COMMENTARY

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Timing of Intubation in COVID-19: When It Is Too Early and When It Is Too Late

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ABSTRACT: The timing of initiating mechanical ventilation in patients with acute respiratory distress syndrome due to COVID-19 remains controversial. At the outset of the pandemic, "very early" intubation was recommended in patients requiring oxygen flows above 6 L per minute but was followed closely thereafter by avoidance of invasive mechanical ventilation (IMV) due to a perceived (yet overestimated) risk of mortality after intubation. While the use of noninvasive methods of oxygen delivery, such as high-flow nasal oxygen (HFNO) or noninvasive positive pressure ventilation (NIV), can avert the need for mechanical ventilation in some, accumulating evidence suggests delayed intubation is also associated with an increased mortality in a subset of COVID-19 patients. Close monitoring is necessary in COVID-19 patients on HFNO or NIV to identify signs of noninvasive failure and ensure appropriate provision of IMV.

KEY WORDS: artificial respiration; COVID-19; intubation; noninvasive ventilation; respiratory distress syndrome

Since the discovery of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there have been hundreds of millions of reported COVID-19 cases and more than 6.5 million reported deaths (1). Severe COVID-19 manifests as acute respiratory distress syndrome (ARDS) and often requires invasive mechanical ventilation (IMV). Mortality rates related to COVID-19 ARDS have varied over the course of the pandemic, influenced by distinct waves, different variants, acquisition of clinical experience, corticosteroids, vaccination, prior immunity, and the development of other COVID-specific therapies (2–4). ICU mortality has remained high despite varying rates of IMV. For example, when comparing a large cohort of more than 3,700 ICU patients with the Alpha and Beta SARS-CoV-2 virus between the first wave and the second and third waves, there were significantly decreased rates of IMV (55% vs 32%), although no significant difference in ICU mortality (31.7% vs 28.8%; $p = 0.06$) (2). Similar ICU mortality rates were seen with Delta variant though a subsequent decline in ICU mortality was observed with the Omicron variant (3). Despite varying rates of IMV and noninvasive respiratory support throughout the pandemic, the optimal timing of endotracheal intubation and IMV has remained controversial.

At the outset of the pandemic, mortality was high, and "very early" intubation for hypoxemia was recommended for hypoxemic patients requiring supplemental oxygen greater than 6 L per minute (5, 6). This largely stemmed from concerns for rapid progression of respiratory failure and the possibility that oxygen flow rates above 6 L per minute could aerosolize the virus. As a result, experts recommended avoiding high-flow nasal oxygen (HFNO) and noninvasive positive pressure ventilation (NIV) and instead using "very early" IMV (5–9). Initial data from January of 2020 in a single center in Wuhan, China, demonstrated 28-day ICU mortality of 61.5%. Seventy-one percent of patients

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required mechanical ventilation (composite of noninvasive ventilation and IMV), of which 42% were received IMV. Of patients who underwent IMV, mortality was 86% (10). However, small studies began to emerge early in the pandemic questioning this narrative and demonstrating the safety of HFNO and NIV in hypoxemic patients with COVID-19 (5). As it became more apparent that healthcare providers wearing appropriate personal protective equipment were at low risk of contracting COVID-19 by aerosols generated by oxygen flow and accumulating evidence showed patients could safely be managed with HFNO and NIV (similar to non-COVID-19 ARDS), providers abandoned the "very early" intubation strategy. This led to a rapid decrease in intubation rates 4 weeks into the pandemic and improved mortality within the first wave of the pandemic (11–13). NIV and HFNO have since been shown to be a viable option for patients to avoid intubation (14).

Several months later, in April of 2020, a retrospective analysis of patients in New York City reported a mortality rate of 88% for patients mechanically ventilated with COVID-19 ARDS (15). This study garnered significant media attention leading many to believe that intubation for COVID-19 should be avoided at all costs. However, that high mortality rate only included patients who had a reported outcome, a denominator of 323 patients, and did not include those still hospitalized, a denominator of 831 patients. The true mortality rate at the time of publication was actually 24.5%, which was more consistent with other reported mortalities of under 50% (16–20). Although the correction was published 2 days after the initial publication, it received less attention, and concerns remained that mechanically ventilating patients with COVID-19 ARDS was harmful and increased mortality. The failure of "very early" intubation at the outset of the pandemic, and the subsequent overestimated mortality from using IMV, likely led to significantly increased use of NIV and HFNO for longer durations to avoid intubation. However, accumulating evidence suggests "delaying" intubation in patients with COVID-19–associated respiratory failure is also associated with a higher mortality (21–25). In a cohort of 574 ICU patients with COVID-19, "very late" intubation (beyond 5 d of HFNO or NIV initiation) had

