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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The impact of timing of initiating invasive mechanical ventilation in COVID-19-related respiratory failure

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ABSTRACT

Purpose: Optimal timing of initiating invasive mechanical ventilation (IMV) in coronavirus disease 2019 (COVID-19)-related respiratory failure is unclear. We hypothesized that a strategy of IMV as opposed to continuing high flow oxygen or non-invasive mechanical ventilation each day after reaching a high FiO2 threshold would be associated with worse in-hospital mortality.

Methods: Using data from Kaiser Permanente Northern/Southern California's 36 medical centers, we identified patients with COVID-19-related acute respiratory failure who reached ≥80% FiO2 on high flow nasal cannula or non-invasive ventilation. Exposure was IMV initiation each day after reaching high FiO2 threshold (T_0). We developed propensity scores with overlap weighting for receipt of IMV each day adjusting for confounders. We reported relative risk of inpatient death with 95% Confidence Interval.

Results: Of 28,035 hospitalizations representing 21,175 patient-days, 5758 patients were included (2793 received and 2965 did not receive IMV). Patients receiving IMV had higher unadjusted mortality (63.6% versus 18.2%, $P < 0.0001$). On each day after reaching T_0 through day >10, the adjusted relative risk was higher for those receiving IMV compared to those not receiving IMV (Relative Risk>1).

Conclusions: Initiation of IMV on each day after patients reach high FiO2 threshold was associated with higher inpatient mortality after adjusting for time-varying confounders. Remaining on high flow nasal cannula or non-invasive ventilation does not appear to be harmful compared to IMV. Prospective evaluation is needed.

1. Introduction

Several types of non-invasive respiratory support (high flow nasal cannula or non-invasive ventilation which includes CPAP or biPAP) are used commonly to treat respiratory failure in patients with COVID-19. [1] High flow nasal cannula (HFNC) provides heated, humidified oxygen to be delivered to the lungs of patients with hypoxemic respiratory failure. HFNC improves patient comfort, allows for communication and oral nutrition, and may allow patients to recover without invasive mechanical ventilation (IMV). [2] Non-invasive ventilation provides positive pressure through a non-invasive interface (nasal mask, face mask, nasal plugs) and can be particularly helpful in certain clinical circumstances: hypercapnic respiratory failure from chronic obstructive pulmonary disease, pulmonary edema and obesity. [3,4]

Survival of critically ill patients with coronavirus disease 2019 (COVID-19)-related acute hypoxemic respiratory failure has improved over the course of the pandemic. [5] However, the risk of mortality in patients with respiratory failure, especially those requiring IMV remains high (~50%). [6] Non-invasive respiratory supports such as HFNC may minimize the risks and sequelae associated with IMV, such as exposure to sedation, immobility and ventilator-associated infections, [7] although prolonged use of non-invasive respiratory supports could also be contrived as injurious, especially when patients are needing high level of supplemental oxygen. Spontaneous breathing, specifically with

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large tidal volumes and wide swings in pleural pressure, is thought to cause self-induced lung injury. [8,9]

Prior to the COVID-19 pandemic, the optimal time of when to initiate IMV in acute respiratory failure was unclear. [10,11] This gap in clinical knowledge remains. In this observational study of COVID-19-related hypoxemic respiratory failure, we sought to assess whether initiation of IMV each day after reaching ≥80% fractional inspired oxygen (FiO2) was associated with increased risk of in-hospital mortality using granular electronic health record data from 36 medical centers and daily propensity scores with overlap weighting. We hypothesized that a strategy of IMV as opposed to continuing non-invasive respiratory support on each day after reaching a high FiO2 threshold would be associated with worse in-hospital mortality.

2. Methods

This was a retrospective, data-only, cohort study. The Kaiser Permanente Southern California (KPSC) and Northern California (KPNC) Institutional Review Boards approved the study.

