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# Prolonged prone position ventilation is associated with reduced mortality in intubated COVID-19 patients

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**Short Running Head**: Prone strategy effect on mortality in COVID-19

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**Keyword List**

Acute hypoxemic respiratory failure

COVID-19

Mechanical ventilation

Prone position ventilation

**Abbreviation List**

| | |
|---|---|
| ARDS | Acute respiratory distress syndrome |
| ΔPF | Change in $P_aO_2$/ $F_IO_2$ after proning |
| aHR | Adjusted hazard ratio |
| aOR | Adjusted odds ratio |
| BMI | Body mass index |
| CCI | Charlson comorbidity index |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease |
| ECMO | Extracorporeal membrane oxygenation |
| $F_IO_2$ | Fraction of inspired oxygen |
| IBW | Ideal body weight |
| ICU | Intensive care unit |
| IL-6 | Interleukin-6 |
| IPTW | Inverse probability treatment weights |
| IQR | Interquartile range |
| LOS | Length of stay |
| LTVV | Low tidal volume ventilation |
| MGH | Massachusetts General Hospital |
| NWH | Newton-Wellesley Hospital |
| $P_aO_2$ | Partial pressure of oxygen in the artery |
| PEEP | Positive end-expiratory pressure |
| PPV | Prone position ventilation |
| RT-qPCR | Quantitative reverse transcription polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAPS | Simplified acute physiology score |
| SH | Salem Hospital |
| SOFA | Sequential organ failure assessment |
| VFD | Ventilator-free days |
| VILI | Ventilator-induced lung injury |
| Vt | Tidal Volume |

## Abstract

**Background**: Prone position ventilation (PPV) is resource-intensive, yet the optimal strategy for PPV in intubated patients with COVID-19 is unclear.

**Research Question**: Does a prolonged (24 or more hours) PPV strategy improve mortality in intubated COVID-19 patients compared to intermittent (~16 hours with daily supination) PPV?

**Study Design and Methods**: Multicenter, retrospective cohort study of consecutively admitted intubated COVID-19 patients treated with PPV between March 11 – May 31, 2020. The primary outcome was 30-day all-cause mortality. Secondary outcomes included 90-day all-cause mortality and prone-related complications. Inverse probability treatment weights (IPTW) were used to control for potential treatment selection bias.

**Results**: Of the COVID-19 patients who received PPV, 157 underwent prolonged and 110 underwent intermittent PPV. Patients undergoing prolonged PPV had reduced 30-day (adjusted hazard ratio [aHR] 0.475, 95% CI 0.336-0.670, *P* value < 0.001) and 90-day (aHR 0.638, 95% CI 0.461-0.883, *P* value = 0.006) mortality compared to intermittent PPV. In patients with $P_aO_2/F_IO_2 \leq 150$ at the time of pronation, prolonged PPV was associated with reduced 30-day (aHR 0.357, 95% CI 0.213-0.597, *P* value < 0.001) and 90-day mortality (aHR 0.562, 95% CI 0.357-0.884, *P* value = 0.008). Patients treated with prolonged PPV underwent fewer pronation and supination events (median 1, 95% CI 1-2 versus 3, 95% CI 1-4, *P* value < 0.001). PPV strategy was not associated with overall PPV-related complications though patients receiving prolonged PPV had increased rates of facial edema and lower rates of peri-proning hypotension.

**Interpretation**: Among intubated COVID-19 patients who received PPV, prolonged PPV was associated with reduced mortality. Prolonged PPV was associated with fewer pronation and supination events and a small increase in rates of facial edema. These findings suggest that

prolonged PPV is a safe, effective strategy for mortality reduction in intubated COVID-19 patients.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease (COVID-19), results in critical illness in up to 5% of patients. Most patients require prolonged mechanical ventilation, with mortality comparable to acute respiratory distress syndrome (ARDS).[1–5] To date, there are few effective therapies for reducing mortality in COVID-19 patients admitted to the intensive care unit (ICU), highlighting the importance in identifying additional therapies for this high mortality group.[6–8]

