Critical Care

CORRESPONDENCE

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Comment to "Very late intubation in COVID-19 patients: A forgotten prognosis factor?"

Ricard Mellado-Artigas[1,2*], Luigi Zattera[1], Enric Barbeta[1,2] and Carlos Ferrando[1,2]

Dear Editor,

We have read the manuscript published by Camous and colleagues in this journal [1]. We want to congratulate the authors for their effort in describing outcomes in ventilated COVID-19 patients and its relationship to the time of intubation. The authors showed that intubation after 7 days of dexamethasone start was associated with a dismal outcome, while intubation between days 1 and 7, as compared to intubation before day 1, was not linked to worse results.

The optimal timing for mechanical ventilation initiation, including COVID-19 patients, has been a matter of debate with studies supporting or refuting the effect of a delay in intubation on outcomes, and overall uncertain results [2, 3]. In the absence of clinical trials to provide high-quality evidence, observational studies are used to sustain daily practice. Unfortunately, observational studies often present with large imbalances in relevant variables between treatment groups that preclude an easy estimation of treatment effects. In other words, groups tend to differ at baseline in the degree of severity of their illness. Nonetheless, if confounding can be controlled for, these data might offer valuable information on a particular treatment effect.

In the present work, very late intubation was associated with higher mortality. While the potential role of a delay in intubation on outcome cannot be ruled out, we want to highlight that patients among groups largely differed in important variables: first, the early intubation group presented at baseline a median ROX index as low as 3, as well as higher illness severity, as reported by higher SOFA score, while the very late group displayed a median ROX of 6, making these patients populations not comparable in terms of both baseline severity and probability to be intubated. We suggest therefore an analysis after adjusting for these important covariates [4]. Second, the very late group received more frequently tocilizumab as an adjunctive therapy: although the authors hypothesized that this was due to a longer time between steroid treatment and intubation, intubation is not a formal contraindication for such treatment. Usually, patients receiving tocilizumab show a higher inflammatory burden despite steroid treatment which has been identified as marker of disease severity [5].

In conclusion, we think that the data presented in this brief report, although of great interest, might present important limitations as residual confounding could not be excluded.

Authors' response

Laurent Camous, Jean-David Pommier, Frederic Martino, Benoît Tressieres, Alexandre Demoule and Marc Valette

Dear Editor,

We thank *Mellado-Artigas* et al. for their interest in our work and for their suggestions. As these authors underline, timing and indications of mechanical ventilation of

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SARS-CoV-2 pneumonia are still debated. We tried to understand the high mortality of lately intubated COVID patients, after careful studies of the potential bias and not comparing strategies of care.

For *Mellado-Artigas* et al. groups of our study are not comparable because of the baseline differences in ROX and SOFA. However, the description of our groups was based on the day of mechanical ventilation. As ROX scores at intubation were not different in between the three groups of intubated patients, we believe that respiratory condition at intubation was similar. Another potential bias discussed by *Mellado-Artigas* et al. was the difference in-between groups in the use of tocilizumab. However, as there are no robust data on mortality, incidence of nosocomial infection and ventilator-free days after tocilizumab treatment, we chose in our center not to use tocilizumab in mechanically ventilated patients in view of the potential infectious risk. There was no difference in inflammatory markers (CRP and D-dimer levels) at baseline between groups.

The impact on prognosis of late intubation in COVID patients has been discussed by others [2, 6]. The different hypotheses were discussed in our study: potential patient-self-induced lung injury (p-SILI) due to prolonged high flow nasal oxygen therapy or worsening of lung damages during steroid treatment.

Randomized trials are needed to confirm our data and to better understand the mechanisms of mortality in late intubated COVID patients. *Mellado-Artigas* et al. proposed the use of a propensity score-based cohort analysis as a tool to compare patients. We think that pairing of ARDS patients is difficult, as PaO_2/FiO_2 ratio or radiological abnormalities on CT-scan are rough markers of lung damage severity.

Author contributions
RMA, CF, LZ and EB have participated in the writing of this manuscript and have approved the final version.

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Data availability
No applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
RMA declares having received lecturing fees from Medtronic and Fisher & Paykel. No other authors declare competing interests.

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