2.1. Study population

KPSC and KPNC care for >9 million patients across 36 medical centers in California. We identified hospitalizations in adult patients (aged ≥18 years) between 2/1/20–12/31/20 for whom there was a first positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (SARS-CoV-2) result during the hospitalization or within the 3 weeks prior to admission. This definition has been used previously. [12]

2.2. Defining a high FiO2 requirement and time windows relative to that threshold

We examined patients who required FiO2 ≥ 80% delivered via HFNC or non-invasive ventilation (CPAP or biPAP) documented in electronic health record oxygenation flowsheets on at least 2 adjacent recordings. We used the timestamp of the first of the 2 EHR recordings as our 'time zero' (T_0) to define when patients required a high degree of FiO2. We excluded patients who initiated IMV or had 'do not intubate' status prior to reaching T_0 because the goal was to compare patients who were both at-risk and eligible for IMV to patients who initiated IMV on the same day relative to T_0. This approach allowed us to compare patients at the same point in their illness when they theoretically became at risk for IMV, rather than using admission date, given that patients present to care at different points in their illness. In so doing, we created 24-h time windows (days) after T_0. For example, day 1 is the first 24 h after T_0. On each day after T_0, we removed patients from that day's analysis who had previously initiated IMV, died, changed to 'do not intubate' status, or recovered, the latter of which we defined as no longer receiving HFNC or non-invasive ventilation. Therefore, we created patient cohorts for each day after T_0 that included only the patients eligible on that given day. Table 1 displays the status of patients on each day after reaching T_0. Patients could contribute to multiple days of analysis if IMV was not initiated on multiple days and patients met inclusion/exclusion criteria. However, patients could not re-enter the cohort if their goals of care changed (would accept IMV as a therapy "full code" after previously being designated as not accepting IMV) or they deteriorated after meeting recovery criteria.

2.3. Exposure and outcome

The study exposure was initiation of IMV on each day after reaching T_0 among patients at-risk and eligible for IMV. The primary outcome was inpatient mortality.

Table 1
Patients' status on each day after reaching high FiO2 threshold.

Day after reaching high FiO2	Compared using propensity score		Recovered	New limitation of code status
	No MV	IMV		
1	4711	659	0	388
2	3989	287	266	120
3	3494	220	187	76
4,5	2859	341	216	64
6,7	2038	273	402	77
8 to 10	1231	291	391	54
>10	446	336	257	55

Sample size is 5758 patients and 21,175 patient-days. Patients who never received MV but did not recover or have a limitation of code status are carried through the "no MV" column and used in each day's analysis. High FiO2 is considered ≥80% on high flow oxygen or non-invasive ventilation. Patients who died, recovered or had a limitation of life support (do not resuscitate, do not intubate, comfort care) were removed from the risk set of subsequent days.
Abbreviations: IMV = invasive mechanical ventilation, FiO2 = fraction of inspired oxygen.

2.4. Propensity score analysis with overlap weighting

To account for patient characteristics associated with the use of IMV, we developed propensity scores for the likelihood of receiving IMV for each day after T_0. The concept of comparing patients each day by propensity score is similar to a previous study. [13] Covariates in the propensity score model included demographic variables (age, sex, smoking status), Comorbidity Point Score version 2 (a scalar measure of 1-year comorbid disease burden), [14] individual Charlson comorbidities, [15] vital signs, laboratory values (e.g. D-dimer, lactic acid, erythrocyte sedimentation rate), receipt of steroid and month of the pandemic. For variables that change during a hospitalization, we used the values from that day to adjust for confounding in the propensity score. For example, the most deranged vital signs (highest heart rate) or laboratory values (lactic acid) from each 24-h window was used in that day's propensity score. In addition, we included time from hospital admission because patients with longer preceding hospitalization could be at higher risk for hospital-acquired complications and mortality. Because the sample size decreased over time due to patients recovering or dying, our analyses combined data from days 4 and 5, 6 and 7, 8 through 10 and > 10 days. As a result, we analyzed 7 cohorts by day after reaching T_0. The final cut off of >10 days was justified clinically as the fibrotic phase of ARDS typically occurs at 14 days and represents the start of a chronic, rather than acute, phase of illness. [16]

We used overlap weighting (calculated as 1-propensity score) as our primary analysis. We estimated the relative risk of inpatient death for patients receiving IMV versus not receiving IMV on each day after reaching T_0. We used generalized linear models with a Poisson distribution and a log link and accounted for within patient clustering. We report 95% confidence intervals (CI). The comparison of interest is patients who were or were not intubated on each day after reaching high FiO2 threshold.