Prone position ventilation (PPV) reduces mortality in ARDS.[9] However, PPV is a resource-intensive intervention requiring multiple highly trained staff to execute each pronation and supination event.[10] Additionally, the optimal duration for PPV is unknown.[11] Current practice tends to follow the protocol set out in the PROSEVA trial, whereby patients were randomized to receive PPV for at least 16 hours per day with daily supination events.[12,13] Meta-analyses have demonstrated a mortality benefit when patients are proned for > 12 hours/day, but the physiologic benefits of PPV continue to accrue through 24 hours of prone ventilation.[14,15] Furthermore, supination is frequently accompanied by a de-recruitment event, possibly increasing lung stress and strain, ventilator-induced lung injury (VILI), and mortality.[16] These observations suggest that prolonged exposure to PPV may offer an additional mortality benefit. Two prior studies evaluated safety and efficacy of PPV longer than 24 hours, however there are no studies comparing this prolonged PPV approach to one including daily supination.[17–19] Additionally, lengthening PPV duration would reduce the frequency of pronation and supination events, decreasing the number of staff required to implement this lifesaving treatment. Thus, determining whether a prolonged PPV strategy is efficacious may benefit both individual patients and strained hospital systems by reducing healthcare resource utilization.

Early in the pandemic, uncertainty about appropriate treatment of critically ill COVID-19 patients led to heterogeneity in clinical practice, providing a unique opportunity to study which PPV parameters contribute to improved mortality. In this study we assessed the association between prolonged (> 24 hours prone) or intermittent (~16 hours prone with daily supination) PPV strategy and mortality in intubated COVID-19 patients.

**Study Design and Methods**

This is a retrospective cohort study of all patients with confirmed COVID-19 and acute respiratory failure consecutively admitted to a medical or surgical intensive care unit (ICU) at three Mass General Brigham hospitals in the Boston, Massachusetts, metropolitan area, from March 11, 2020, through May 31, 2020. These hospitals included both academic medical centers and community hospitals. Each hospital employed dedicated proning teams comprised of individuals with prior experience with PPV. Positive end-expiratory pressure (PEEP) was set at each institution either based on ARDSNet PEEP/$F_IO_2$ tables[20] or best compliance during a decremental PEEP titration trial. Remdesivir was given as a 200mg single dose on day one followed by 100 mg daily for five days. Tocilizumab was the anti-IL-6 monoclonal antibody administered most often in this cohort, and typically given as a 400mg single dose. Most patients did not receive high dose steroids early in the course of the disease. Inclusion criteria were age 18 years or older, positive SARS-CoV-2 RT-qPCR test, need for mechanical ventilation, and at least one PPV episode.

Prone strategy was classified based on exact dates and times of pronation and supination events. Prolonged PPV was defined as a prone duration lasting at least 24 hours before supination. Intermittent PPV was defined as daily pronation and supination events. Patients who

underwent a single PPV event during their ICU stay, or who had prone sessions on non-consecutive days, were classified as intermittent if the longest prone session length was less than 24 hours. Hospital-wide guidelines were not available during the study for choice of prone strategy, but physicians typically used clinical improvement and subsequent stability as a means for determining whether patients should receive intermittent or prolonged PPV.

Study data were collected and managed using the REDCap electronic data capture tool hosted at Mass General Brigham.[21,22] Data were abstracted through May 31, 2021, by board certified or board eligible physicians. The study protocol was approved by the Institutional Review Board at Massachusetts General Hospital (2020P001119). The need for informed consent was waived.



## Outcomes

The primary outcome was 30-day all-cause mortality. Secondary outcomes included 90-day mortality, hospital length of stay (LOS), ICU LOS, ventilator-free days (VFD) at 28 days, and pre-specified complications of PPV. Pre-specified subgroup analysis included patients with $P_aO_2/F_IO_2$ ratio $\leq 150$ immediately prior to PPV, based upon the PROSEVA trial and existing clinical guidelines.[9,12]

## Statistical Analyses

To control for potential treatment selection bias between the intermittent and prolonged prone strategies, we carried out a propensity score based inverse probability treatment weighted (IPTW) analysis. Propensity scores were calculated through a multivariable logistic regression model that included admission hospital, time-to-intubation in days, positive end-expiratory

pressure at time of intubation, and need for dialysis at time of proning. Variables were chosen based upon an *a priori* assessment of the likelihood that they would contribute to the clinical decision to repeatedly pronate/supinate a patient. Standardized mean (or proportional) difference less than 0.1 for each variable was used to verify balance between treatment groups. A sensitivity analysis was performed incorporating additional variables in the propensity score model.

