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Early intubation and patient-centered outcomes in septic shock

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Dear Editor,

In a recent study [1], Dr. Mellado-Artigas investigated the efficacy of early intubation (within eight hours after vasopressor use) in patients with septic shock. After propensity score matching (PSM), they reported that compared to non-early intubation, early intubation did not improve in-hospital mortality or ICU/hospital length of stay in the matched cohort. We noted that in the non-early intubation group, only 33% (27/78) of these patients finally needed intubation. Therefore, the comparison between early intubation and non-early intubation group is actually the comparison between patients with early intubation and those (67%) who do not need intubation mixed with a small proportion (33%) of patients with non-early intubation. In clinical practice, patients who do not need intubation always tend to have milder conditions and a relatively better prognosis than those who need intubation. Therefore, we speculated that the non-significant comparisons in the current study may have been affected by several factors.

First, the major issue with PSM in the current study is the external validity. A total of 137 patients were included in the early intubation group, 43% (59/137) of whom were excluded from PSM. In Table 1, we note that in the early intubation group, the mortality was significantly higher in patients excluded from PSM than that in those kept in the PSM (41/59 (69%) vs. 35/78 (45%), $p = 0.004$).

On the contrary, in the non-early intubation group, the mortality was significantly lower in patients excluded from PSM than that in those kept in the PSM (85/520 (16.3%) vs. 26/78 (33%), $p < 0.001$). This means that only mild patients in the early intubation group and severe patients in the non-early intubation group were included in the PSM analysis. Therefore, the exclusion of these patients in PSM may lead to poor sample representation and affect the external validity of these results.

Second, a total of 22 variables were included in the PSM analysis. Although most of these selected variables were balanced in the matched cohort, hidden bias [2–4] due to unmeasured confounders likely remains. For instance, severe hypoxemia was one common indication for intubation in clinical practice. Aiming to identify patients with similar oxygenation status, the worst PaO₂/FiO₂ level should be used for matching in the PSM. However, in the current matched cohort, the mean PaO₂/FiO₂ was 141 and 153 mmHg in the early intubation and non-early intubation groups, which unlikely reflects the worst oxygenation status. Therefore, some clinical or laboratory indications for intubation may be missing in the PSM analysis. In addition, the balance of several binary variables should not be measured using standardized mean differences (SMD). For instance, although the SMD is small, the accessory muscle use (43/78 (0.55%) vs. 36/78 (0.46%)) is still not well balanced. Sensitivity analysis for unmeasured confounding, such as Rosenbaum bounds (Gamma value) [5] or other models [2], should be reported to quantify the hidden bias.

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Table 1 Mortality comparisons between patients kept and excluded from the PSM in two groups

	Used for PSM	Excluded from PSM	<i>p</i>
Early intubation group	N = 78	N = 59	
Mortality rate* [n (%)]	35 (45.8%)	41 (69.0%)	0.004
Non-early intubation group	N = 78	N = 520	
Mortality rate [n (%)]	26 (33.3%)	85 (16.3%)	< 0.001
<i>p</i> [#]	0.140	< 0.001	

*The overall mortality rate was extracted from their supplementary Table S2 (mortality by day 60)

[#] Comparisons between early intubation and non-early intubation groups

Authors reply to: Early intubation and patient-centered outcomes in septic shock

Ricard Mellado-Artigas, Carlos Ferrando, Frédéric Martino, Agathe Delbove, Bruno L. Ferreyro, Cedric Darreau, Sophie Jacquier, Laurent Brochard and Nicolas Lerolle

Dear Editor,

We thank Dr. Hu and colleagues for their interest in our work and for the time taken to describe some concerns around our results [1].

In first place, the authors mentioned that our analysis compared not only intubated patients but also a subgroup of patients who never received mechanical ventilation. This approach, also known as the target trial framework, was followed to aim at resembling the construction of a hypothetical trial [6]; where patients would have been randomized to two different strategies, namely one including expeditious intubation and another one focusing on a more conservative approach. In the latter some patients would have likely ended up receiving intubation while many others would have not. In our opinion and in others', only including patients receiving intubation might result in biased estimates [7].

Second, the authors pointed out that our PSM might have negatively affected the external validity of our results since only a subgroup of patients was included in the matched analysis. We fully agree with the authors, but we cannot help but remind that we repeatedly warranted caution about the risk of extrapolating the results to the whole population, which would be similar to negate the usefulness of mechanical ventilation in critical illness. In our analysis, we were only able to include 78 out of 137 (57%) of those intubated in the first 8 h and the findings only apply to this subgroup. Although, it would have been interesting to estimate the effect of early intubation in the whole population, it was simply not possible since

the higher disease severity on the other half of the early-intubated subgroup did not allow for a proper matching.

Third, the authors raised the concern that balance might have not been achieved for several variables. Although the discussion about the number of variables and parameters to assess balance could be of great interest, space constraints limit it here. Nonetheless, for the present work, we developed several sensitivity analyses using overlap weighting, an inverse-probability of treatment weighting-based technique, which virtually eliminates imbalance between groups [8]. These analyses, although focused on a smaller subgroup also confirmed the previous findings.

Finally, we have computed the E-value which represents the magnitude of a potential unmeasured factor in the risk ratio scale to explain away the observed effect [9]. For the main hazard ratio (HR) to be 1, E-value was 1.92; for HR 0.90, E-value was 2.11 and for HR 0.80, E-value was 2.37.

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Author contributions

JQ came up with the question, and YS and HZ were responsible for writing. All authors read and approved the final manuscript.

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