2.5. Post-hoc analyses

We performed the following two additional analyses to confirm the results in the primary analysis. 1) We developed propensity scores by day with inverse probability of treatment weighting (99th percentile truncation) and then performed Poisson regression for inpatient mortality comparing patients who received IMV versus those who did not receive MV. 2) We did Poisson regression for relative risk of inpatient death by day for the outcome adjusting for the same covariates above without generating propensity scores first.

2.6. Statistical details

Continuous variables are presented as means with standard deviations. Categorical variables are presented as number with percent. *P*-values were generated using *t*-tests or Chi squared tests where appropriate. If the missingness for labs and vital signs was low (<5%), the most recent value was used; if no value was recorded, then the mean on that day was used. If the overall missingness for lab values was ≥5%, we replaced values with indicator variables for the presence or absence of the lab test on that day. We generated a Sankey diagram to visualize the changes in patients' status over time (meeting high FiO2 threshold, ventilated, limitation of code status, death, recovered, discharged).

All analyses were conducted using SAS 9.4 (Cary, NC) using two-sided 0.05 as the threshold for significance.

3. Results

Of 28,035 hospitalizations, 5758 patients met the inclusion/exclusion criteria, which represented 21,175 patient days. Table 1 displays the number of patients who did ($n = 2793$) and did not ($n = 2965$) receive IMV on each day after reaching T_0. Table 1 also displays the number of patients who recovered or had a new limitation of code status on each day after reaching T_0. Patients who never received IMV and did not recover or have a limitation of code status are represented in each row of the "no IMV" column and used in multiple days' analysis. The median time between reaching T_0 and receiving IMV in those who received IMV was 4 days. The median time between reaching T_0 and recovering in those who recovered and did not have a limitation of code status or die was 8 days.

Table 2 displays patient characteristics, including those who received IMV and those who did not receive IMV. Patients receiving and not receiving IMV were similar in smoking status and overall comorbidity burden. Patients receiving IMV were older (62.4 versus 60.8 years, $P < 0.0001$). A greater percentage of males received MV (68.3% versus 63.0%, $P < 0.0001$). A greater percentage of patients with diabetes (49.3% versus 42.3%, $P < 0.0001$) and renal disease received IMV (23.3% versus 17.3%, $P < 0.0001$). Unadjusted mortality was higher for patients who received IMV (63.6% versus 18.2%, $P < 0.0001$). **Table E1** shows characteristics of patients at day 1,3 and 6,7 broken down by patient status, including receiving and not receiving IMV, new limitation of code status and whether they had recovered. Variables conditionally formatted in red are ones in which there was large variation (>100%) across groups.

Fig. 1 is a Sankey diagram showing the evolution of patients' statuses in the 30 days from T_0. At day 5, 6% had died, 10% had a limitation of code status, 20% were receiving IMV, 8% were discharged, 10% recovered but not yet discharged, and 47% remained with high FiO2. At day 30, 34% had died, 5% had a limitation of code status, 8% were receiving IMV, 50% were discharged, 2% recovered but not yet discharged, and 1% remained with high FiO2.

Among those eligible for intubation each day after reaching 80% FiO2, we describe the raw inpatient mortality by whether they were intubated or not on each day. Among those who received IMV, unadjusted mortality each day after patients reached the high FiO2 threshold increased from 50% for those intubated on day 1 to 78% for those intubated on days 8–10 (Fig. 2 **dark blue**). Conversely, for patients who did not receive IMV, the raw mortality decreased from 46% for those eligible but not intubated on day 1 to 29% for those remaining eligible but still not intubated on days 8–10 (Fig. 2 **light blue**).

Distributions of the propensity score by treatment group and day are shown in **Fig. E1**. Using propensity scores for the likelihood of MV along with overlap weighting, the relative risk of death was higher in those receiving MV compared to those not receiving MV on each day of analysis (Relative Risk >1; Fig. 3). The adjusted relative risks by day were day 1 1.23 (95% CI 1.08–1.39), day 2 1.39 (95% CI 1.20–1.62), day 3 1.34 (95% CI 1.13–1.58), days 4,5 1.51 (95% CI 1.31–1.73), days 6,7 1.64 (95% CI 1.42–1.89), days 8–10 1.82 (95% CI 1.57–2.10), day >10 3.90 (95% CI 2.72–5.59).