To determine the association between PPV strategy and mortality, a parametric outcome survival model was fit using the Weibull distribution with the survreg package (version 3.2-13) incorporating stabilized IPTW weights to adjust for potential treatment selection bias. This outcome model adjusted for potential confounders including age, sex, Charlson comorbidity index (CCI), sequential organ failure assessment (SOFA) score at hospital admission, $P_aO_2/F_IO_2$ ratio immediately prior to pronation, BMI, treatment with anti-IL-6 therapy, and treatment with paralytics, while stratifying on admission hospital. Survival time was calculated from the time of PPV initiation to death. We performed a pre-specified subgroup analysis focused only on patients with $P_aO_2/F_IO_2 \leq 150$ just prior to pronation as described above. Propensity score weights were re-calculated for this subgroup analysis and the outcome models adjusted for the same set of covariates in the primary analyses. Only 4 patients (1.5%) were excluded from the analysis due to missing IPTW covariates, thus we did not adjust for missingness in the final outcome models.

Predictors of complications due to PPV were identified using generalized linear models. Penalized splines were initially used to test for non-linear relationships between continuous predictors, such as duration of PPV, and outcomes. These models showed that there was a linear relationship between duration of PPV and complications, thus the final model incorporated prone duration as a linear covariate.

Secondary analyses focused on understanding the role of change in $P_aO_2/F_IO_2$ ratio with proning (ΔPF). Patients were determined to have an improved ΔPF if the $P_aO_2/F_IO_2$ ratio after proning was greater than prior to proning (i.e. ΔPF > 0 mmHg). Parametric survival models using the Weibull distribution were used to estimate the association between mortality and improvement in $P_aO_2/F_IO_2$ ratio alone and after adjusting for potential confounders including age, sex, CCI, SOFA score, $P_aO_2/F_IO_2$ ratio prior to PPV, BMI, treatment with anti-IL-6 therapy, and treatment with paralytics, while stratifying on admission hospital.

Two-sided P-values less than 0.05 were considered significant. All data analysis was performed using R (version 4.2.1). Continuous variables are presented as median (interquartile range) and categorical data are presented as number (%). The R code used for this analysis is uploaded as a supplemental file.

## Results

Patient Characteristics

A total of 267 patients received PPV while mechanically ventilated for confirmed COVID-19; 157/267 (58.8%) received prolonged PPV (**Figure 1**). The median age was 62 years; 64.4% were male; and 55.4% were White (**Table 1**). Prolonged PPV patients were less likely to be treated with paralysis (27.4% versus 43.6%, *P* value = 0.009) and less likely to receive anti-IL-6 therapy (9.6% versus 32.7%, *P* value < 0.001) than intermittent PPV patients. There were no group differences in severity of illness at admission assessed using SOFA, SAPS II, and $P_aO_2/F_IO_2$ ratio. Similar trends were seen between PPV strategies in the subgroup of patients with $P_aO_2/F_IO_2 \leq 150$ just before pronation (**e-Table 1**). Low tidal volume ventilation was achieved in the cohort, with an average tidal volume of 6.01 (5.84-6.27) cc/kg ideal body weight, and an

average driving pressure of 11.0 (9.5-13.0) cm $H_2O$ prior to pronation. Of the patients initially receiving intermittent PPV, 24/110 (21.8%) transitioned to a prolonged strategy (defined as subsequent prone sessions lasting 24 or more hours), while of patients initially receiving prolonged PPV, 5/157 (3.2%) transitioned to an intermittent strategy (defined as daily supination events).

IPTW weights were constructed separately for all patients and those with $P_aO_2/F_IO_2 \leq 150$ before pronation. Of all 267 patients receiving PPV, the IPTW cohort included 263 patients (**Figure 1**, study flow diagram). Demographics of the 4 excluded patients due to missing covariates are available in **e-Table 2**. After adjusting for potential treatment selection bias with stabilized IPTW in the overall cohort, there were no differences in key variables between PPV strategies (**e-Table 3** and **e-Figure 1**). In patients with $P_aO_2/F_IO_2 \leq 150$ before pronation, the IPTW cohort included 166 patients; there were no differences in key variables between PPV strategies (**e-Table 4** and **e-Figure 2**).



