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RESEARCH

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Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies

Eleni Papoutsi^{1†}, Vassilis G. Giannakoulis^{1†}, Eleni Xourgia¹, Christina Routsi¹, Anastasia Kotanidou¹ and Ilias I. Siempos^{1,2*}¹⁰

Background

Since the early phase of the COVID-19 epidemic, several guidelines from different countries **recommend early intubation of critically ill patients with COVID-19** as a means to protect health care workers from cross-infection and to avoid complications (including cardiac arrest) associated with "crash" intubations.

Experts of clinical respiratory physiology seemed t back this approach with notions that early intubation might prevent ensuing patient self-inflicted lung injury.

- However, on the basis of physiological principles, other experts argued against early intubation. Therefore, there seemed to be reasonable arguments in favor of either an early or a late intubation approach in COVID-19 and relevant studies were subsequently planned to address this clinical question.
- Thus, this study is a systematic review and meta-analysis in an attempt to investigate the effect (if any) of timing of intubation on clinical outcomes of critically ill patients with COVID-19.

Methods

PubMed and Scopus were systematically searched, while references and preprint servers were explored for relevant articles up to December 26, 2020, to identify studies which reported on mortality and/or morbidity o patients with COVID-19 undergoing early versus late intubation. "Early" was defined as intubation within 24 h fro intensive care unit (ICU) admission, while "late" as intubation at any time after 24 h of ICU admission. All-cause mortality and duration of mechanical ventilation (MV) were the primary outcomes of the meta-analysis. Pooled risk ratio (RR) pooled mean difference (MD) and 95% confidence intervals (CI) were calculated using a random effects model.

Results

A total of **12 studies** from Africa, Asia, Europe and America, involving **8944** critically ill patients (**7639 early, 1305 late**) with COVID-19, were incorporated in our meta-analysis.

Primary Outcomes

All Cause Mortality

There was **no statistically** detectable difference between patients undergoing early versus late intubation regarding all-cause mortality (3981 deaths; 45.4% versus 39.1%; RR 1.07, 95% CI 0.99–1.15, p = 0.08)

Duration of MV

There was **no statistically detectable difference** between patients undergoing early versus late intubation regarding duration of MV (1892 patients; MD – 0.58 days, 95% CI – 3.06 to 1.89 days, *p* = 0.65)

Secondary Outcomes

ICU Length of Stay

There was no statistically detectable difference

between patients undergoing early versus late intubation regarding ICU length of stay (433 patients; MD – 1.83 days, 95% CI – 6.05 to 2.38 days, *p* = 0.39).

Renal Replacement Therapy

Need for renal replacement therapy **was comparable** between early and late intubation groups (547 patients; 30.3% versus 29.0%; RR 1.04, 95% CI 0.83– 1.29, p = 0.75).

Subgroup Analysis

• In a pre-specified subgroup analysis of eight studies, all-cause mortality was higher in the early than the late or no intubation group (2377deaths; 41.2% versus 24.8%; RR 1.54, 95% Cl 1.20–1.97,p = 0.0007). All-cause mortality was comparable between the early and late intubation group in the subgroup analysis of studies with low risk of bias (four studies; 886 deaths; 51.2% versus 47.7%; RR 1.04, 95% CI 0.89-1.20, p = 0.64, 12 = 0%) and of studies taking place in regions with low disease burden (871 deaths; 51.7% versus 48.1%; RR 1.04, 95% CI 0.89–1.21, p = 0.63, I2 = 0%).

Sensitivity Analysis

Finally, in the sensitivity analysis using an alternate definition of early/late intubation, there was no statistically detectable difference on all-cause mortality between patients undergoing intubation without versus with a prior trial of HFNC/NIV (eight, 1128 deaths; 48.9% versus 42.5%; RR 1.11, 95% CI 0.99–1.25, p = 0.08, I2 = 0%).

Discussion

Timing of intubation may have no effect on all-cause mortality, duration of MV, ICU length of stay and renal replacement therapy. Despite the above guidelines, clinicians caring of patients with COVID- 19 seem to become eager to favor a wait-and-see strategy over time. Indeed, in a multicentre study from three European countries, involving 4244 critically ill patients with COVID-19, the percentage of patients receiving invasive MV descended from 82 to 68%. A similar trend was reported in a large study from the USA.