Fig. E2 confirms the result of the main analysis, where patients receiving MV each day after reaching T_0 had higher risk of inpatient mortality using both A) propensity score with inverse probability of treatment weighting and B) standard risk adjustment without propensity

Table 2
Baseline characteristics of patients admitted for COVID-19 related respiratory failure by receipt of invasive mechanical ventilation.

Characteristics	All (n = 5758)	Patients never receiving invasive mechanical ventilation (n = 2965)	Patients receiving invasive mechanical ventilation (n = 2793)	*P* value
Age	61.6 ± 14.1	60.8 ± 15.3	62.4 ± 12.7	<0.0001
Sex, male	3776 (65.6)	1868 (63.0)	1908 (68.3)	<0.0001
Smoking				
Never/Passive	4006 (69.6)	2076 (70.0)	1930 (69.1)	0.45
Current/Former	1752 (30.4)	889 (30.0)	863 (30.9)	
Body mass index normal	644 (11.2)	382 (12.9)	262 (9.4)	<0.0001
Comorbidity Point Score, version 2	26.3 ± 31.3	26.4 ± 32.7	26.2 ± 29.8	0.76
Diabetes	2633 (45.7)	1255 (42.3)	1378 (49.3)	<0.0001
Peripheral vascular disease	1402 (24.3)	670 (22.6)	732 (26.2)	0.001
Renal disease	1164 (20.2)	512 (17.3)	652 (23.3)	<0.0001
Chronic pulmonary disease	1066 (18.5)	534 (18.0)	532 (19.0)	0.31
Congestive heart failure	558 (9.7)	270 (9.1)	288 (10.3)	0.12
Cancer	271 (4.7)	138 (4.7)	133 (4.8)	0.84
Ischemic heart disease	269 (4.7)	135 (4.6)	134 (4.8)	0.66
Cerebrovascular disease	222 (3.9)	111 (3.7)	111 (4.0)	0.65
Liver disease	50 (0.9)	26 (0.9)	24 (0.9)	0.94
Vital signs on day of reaching high FiO2				
Temperature	98.3 ± 0.8	98.3 ± 0.8	98.3 ± 0.8	0.74
Respiratory rate	23.6 ± 4.0	23.4 ± 3.6	23.8 ± 4.3	<0.0001
Oxygen saturation	93.0 ± 3.4	93.2 ± 2.6	92.8 ± 4.1	<0.0001
Heart rate	83.2 ± 11.3	82.7 ± 11.4	83.6 ± 11.2	0.003
Laboratory values				
White blood cell count, x10^9/L	10.2 ± 6.7	10.1 ± 8.1	10.3 ± 4.9	0.40
Hemoglobin, g/dL	13.3 ± 1.9	13.2 ± 1.8	13.3 ± 1.9	0.05
Platelets, x10^9/L	256.2 ± 97.6	265.8 ± 99.8	246.0 ± 94.2	<0.0001
Bicarbonate, mEq/L	23.8 ± 3.9	24.3 ± 3.7	23.3 ± 3.9	<0.0001
Blood urea nitrogen, mg/dL	24.4 ± 18.5	23.8 ± 18.0	25.0 ± 19.0	0.01
Creatinine, mg/dL	1.3 ± 1.7	1.2 ± 1.6	1.4 ± 1.9	0.0002
Raw in-hospital mortality	2316 (40.2)	539 (18.2)	1777 (63.6)	<0.0001

Continuous variables are expressed mean with standard deviation. Categorical variables are expressed as numbers with percent.
Abbreviation: COVID-19, coronavirus disease 2019.