Primary Outcome

Kaplan-Meier curves for 90-day survival are shown in **Figure 2.** In multivariable Weibull survival models, prolonged PPV was associated with reduced 30-day mortality (aHR 0.475, 95% CI 0.336-0.670, *P* value < 0.001) and 90-day mortality (aHR 0.638 95% CI 0.461-0.883, *P* value = 0.006) compared to intermittent PPV in the overall cohort. In prespecified subgroup analyses focused on patients with $P_aO_2/F_IO_2 \leq 150$ prior to pronation, the protective effect of prolonged PPV on mortality was stronger. Prolonged PPV was associated with both reduced 30-day (aHR 0.357, 95% CI 0.213-0.597, *P* value < 0.001) and 90-day mortality (aHR 0.562, 95% CI 0.357-0.884, *P* value = 0.008) compared to intermittent PPV. Sensitivity analysis incorporating

additional covariates in the IPTW model showed similar results (**e-Table 5**). Hospital LOS, ICU LOS, and VFDs at 28 days differed between survivors and non-survivors but not between PPV strategies (**e-Table 6**).

Proning Characteristics and Complications

There were no differences in time from intubation to proning between PPV strategies (**Table 2**). Patients receiving prolonged PPV had longer cumulative length of time in the prone position (median 68 hours, IQR 46-120, versus 48 hours, IQR 19-80, *P* value < 0.001) and fewer pronation and supination events compared to the intermittent PPV group (median 1, IQR 1-2, versus 3, IQR 1-4, *P* value < 0.001). Duration of first prone session was longer in patients receiving prolonged PPV (median 40 hours, IQR 27-55, versus 17 hours, IQR 14-20, *P* value < 0.001). The empirical cumulative distribution functions of PPV session duration are available in **e-Figure 3**.

When comparing the effect of PPV strategy on changes in $P_aO_2/F_IO_2$ ratio with the first proning event, there was no overall difference between groups in the $P_aO_2/F_IO_2$ ratio before or after proning nor did the magnitude of change in $P_aO_2/F_IO_2$ ratio with the first proning event differ (**Table 2**). In univariable analysis, improvement in $P_aO_2/F_IO_2$ ratio (i.e., change in $P_aO_2/F_IO_2$ ratio > 0 mmHg) with proning was associated with improved 30-day (HR 0.576, 95% CI 0.382-0.868, *P* value = 0.009) and 90-day mortality (HR 0.617, 95% CI 0.414-0.919, *P* value = 0.02). Similarly, for patients with $P_aO_2/F_IO_2 \leq 150$ at the time of proning, improvement in $P_aO_2/F_IO_2$ ratio with proning was associated with 30-day (HR 0.467, 95% CI 0.277-0.789, *P* value = 0.005) and 90-day (HR 0.547, 95% CI 0.326-0.917, *P* value = 0.02) mortality. In the multivariable Weibull model in the overall cohort, improvement in $P_aO_2/F_IO_2$ ratio remained

associated with improved 30-day (aHR 0.329, 95% CI 0.211-0.512, P value < 0.001) and 90-day mortality (aHR 0.447, 95% CI 0.287-0.694 P value < 0.001). Inclusion of improvement in $P_aO_2/F_IO_2$ ratio did not alter the association between prolonged PPV and 30-day (aHR 0.409, 95% CI 0.289-0.579, P value < 0.001) or 90-day mortality (aHR 0.577, 95% CI 0.414-0.805, P value < 0.001).

There were no differences in ventilator mode, settings, or mechanics between patients receiving either PPV strategy (**Table 2 & e-Table 7**). A total of 48.3% of patients had a complication associated with PPV, the most common of which were pressure injuries (29.2%) and facial edema (11.6%). Patients receiving prolonged PPV had a higher rate of facial edema (15.3% versus 6.4%, *P* value = 0.04) and a lower rate of peri-proning hypotension (1.3% versus 7.3%, *P* value = 0.03). PPV strategy was not associated with overall increased risk of complications related to prone position (prolonged vs. intermittent, aOR 0.658, 95% CI 0.388-1.106, *P* value = 0.116, **e-Table 8**).