We found no statistically detectable difference between patients undergoing early versus late intubation in terms of morbidity, namely duration of MV, ICU length of stay and renal replacement therapy. These findings referring to severe respiratory failure associated with COVID-19 are not in line with findings from observational studies on acute respiratory distress syndrome (ARDS) not associated with COVID-19. The latter studies reported that **delaying intubation of** critically ill patients with ARDS may be associated with adverse outcomes. This is an interesting observation, which fuels the skepticism regarding the potential differences between ARDS associated with versus without COVID-19.

Conclusion

The synthesized evidence of almost 9000 patients suggests that timing of intubation may have no effect on mortality and morbidity of critically ill patients with COVID-**19**. These results might justify a **wait-and-see** approach, which may lead to fewer intubations. Relevant guidelines may therefore need to be updated.

ORIGINAL CLINICAL REPORT



Early Intubation and Increased Coronavirus Disease 2019 Mortality: A Propensity Score-Matched Retrospective Cohort Study

Introduction

Early and continued reports of the management of respiratory failure in patients with severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) (coronavirus disease 2019 [COVID-19]) suggest that mechanical ventilation is the mainstay of therapy, and the mortality rate of COVID-19 patients receiving mechanical ventilation is high. There has been controversy about the optimal timing of mechanical ventilation and selection of COVID-19 patients who require invasive mechanical ventilation.

Delayed invasive mechanical ventilation in patients with acute respiratory distress syndrome from sepsis and pneumonia has been shown to be associated with increased mortality compared with those intubated within 48 hours.

- COVID-19 patients should have an earlier threshold for receiving invasive mechanical ventilation due to high inspiratory efforts and transpulmonary pressures causing self-inflicted lung injury.
- There are no robust data on the timing of tracheal intubation and its relationship to mortality for COVID-19 patients, and the existing studies have inconsistent findings, suggesting either no relationship between time to invasive mechanical ventilation and mortality or that early intubation may affect mortality.

In this observational study using data from 11 public hospitals in New York City gathered from March to December 2020, we examined the relationship between invasive mechanical ventilation and inhospital mortality, using propensity score matching and adjustment to reduce confounding. We looked at the effect on mortality of intubation within 48 hours of hospital triage, as well as the effect of intubation at any time point.

Methods

SETTING: Eleven municipal hospitals in New York City from March 1, 2020, to December 1, 2020.

PATIENTS: Adult patients who tested positive for coronavirus disease 2019 in the emergency department were subsequently admitted. Patients with do-not-intubate orders at admission were excluded.

INTERVENTIONS: Intubation within 48 hours of triage and intubation at any point during hospital stay.

Results

a total of 82,578 adult patients were tested forCOVID-19 in the ED; of these tests, 12,902 (15.6%) were positive. Of these patients, 3,377 (26.2%) were discharged home, 487 (3.8%) were transferred to another facility outside the hospital system, 129 (1.0%) left against medical advice, 272 (2.1%) died before admission, and 8,637 (66.9%) were admitted. Of these, 8,510 (98.5%) represented a unique patient admission. Of these unique patients, 263 (3.1%) died within 48 hours of triage and were excluded. Of the remaining 8,247 patients, 650 (7.9%) had DNI orders placed within 48 hours of triage and were excluded, leaving 7,597 patients in the primary data set for this study.

As of December 1, 2020, 1,628 of these patients (21.4%) had been intubated and 1,898 had died (25.0%). Of the 1,628 intubations, 807 (49.6%) occurred within 48 hours of triage. The distribution of days until death or discharge and days between triage and intubation.

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Rate of Intubation Over Time and Across Hospitals

- Intubation rates varied significantly from hospital to hospital, with as few as 11.4% of admitted patients being intubated to as many as 35.3%. Location was <u>significantly</u> associated with intubation in multilevel logistic regression (median OR, 1.60; p = 0.0013).
- Mortality decreased over time; the per-week OR for inhospital mortality was 0.93 (0.92–0.94) (p < 0.0001).
- Intubation rates also decreased with time (perweek OR, 0.96 [0.95–0.97]; p < 0.0001)

Intubation and Mortality

- intubation within 48 hours of triage was associated with increased inhospital mortality (HR, 2.26 [2.05–2.49]; p < 0.0001).</pre>
- Before matching, median survival was 10.8 days (9.8–12.1 d) for intubated patients versus 25.8 days (24.3–27.8 d) for controls; after matching, median survival was 10.8 days (9.8– 12.1 d) for intubated patients versus 15.3 days (14.2–17.7 d) for controls.