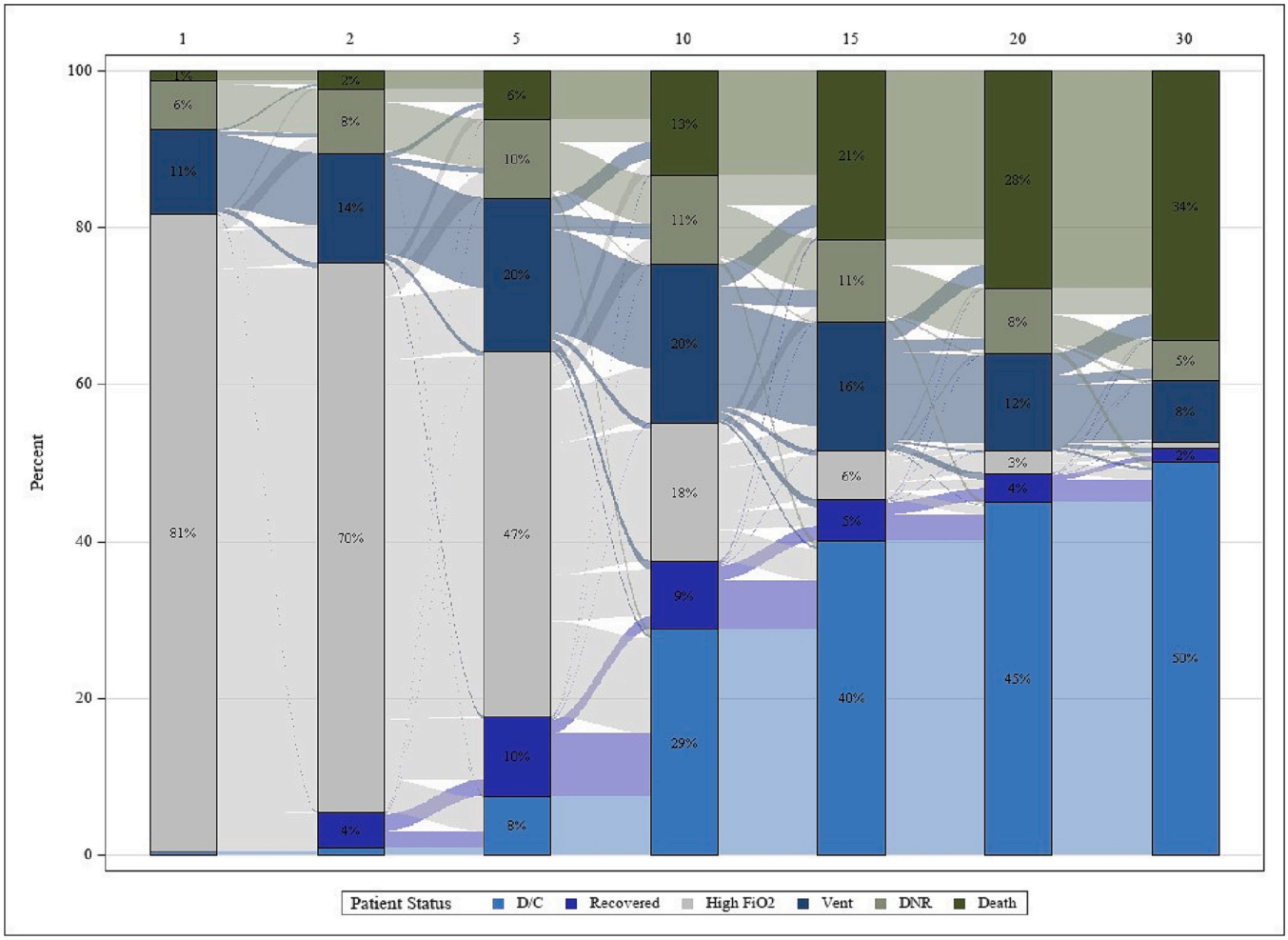


Fig. 1. Stacked bar chart showing patients' status over 30 days from reaching high FiO2 threshold.
Sankey diagram of patients' clinical status in the 30 days after reaching high FiO2 threshold. The DNR (do not resuscitate) are patients who are not eligible for intubation because of their goals of care.
Abbreviations: D/C = discharged, DNR = do not resuscitate.

score.