## Discussion

In this study of intubated COVID-19 patients, prolonged PPV was associated with higher 30-day and 90-day survival compared to intermittent PPV in both the overall cohort and in a pre-specified subgroup of patients with $P_aO_2/F_IO_2 \leq 150$ prior to pronation. PPV strategy was not associated with an overall higher rate of proning-related complications and resulted in significantly fewer pronation and supination events. These findings suggest that intermittent supination, especially in patients with more severe disease, may be injurious. Prolonged PPV has a favorable safety profile and reduces resource utilization due to the need for fewer pronation and supination episodes.

This study is an important addition to the literature on PPV in acute respiratory failure. First, while prior studies have characterized safety and efficacy of PPV for greater than 24 hours, this is the first to directly compare a prolonged PPV approach to the intermittent strategy laid out in the PROSEVA trial, addressing a long standing question on whether lengthening the duration of PPV improves outcomes.[9,11,17–19,23] Second, this study contributes detailed information on the number of pronation/supination episodes with implications on resource utilization, and further extends our knowledge of the effects of PPV on oxygenation and lung mechanics.[24] Third, this study provides a comprehensive look at complications of PPV, highlighting the areas to focus development of preventative measures.[10]

There are several potential benefits to choosing prolonged rather than intermittent PPV in patients intubated for COVID-19. First, the physiological benefits of PPV, including improved compliance of the respiratory system and reduced lung strain, improve continuously over 24 hours of prone ventilation.[15] The de-recruitment associated with repeated supination may lead to increased atelectotrauma and VILI, possibly contributing to mortality.[25,26] In addition, meta-

analyses have indicated that PPV reduces mortality only if its duration is greater than 12 hours per day[14,27,28] and in patients receiving LTVV (≤ 8 mL/kg ideal body weight).[29] As the PROSEVA trial showed that LTVV plus 17 hours of PPV is superior to LTVV while supine, our findings that prolonged PPV is associated with improved mortality compared to intermittent PPV logically follows. Second, from a resource utilization standpoint, prolonged PPV requires significantly fewer healthcare personnel to implement due to fewer pronation and supination episodes. Third, while our data suggests that the safety profile of prolonged PPV is comparable to traditional intermittent PPV, it will be important to conduct additional research into methods to reduce the risk of potential complications related to prolonged PPV. A randomized control trial comparing prolonged to intermittent PPV will be important to verify these findings.

Prior work has indicated that improvement in $P_aO_2/F_IO_2$ ratio with proning is associated with reduced mortality in COVID-19, although this is less clear for other etiologies of ARDS.[30–33] We find no differences in the change in $P_aO_2/F_IO_2$ ratio with PPV based upon strategy nor does the change in $P_aO_2/F_IO_2$ ratio explain the association with improved mortality seen with prolonged PPV. Evaluating the $P_aO_2/F_IO_2$ ratio over time in patients receiving either PPV strategy may reveal a difference in oxygenation response to prolonged PPV as has previously been seen with PPV and recruitment maneuvers.[34,35] Additionally, the relative balance between resolution of dorsal atelectasis and development of ventral atelectasis may contribute to initial changes in $P_aO_2/F_IO_2$ ratio with PPV or contribute to a diminished response with prolonged PPV.[36] Further research will be necessary to determine how prolonged PPV affects ventilation inhomogeneity during ARDS and the contribution of this effect to the associated improvement in mortality.

Ventilator mechanics are known to influence outcomes in severe ARDS. First, higher PEEP has been associated with improved mortality in patients with ARDS and $P_aO_2/F_IO_2$ ratio < 200 mm Hg.[37] Although we found no difference in PEEP before or after pronation based upon PPV strategy, we only measured mechanics up to 6 hours after the first pronation episode. Future work evaluating the change in PEEP over time may reveal an important interaction between PEEP and PPV strategy, as it is possible that patients who did not manifest improved $P_aO_2/F_IO_2$ ratio with proning may have undergone another PEEP titration to increase recruitment. Second, lower driving pressure is associated with reduced mortality and is hypothesized to be one pathophysiologic rationale by which PPV improves outcomes in ARDS.[16,38] We observed a slightly higher driving pressure in patients receiving intermittent PPV but found no change in driving pressure or compliance after PPV. Information on driving pressure was missing in 35.6% patients, limiting the ability to evaluate whether a change in driving pressure is associated with mortality or interacts with PPV strategy. Future work examining changes in respiratory mechanics will be necessary to assess whether changes in driving pressure are the mechanism underpinning improved mortality with prolonged PPV.