Sensitivity Analysis

Notably, not excluding patients with DNI orders and restricting only to patients with significant oxygen requirements (those receiving HFNC, NIPPV, or mechanical ventilation) and/or those admitted to the ICU did not change the direction of the effect. In addition to the effect of intubation within 48 hours, we found intubation at any time point to still be associated with increased mortality after matching (HR, 1.62 [1.45–1.80]; p < 0.0001).

we also found that when restricting to intubated patients (*n* = 1628), *intubation within* 48 *hours* of triage (*n* = 807) was not associated with significantly increased mortality compared with those intubated later in their hospital course (HR, 1.09 [0.94–1.26]; *p* = 0.26).

Post Hoc Power Analysis

Given 1,898 (25.0%) deaths and 807 (10.6%) intubations within 48 hours of triage, assuming α = 0.05 and a power of 80%, our study was adequately powered to detect an HR of approximately 0.811 or an HR of approximately 1.23. For the primary effect size detected (HR, 1.30 [1.15–1.48]), our study had a post hoc power of approximately 94.1% (46.6 - 100.0%).

Discussion

- Previous studies have focused on recommendations for safe intubations, reported data regarding intubation success and safety, or analyzed the effect of timing of intubation on mortality in COVID-19 patients.
- We found rates of intubation to vary significantly from hospital to hospital, with providers at certain hospitals having intubated significantly more patients than others, even after adjusting for a variety of available confounders such as age or markers of disease severity. This difference may be due to local practice standards (such as lower clinical thresholds to intubate) that may have been amplified by the uncertainty of a novel viral pandemic.

We found intubation to have decreased significantly over time, alongside mortality, and relationships that again remained stable after controlling for potential confounding variables. A portion of this change may be due to less severe cases presenting later in the pandemic; some amount, however, may be due to changes in clinical practice as understanding of the disease and treatment options grew.

In the early stages of the pandemic, it was uncertain which patients would benefit from early intubation and mechanical ventilation.

The potential benefit of adjunctive airway treatments such as HFNC or NIPPV or awake proning was uncertain. Hence, even within one hospital system and after controlling for confounders, there was significant variation in rates of intubation. Intubation and mechanical ventilation carry a variety of risks. Early complications of tracheal intubation include cardiovascular collapse, hypoxemia, and aspiration. Longer term complications include ventilator induced lung injury and ventilator-associated pneumonia . Mortality in intubated COVID-19 patients is remarkably high. There have been reports of increased rates of barotrauma, high rates of ventilator-associated pneumonia, as well as severe acute kidney injury resulting from intubation in these patients. Additionally, mechanically ventilated patients require substantially increased nursing and provider time, resources that may become increasingly limited during a pandemic surge. A recent study found that greater ICU patient load was associated with increased mortality for COVID-19 patients.

Notably, we did not find a significant association between and timing of intubation (within 48 hr of triage vs later in hospital course), when restricting only to intubated patients. This differs from the results of Hyman et al, who found that earlier intubation was associated with significantly reduced mortality, with each additional day increasing the hazard of death by 3%. The differences between our results and theirs may be due to baseline differences in populations, differing clinical decision thresholds for intubation, the inclusion of early laboratory markers of disease severity in our propensity score model (such as ferritin and d-dimer), or different study timeframes (from March 1, 2020, to December 1, 2020, in our study vs from January 30, 2020, to April 30, 2020, in theirs). Their study also focused on timing of intubation and did not compare intubated patients with non intubated patients. Further studies from other populations and locations investigating this issue are needed.

Conclusion

Given the wide variation of intubation rates across hospitals and time points in this cohort, alongside the robust effect of increased mortality in intubated patients, there may have been patients who were intubated prematurely or unnecessarily. The decision to intubate is complex, even more so in face of an unprecedented viral pandemic. Future prospective studies should further explore the impact of intubation on mortality in COVID-19 patients and other techniques that may reduce or delay the need for intubation in these patients.

