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Bias Due to Cohort Construction in the Study of Timing of Invasive Ventilation

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To the Editor:

We congratulate the authors of Dupuis et al (1) for their thoughtful and topical article published in the recent issue of *Critical Care Explorations*. The question of which patients with hypoxemic respiratory failure truly benefit from invasive ventilation, both during and before the coronavirus disease 2019 (COVID-19) pandemic, is a core controversy in *Critical Care Medicine*. The pandemic has highlighted the fundamental lack of data and analyses that appropriately answer this question. Dupuis et al (1) attempt to address this important and challenging question in their study and found an increased odds of death among COVID-19 pneumonia patients who experienced invasive ventilation in the first 2 days of ICU admission as opposed to patients who did not experience invasive ventilation in the first 2 days of ICU admission. They used inverse probability of treatment weighting to reduce the impact of measured confounding on their results. We wish to highlight bias due to cohort construction in the study by Dupuis et al (1) that cannot be removed by statistical analysis and to explain how a "target trial" approach can help minimize such bias.

In this cohort analysis, patients were compared according to whether or not they received "early" invasive ventilation (within 2 d of ICU admission). However, many of the patients classified as receiving early invasive ventilation were already invasively ventilated on ICU admission, which introduces both confounding and selection bias by comparing patients already ventilated to patients who were never ventilated (2). The bias has likely shifted the results toward finding early invasive ventilation harmful because patients who were already invasively ventilated at ICU admission were likely to be sicker than those who were not ventilated early. Inverse probability weighting may not even resolve the measured confounding for these patients because the adjusted covariates are measured after invasive ventilation has been already initiated. The inclusion of these patients also impedes clinical application of the results by a physician seeing a patient at ICU admission because the question of when to initiate invasive ventilation is irrelevant for patients who are already invasively ventilated. Similar bias due to cohort construction has appeared in other studies of timing of invasive ventilation (3–6).

Identifying and minimizing bias due to cohort construction is more straightforward in randomized trials because the enrolment process makes it obvious that intervention and control populations must meet the same eligibility criteria. The "target trial" is a helpful concept intended to reduce bias in observational studies (7). It uses the inclusion and exclusion criteria from a hypothetical randomized trial to ensure that all patients included in an observational study were eligible for the intervention (2, 8). To use the target trial concept, first you imagine the hypothetical randomized trial that would answer your research question. Then, you adapt the inclusion and exclusion criteria of that trial to your observational data. The target trial for the research question addressed by Dupuis et al (1) could be one that enrolls patients with COVID-19 pneumonia

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at admission to ICU and randomizes them to invasive ventilation within the first 2 days ("early") or not ("nonearly"). This makes it clear that you must exclude patients already invasively ventilated on ICU admission because they would not have been eligible for the hypothetical randomized trial. They could not have been randomized to the "nonearly" invasive ventilation arm.

In conclusion, we congratulate once more Dupuis et al (1) for their contribution to the problem of identifying which patients with hypoxemic respiratory failure truly benefit from invasive ventilation. We suggest future studies of invasive ventilation consider using the target trial concept in order to minimize bias and maximize the clinical applicability of results.

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