High-Flow Nasal Cannula in COVID-19 Pneumonia: Practical Issues

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To the Editor:

We read with great interest the study by Burnim et al (1), recently published in *Critical Care Medicine*, in which authors conducted a retrospective review of 504 patients with severe COVID-19 treated with high-flow nasal cannula (HFNC). The authors concluded that HFNC was associated with a paradoxically longer median time to discharge and was not associated with a mortality benefit; however, a secondary analysis showed a reduction of the hazard of death at 28 days among patients not mechanically ventilated within 6 hours of admission. In addition, the authors reported a poor performance of the rate-oxygenation index (ROX) to predict progression to invasive mechanical ventilation (IMV) (1).

Although this study contributes to existing literature on HFNC, we consider some aspects worthy of discussion. First, although the authors focused on hospital discharge, it would have been interesting to know the effect of the intervention in ICU outcomes, such as ICU length of stay (LOS), ICU mortality, days of mechanical ventilation, and the need of tracheostomy, among others, and how these ICU outcomes affected hospital LOS. Second, regarding the utility of the ROX index, the authors contradicted the results of a recent meta-analysis (2). For Burnim et al (1), this index performed poorly, as recently reported in another cohort (3). The authors performed an additional model including "demographic, clinical, and laboratory variables" and found a better predictor of IMV. It would be useful to know what variables were included to be able to replicate the findings in retrospective and prospective studies.

Finally, it is essential to highlight that retrospective studies during the COVID-19 pandemic are at risk of being affected by a cohort effect given rapid and constant treatment changes, a better understanding of the disease, and new interventions over time. The authors addressed this point by matching patients according to whether they were admitted before or after June 1, 2020, when the evidence of mortality benefit of glucocorticoids use came to light (4). Nonetheless, other clinical interventions, such as conscious pronation, muscle paralysis, or other immunomodulation strategies, should have been considered. These factors are particularly relevant as several clinical trials were recruiting patients from the Johns Hopkins health system during the inclusion period (5). These interventions may have influenced the mortality effect estimate and the assumption of a stable hazard ratio between the groups throughout follow-up; this secondary analysis can be explored in another study with the same population.

In summary, Burnim et al (1) provide relevant information about the use of HFNC in a big cohort of COVID-19 patients. Although some details would have been interesting to know regarding this sample population, the study suggests that HFNC may be associated with a 28-day mortality benefit in appropriately

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selected patients, such as patients with severe hypoxemia but at low risk for rapid progression to IMV.

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The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

We thank Laserna et al (1) for their interest in our study (2) and their insights. Although the rate-oxygenation index (ROX) index did perform poorly in predicting progression to invasive mechanical ventilation in our cohort of high-flow nasal cannula (HFNC) patients, a

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TABLE 1.
Variables in Model Predicting Time to Ventilation or Death

Variables	Adjusted Hazards (*p*)
Rate-oxygenation index < 3.85	0.50 (< 0.001)
Do-not-resuscitate/do-not-intubate order	0.52 (< 0.001)
Spo_2/Fio_2 ratio	0.76 (< 0.001)
Alanine transaminase	0.79 (0.02)
Estimated glomerular filtration rate	0.79 (0.001)
Systolic blood pressure	0.84 (0.03)
Hemoglobin	0.87 (0.07)
Albumin	0.93 (0.32)
C-reactive protein	0.96 (0.52)
Temperature	1.21 (0.007)
White race	1.24 (0.017)
Pulse	1.31 (< 0.001)

These variables were selected from a larger pool of variables using the least absolute shrinkage and selection operator regularization method. The complete list of variables considered also included age, sex, Charlson comorbidity index, body mass index, diastolic blood pressure, respiratory rate, absolute lymphocyte count, D-dimer, and ferritin.

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