4. Discussion

In this retrospective study, we identified a large, multicenter cohort of patients with COVID-19-related acute respiratory failure and examined whether receipt of IMV was associated with worse inpatient mortality compared to patients who did not receive IMV at the same day in their illness. Overall, we found that 20.5% of all patients admitted with COVID-19-related acute respiratory failure reached our high FiO2 threshold. Of those, approximately half (49%) ultimately required IMV. Raw inpatient mortality was high for those who received IMV (64%) compared to those who did not receive IMV (18%), despite relatively few clinical differences between patients. At 30 days after reaching high FiO2, the majority (52%) had recovered or been discharged.

On each daily estimate, the relative risk of mortality was higher among patients receiving IMV, which could be the result of unmeasured confounding or increased harm from IMV or both. It is impossible to tease apart which is the driving factor except with a randomized prospective clinical trial, as confounding would be mitigated in a trial. While we tried to adjust for measured confounding, including vital signs as they varied each day, there could be confounders that remain unmeasured each day, such as bedside measures of work of breathing (presence of retractions, tripoding, etc.). An important takeaway is that remaining on non-invasive respiratory supports does not appear to be harmful, at least compared to IMV, which many clinicians worried about during the height of the pandemic. However, a prospective trial is needed to truly understand the role of confounding and effect of different treatment strategies in this clinical scenario.

This study builds on previous studies addressing the optimal timing of initiation of IMV, many of which were conducted prior to the pandemic. In a pre-COVID-19 study on the timing of IMV in sepsis, Delbove et al. found a statistically significant association between deferred IMV and fewer days alive without organ support by day 28. [11] In another study from the pre-COVID-19 era that used previously collected prospective, multicenter data, Kangelaris et al. showed that patients intubated after the first 24 h of reaching criteria for ARDS had higher hospital and 2-year mortality compared to patients intubated on the day of reaching criteria for ARDS. [10]

More recently, Gershengorn et al. used the control group of a prospective clinical trial in COVID-19 patients to study the association between duration of HFNC and the combined outcome of IMV initiation or death within 28 days of study enrollment. [17] They found no increased risk of the outcome in those who received HFNC for longer periods of time. The benefit of this study was the protocolized initiation of IMV and the diverse, international study population. They answered a slightly different question than us, however. They created cohorts based on number of days of HFNC exposure, and their composite outcome included IMV; we defined a threshold for high FiO2, created cohorts by day after reaching that threshold and evaluated death as the outcome

