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## Comments on “Non-invasive positive pressure ventilation versus endotracheal intubation in treatment of COVID-19 patients requiring ventilatory support”



Dear Editor,

The outbreak of COVID-19 suddenly increased the number of patients with acute severe respiratory failure requiring ventilator support. The consequent shortage of resources for critically ill patients created new challenges for the medical community. It became of utmost importance to identify patients who needed early intubation and those who could undergo a trial with a non-invasive support.

In a recent issue of the American Journal of Emergency Medicine, Daniel and coll. presented a retrospective study, with the aim to compare all-cause 30-day mortality for hospitalized patients with COVID-19 and respiratory failure, who underwent intubation first, intubation after non-invasive ventilation (NIV), or NIV only [1]. The study population is relatively small and the three subgroups present significant differences, as patients treated with NIV only showed a lower Body Mass Index and a minor prevalence of altered mental status and need of vasopressors, compared to those who underwent *endo*-tracheal intubation (ETI) as first or second option. The only data about the severity of respiratory failure is O<sub>2</sub> saturation (SO<sub>2</sub>) at Triage. Patients, who were immediately intubated, showed the best early SO<sub>2</sub>, followed by those treated with NIV only and finally those who underwent intubation after NIV, suggesting that O<sub>2</sub> saturation was not a parameter used to select the respiratory support. Day-30 mortality rate was similar in the first and third subgroups and lower in the group treated with NIV only. The first conclusion is that “Utilization of NIV as the initial intervention in COVID-19 patients requiring ventilatory support is associated with significant survival benefit.”

In the period February 2020–January 2021, 1208 patients have been admitted in our hospital for COVID-19. Among them, 170 underwent only NIV, 33 were directly intubated and 80 underwent ETI after a trial of NIV. The mean age ( $69 \pm 15$ ,  $69 \pm 13$  and  $71 \pm 10$  years,  $p = \text{NS}$ ) and the peripheral O<sub>2</sub> saturation ( $91 \pm 7\%$ ,  $90 \pm 10\%$  and  $90 \pm 8\%$ ,  $p = \text{NS}$ ) were similar among the three subgroups. Patients treated with ETI only showed a higher SOFA score compared to those treated with NIV only or with ETI after NIV ( $5.9 \pm 2.4$  vs  $4.5 \pm 1.4$  and  $4.7 \pm 1.8$ ,  $p < 0.01$ ). The mortality rate in the 3 subgroups were 22%, 61% and 46% ( $p < 0.001$  between the first subgroup compared to the second and the third ones).

We cannot ignore that patients treated with NIV only presented several characteristics indicative of a lower severity of the clinical presentation and this is why it was possible to manage them with non-invasive support only. Whether the reduced mortality was due to the avoidance

of ETI and mechanical ventilation or to a less compromised clinical condition is hard to say. The authors also stated, “For patients intubated after NIV, the mortality rate is not worse than those who undergo intubation as their initial intervention”. As we do not know parameters, on which physicians based their decision to intubate or not, in my opinion this conclusion could be dangerous. In fact, in the absence of clear criteria to indicate the need and the timing of ETI for COVID-19 patients, we are facing two risks: on one hand, we could intubate them too early, with an unnecessary exposure to the negative consequences of mechanical ventilation. On the other hand, we could delay too much the employment of mechanical ventilation, when the pulmonary damage is advanced and potentially irreversible.

In the early phase of the pandemic, it has been suggested that an early intubation and invasive mechanical ventilation could improve the prognosis of patients with severe respiratory failure due to interstitial pneumonia by COVID-19 [2]. However, there was not a global agreement as to whether or not ventilator management should differ in COVID-19 patients from other patients with hypoxic respiratory failure, both in terms of indication to begin the treatment and management modalities. The high mortality reported by several authors among intubated patients induced the scientific community to reconsider whether the early employment of invasive ventilation is the best option for these patients and which could be the role of NIV [3].

We have to be aware that the physiology of conventional ARDS is not immediately applicable to patients with pneumonia caused by COVID-19. In fact, the former always involves an acute alveolar damage, while, in its early stages, lung injury induced by COVID-19 is mainly determined by a disrupted vasoregulation, with loss of vasoconstriction in poorly perfused areas and consequent ventilation-perfusion mismatch, as well as microthromboses and vasoconstriction in other areas. This association of damages determines severe hypoxemia, frequently in the absence of severe dyspnea because pulmonary compliance is initially preserved. In this phase, a non-invasive ventilator strategy could be employed [4].

In following stages, lung oedema and worsening consolidation can contribute to disease progression, with features resembling more typical ARDS and might respond to treatments generally used in this condition. The evolution through different stages can be hyperacute or indolent and poses relevant challenge in the choice of the best ventilation modality for the single patient. The challenge is finding reliable criteria to identify the transition between different stages. In fact, adequating the ventilator support to the physiology of the underlying respiratory failure could be a possibility to test [5].

In conclusion, our preliminary results partially confirmed the results published by Daniel and coll. But the dilemma between “intubate or not intubate as soon as possible” remains unresolved.

### Declaration of Competing Interest

None.

## References

- [1] Daniel P, Mecklenburg M, Massiah C, Joseph MA, Wilson C, Parmar P, et al. Non-invasive positive pressure ventilation versus endotracheal intubation in treatment of COVID-19 patients requiring ventilatory support. *Am J Emerg Med.* 2021;43:103–8. <https://doi.org/10.1016/j.ajem.2021.01.068>.
- [2] Gattinoni L, Sibilla S. ARDS, searching for treatment modes or understanding the “rules”? *Neth J Med.* 1998;53(5):212–3. [https://doi.org/10.1016/s0300-2977\(98\)00106-5](https://doi.org/10.1016/s0300-2977(98)00106-5).
- [3] Bahl A, Van Baalen MN, Ortiz L, Chen NW, Todd C, Milad M, et al. Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort. *Intern Emerg Med.* 2020;15(8):1485–99. <https://doi.org/10.1007/s11739-020-02509-7>.
- [4] Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a “typical” acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2020;201(10):1299–300. <https://doi.org/10.1164/rccm.202003-0817LE>.
- [5] Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management

warranted? *Lancet Respir Med.* 2020;8(8):816–21. [https://doi.org/10.1016/S2213-2600\(20\)30304-0](https://doi.org/10.1016/S2213-2600(20)30304-0).

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