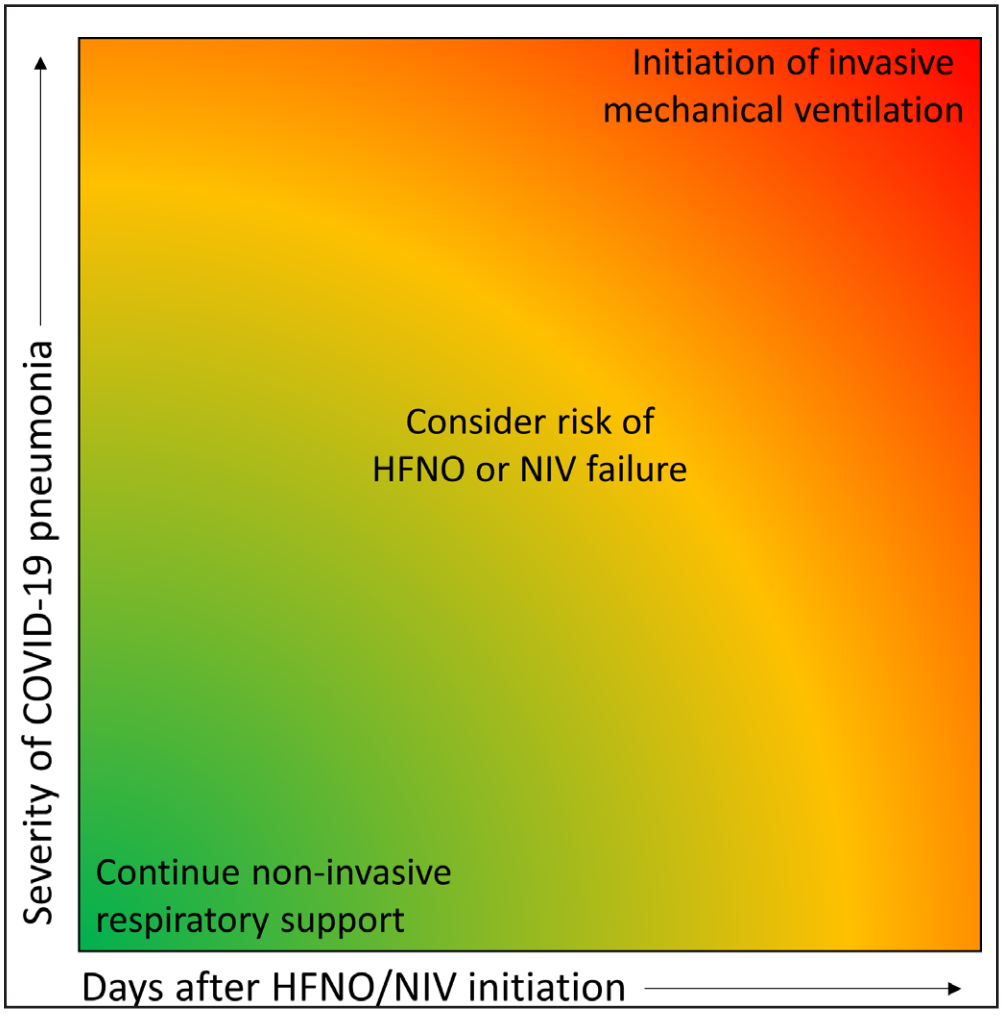

Figure 1. Color-mapped conceptual framework showing optimal timing of intubation of patients with COVID-19 pneumonia/acute respiratory distress syndrome as a function of disease severity (*y*-axis) and duration of noninvasive therapy (*x*-axis). HFNO = high-flow nasal oxygen, NIV = noninvasive positive pressure ventilation.

the highest rate of mortality (87%) (26). Another study showed patients managed with NIV for more than 3 to 5 days had higher rates of failure and increased mortality (27). The mechanism remains unclear; however, it has been proposed that patients with high respiratory drive can develop patient self-inflicted lung injury, which may be mitigated by IMV and strict tidal volume control (28).

If both "very early" intubation and "delayed" intubation may carry risk of increased mortality, what is the optimal timing for implementing IMV in patients with COVID-19? While this remains unknown, what is clear is that patients deemed eligible for support with HFNO or NIV should be monitored closely for signs of failure and potential need for intubation (**Fig. 1**). Signs of possible failure include high minute ventilation and respiratory rate greater than 30 breaths per minute, high inspired oxygen fraction (≥ 60%), and prolonged use of HFNO and/or NIV (≥ 3–5 d). Validated decision support tools exist that can help predict HFNO and NIV failure and aid in determining optimal intubation timing. In HFNO, an index combining respiratory rate and oxygenation (ROX index) has been validated to predict HFNO failure: Patients exhibiting a lower ROX index (< 3.85) should be considered candidates for earlier intubation and IMV (29, 30). For NIV, a recent model, the pulmonary ARDS (ARDSp) score, incorporating respiratory rate, oxygenation, etiology of ARDS, SOFA score, and age could predict NIV failure (i.e., progression to IMV) with reasonable discrimination. Patients with ARDSp scores greater than 5.5 points (out of a total of 18 points) strongly predicted NIV failure (area under the curve 0.81) (31).

Throughout the COVID-19 pandemic, mortality for mechanically ventilated patients has remained high, however, not nearly as high as initially reported. The provision of IMV remains a critical component of caring for patients with COVID-19–associated respiratory failure, and the timing of IMV may be just as important. Mortality appears to be higher when either a "very early" intubation strategy or a "delayed" intubation strategy is used. HFNO and NIV are safe in patients with respiratory failure requiring noninvasive respiratory support and can reduce the need for IMV. However, such patients should be monitored closely for signs of HFNO and NIV failure, as delaying intubation is associated with increased mortality too.

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