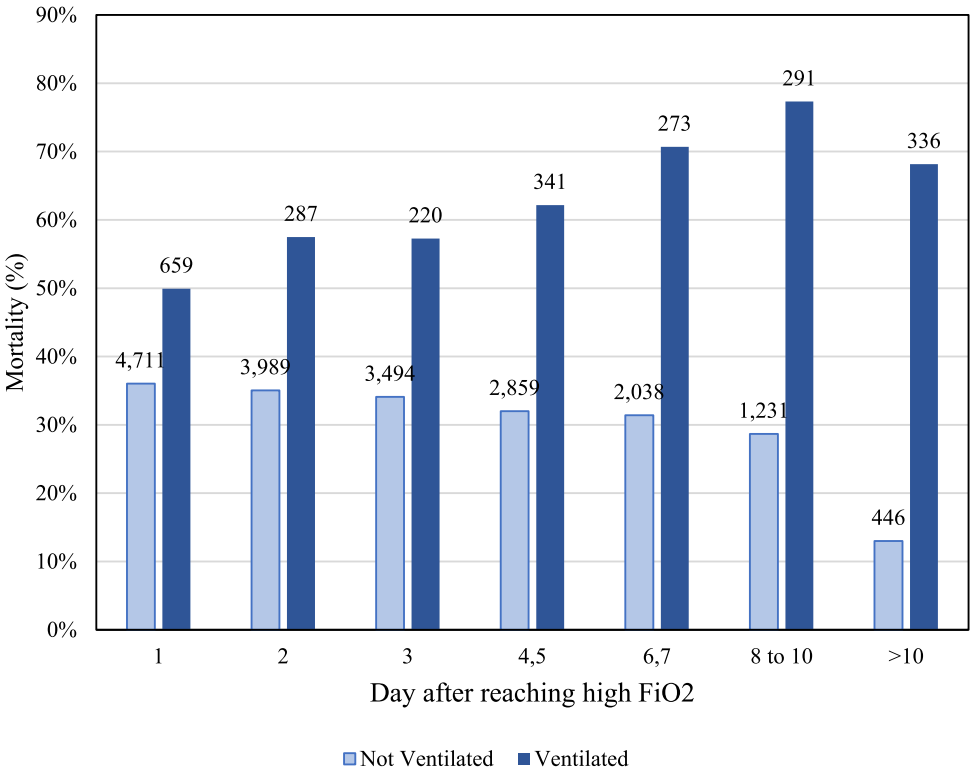
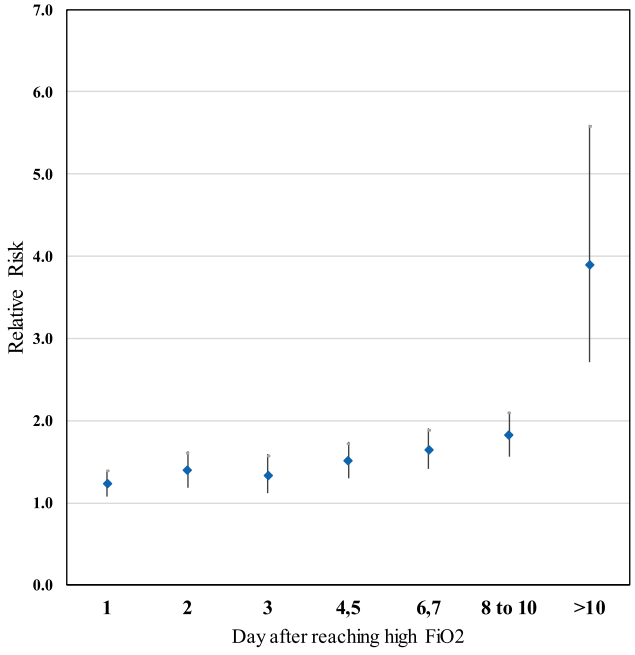


Fig. 2. Raw in-hospital mortality over time after reaching high FiO2 threshold by whether patients were ventilated or not.
The bar chart shows the raw mortality of patients changing over time by ventilation status. Raw mortality increased each day for patients who were ventilated (dark blue) and decreased each day for patients who were not ventilated (light blue). The denominators each day were patients who were eligible for intubation, which meant meeting the following criteria: not previously intubated, goals of care consistent with accepting intubation as a therapy and not yet recovered, which we defined as no longer needing high flow or non-invasive mechanical ventilation. Ventilation day was relative to the day when a patient received 80% FiO2 on high flow or non-invasive ventilation. Mortality was assessed while patients were in the hospital. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Abbreviation: FiO2=fraction of inspired oxygen

Fig. 3. Adjusted relative risk for death by day after reaching high FiO2 threshold using propensity scores with overlap weighting.
The relative risks were day 1 1.23 (95% CI 1.08–1.39), day 2 1.39 (95% CI 1.20–1.62), day 3 1.34 (95% CI 1.13–1.58), days 4,5 1.51 (95% CI 1.31–1.73), days 6,7 1.64 (95% CI 1.42–1.89), days 8–10 1.82 (95% CI 1.57–2.10), day >10 3.90 (95% CI 2.72–5.59).
Abbreviation: FiO2 = fraction of inspired oxygen.

depending on whether patients received IMV.

