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Response to: The effect of advanced directive restriction

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Response

We thank Dr. Kuo and Chao [1] for raising the issue of advanced directive restrictions in our recent study on noninvasive and invasive ventilation in critically ill patients with acute exacerbation of COPD. [2] In this study, we performed several multivariate analyses to assess the effectiveness of noninvasive ventilation (NIV) compared with invasive mechanical ventilation (IMV) on the intensive care unit and hospital mortality in a large, multicenter database. In a propensity matched analysis, we matched on the propensity of receiving NIV derived from a regression model that used patient demographics, comorbidities, and the SAPS-II score (a measure of acuity). The propensity model also had a hierarchical structure that adjusted for the hospital where the patient received treatment. We had information on advance directive (eg, if the patient had a Do Not Resuscitate (DNR) in approximately two third of the patients. (Table 1) We did not include this variable in our propensity model as we would have had to either impute a large amount of missing data or restrict the sample to patients without missing data—both of which are methodologically problematic. [3] Importantly, we found that the advanced directive restriction variable was balanced in the propensity matched sample (ie, it was no longer statistically different between the NIV and IMV patients). (Table 1) This means it was no longer a confounder and did not bias our results. This highlights a strength of propensity score matching in that the matched samples may be similar in ways that are not directly observable due to matching on a large number of clinically relevant covariates.

We agree that patients who have an advance directives that include the patient's wish to not be intubated, would only receive NIV, and these patients may well be more acutely or chronically ill or differ in other ways from study subjects without such restrictions. These patients are at a higher risk of death, because if the NIV is not successful there is no other

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way to escalate their care. If we only included patients with no advanced directive in this analysis, our results will be less applicable to a general COPD population and would likely *lower* the observed mortality in the NIV group. We did take advanced directives into account when assessing NIV failure because the intent of that analysis was clearly different.

In conclusion, we believe our study supports the use NIV as a first line therapy in appropriately selected critically ill patients with COPD with our manuscript's stated caveats that this is an observational study and not a randomized control trial (RCT). Our findings are supported by other studies in the literature as well. [4] We encourage future research to take advance directive restrictions into account as they can distort multivariate results even when sophisticated propensity score methods are used.[5]

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Table 1

Advanced Directive Restrictions and Outcomes Before and After Propensity Matching

Variable	Initial NIV N = 974	Initial IMV N = 1603	P-value	Initial NIV after Propensity Matching N = 389	Initial IMV after Propensity Matching N = 389	P-value
Full Code (No Advanced Directive Restrictions)	597 (61.29%)	908 (56.64%)	<0.001	216 (55.53%)	229 (58.87%)	0.421
DNR/Limited Interventions	87 (8.93%)	83 (5.18%)		43 (11.05%)	33 (8.48%)	
Missing	290 (29.77%)	612 (38.18%)		130 (33.42%)	127 (32.65%)	
ICU Mortality Rate	30 (3.08)	168 (10.48%)	<0.001	9 (2.31%)	23 (5.91%)	0.011
In-Hospital Mortality Rate	72 (7.39%)	258 (16.09%)	<0.001	23 (5.91%)	39 (10.03%)	0.034

DNR = Do Not Resuscitate

CPR = Cardiopulmonary Resuscitation