initiation is complex and made more so by constantly evolving understanding of a novel disease. Our methodology found matches across a period of nearly a year, during which our understanding of coronavirus disease 2019 (COVID-19) developed, national selection criteria varied, and patient characteristics changed. It is likely these variances contributed to the finding of many close matches based on clinical and physiological data. The finite nature of ECMO as a resource must also be considered, and this was indeed at the forefront of clinicians' minds worldwide during this time. The United Kingdom (UK) significantly expanded its ECMO capacity, and due to collaboration between UK ECMO centres to facilitate "out of area" transfers and the establishment of "surge" centres, we are not aware of any patients being declined ECMO due to lack of availability. However, the observed closeness of matches must be a source of introspection. It is possible patients who would have benefited from, and should have received ECMO, remained untreated. We agree the "imperceptible difference" remains a concern, as analysable data may not paint the entire picture for all referrals. Despite this, we are re-assured by the factors discussed, and the significant degree of unmeasured confounding that would be required to nullify the treatment effect found.

This study focuses on treatment within a UK pathway, which concentrates care amongst experienced centres. Strict criteria led to a more 'well' starting population, compared to other studies demonstrating worse outcomes on ECMO. Despite this, we agree that it is hard to argue for limitation of ECMO provision. However, in this context, careful evaluation of ECMO initiation criteria must be undertaken to understand who will derive the most benefit. Future prospective research should focus on "who" not "if".

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Declarations

Conflicts of interest
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