Most studies addressing the issue of timing of IMV used hospital or intensive care unit admission as their T_0. However, this is a major methodologic flaw, as these timepoints do not represent the same point in a patient's disease course. Patients present to care at different times due to barriers to care, support at home, symptom severity, etc. [18] Le Terrier conducted a prospective observational study in Switzerland and reported a significant association between longer time from hospital admission for COVID-19 and receipt of IMV with intensive care unit mortality, particularly when patients were intubated after 7 days. [19] Hernandez-Romieu et al. reported no association between later IMV and lung compliance, duration of IMV or intensive care unit length of stay in 231 patients with COVID-19 related respiratory failure in Atlanta. [20] Pandya et al. found no difference in the raw mortality of 75 consecutive patients intubated early (≤1.27 days) versus late (>1.27 days) (mortality 46% versus 54%, respectively, $P = 0.56$). [21] However, only univariate analyses were conducted. A meta-analysis pooling 9000 patients across 12 non-randomized studies found no difference between raw mortality rates among patients with COVID-19-related acute respiratory distress syndrome who were intubated early (<24 h after intensive care unit admission) vs later (45% versus 39%, respectively, $P = 0.07$). [22] Our approach of creating an FiO2 threshold, above which IMV would be reasonably considered clinically, and *defining T_0 from that threshold*, was critical to be able to compare outcomes of patients receiving IMV on a given day relative to a time point in the disease.

There are several limitations to our study. First, as mentioned above, unmeasured confounding could explain the increased risk of patients who did receive IMV each day. We were also not able to account for some clinical factors (e.g., patients with shunt or right ventricular failure, pulmonary embolism, etc.) that could influence the decision to proceed with IMV or not. Second, the risk of mortality over the course of the pandemic has decreased. [5] We pooled data over time to maximize sample size, although notably the majority of the cohort (>80%) was enrolled following the publication of the RECOVERY trial. [23] We did adjust for treatment with steroids to address this issue. Third, evidence suggests that mortality increased among COVID-19 critically ill patients

during surge periods. [24,25] Periods of high census may have influenced clinicians' decisions about initiation of IMV, so we did adjust for month of the pandemic to address this issue. Fourth, we defined the high FiO2 threshold using clinical recordings of oxygen supplementation from the electronic health record rather than on arterial blood gas values. However, it seemed reasonable that physicians would be considering IMV in patients requiring at least 80% FiO2. Fifth, different weighting strategies used in propensity score analyses can introduce bias. We used overlap weights because they perform well compared to inverse probability of treatment weight in simulation studies. Overlap weights allow us to focus on the patients who could reasonably fall into the treated or not treated group, not the outliers (i.e., patients in whom there is clinical equipoise). [26-28] We also performed two sensitivity analyses using inverse probability of treatment weighting. It was reassuring that the results were similar. Sixth, we defined the high FIO2 threshold to be 80% but further investigation is needed to see if there is a better or more obvious threshold that alters the risk ratio of the two treatment strategies.

There are also many advantages to our study. We leveraged a large data set across many medical centers that contained rich, granular respiratory and vital sign data to answer an important clinical question. We employed robust methods including propensity scores with overlap weighting comparing patients who were intubated or not on a given day after reaching the objective respiratory threshold we defined as severe hypoxemia. We also accounted for patients who recovered, died or had a limitation of code status (do not resuscitate), because these patients were no longer eligible for IMV. Not accounting for patients who recover from respiratory failure has been a criticism of previous respiratory cohorts. [29]

5. Conclusion

We demonstrated that a large proportion of patients (>50%) improved and/or were discharged by 30 days after reaching high FiO2 threshold, which is reassuring. However, our results suggest that patients with COVID-19-related respiratory failure who received IMV on each day after reaching high FiO2 threshold had higher in-hospital mortality. Remaining on non-invasive respiratory supports does not appear to be harmful. This study lays the foundation for a prospective trial for definitive evidence that intubating is associated with worse outcomes given the aforementioned issues with unmeasured confounding.

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Author contributions

LCM conceived of the idea and drafted the manuscript. PK performed the analysis. JDG and AC pulled the data. BC coordinated data transfer and IRB submission. SX provided statistical consultation and helped to interpret the results. VS and NR provided clinical consultation. ALG and MKG contributed to the study design and interpreted the results. VXL oversaw the analysis and interpreted the results. All authors critically reviewed the manuscript.

Author statement

On behalf of my co-authors, I am pleased to submit an original manuscript to your journal. The paper is titled, "Timing of initiating mechanical ventilation in COVID-19-related respiratory failure." All authors have read and approved the manuscript. The manuscript has not been published previously and is not under consideration for publication elsewhere.

Access to data

Drs. Myers and Kipnis had full access to the data and take responsibility for the accuracy of the analysis.

Declaration of Competing Interest

The authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154322.

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