Our study has several strengths. We included all patients consecutively admitted to three Boston area community hospitals and academic centers thus minimizing selection bias. Chart review was performed by board certified or board eligible physicians. While our study has identified a benefit of PPV strategy on mortality in intubated COVID-19 patients, it is plausible that the effects of PPV strategy may extend to other causes of acute respiratory failure and merits further study. There are several limitations to our study. First, while this was a multicenter study, it was conducted within the same hospital system. Second, the study was retrospective in nature. Although we adjusted for potential treatment selection bias and confounders selected based on

prior known biology, unmeasured confounding is always a possibility in observational studies and thus these findings should be confirmed in future randomized controlled trials. Third, patients in the prolonged PPV group benefitted from a greater cumulative duration of PPV. Although this is probably because their clinical state was more severe, we cannot completely exclude that the effect on mortality lies in this difference. Finally, our patient population represents the first wave of the COVID-19 pandemic in Boston when there were no proven COVID-19 specific treatments. However, our overall 30-day mortality was 30.0%, comparable to pre-pandemic patients intubated for acute respiratory failure,[39] and patients received low tidal volume ventilation after intubation, suggesting that our results were not influenced by an overwhelmed hospital system. Current literature suggests that ICU mortality has not improved over successive COVID-19 waves,[40] highlighting the importance of identifying effective treatments in this vulnerable patient population.

**Interpretation**

Among intubated COVID-19 patients, prolonged PPV was associated with improved 30-day and 90-day survival, fewer pronation and supination episodes, and no increased risk of overall complications compared to intermittent PPV.

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**Take-Home Points**

Study Question: Does prolonged prone position ventilation (PPV) improve mortality in patients intubated for COVID-19?

Results: Prolonged PPV (>24 hours) is associated with improved 30-day and 90-day survival in patients intubated for COVID-19 compared to intermittent PPV (~16 hours prone with daily supination) without an increased risk of overall complications and reduces the total number of pronation and supination episodes.

Interpretation: Among intubated COVID-19 patients, prolonged PPV was associated with improved 30-day and 90-day survival, fewer pronation and supination episodes, and no increased risk of overall complications compared to intermittent PPV.

**References**

1. Kim L, Garg S, O'Halloran A, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality among Hospitalized Adults Identified through the U.S. Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis* 2020;ciaa1012.

2. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intens Care Med* 2020;46(12):2200–2211.

3. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019. *Crit Care Med* 2020;48(9):10.1097/CCM.0000000000004457.

4. Buffières W, Sarton B, Zadro C, et al. Clinical Course and Risk Factors for severe Disease and Death of Adult Critically Ill Inpatients with COVID-19 in Toulouse, France: A Retrospective Cohort Study. 2020;

5. Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. *Am J Resp Crit Care* 2020;0(ja):1560–1564.

6. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *New Engl J Medicine* 2021;384(8):NEJMoa2021436.

7. Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *New Engl J Medicine* 2021;384(16):NEJMoa2100433.

8. Group TWREA for C-19 T (REACT) W, Domingo P, Mur I, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19. *Jama* 2021;326(6):499–518.

9. Guérin C, Reignier J, Richard J-C, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *New Engl J Medicine* 2013;368(23):2159–2168.

10. Lucchini A, Bambi S, Mattiussi E, et al. Prone Position in Acute Respiratory Distress Syndrome Patients: A Retrospective Analysis of Complications. *Dimensions Critical Care Nurs* 2020;39(1):39–46.

11. Albert RK. Prone Ventilation for Patients with Mild or Moderate Acute Respiratory Distress Syndrome. *Ann Am Thorac Soc* 2019;17(1):24–29.

12. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care* 2019;9(1):69.

13. Fan E, Sorbo LD, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Resp Crit Care* 2017;195(9):1253–1263.

14. Munshi L, Sorbo LD, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S280–S288.

15. Jochmans S, Mazerand S, Chelly J, et al. Duration of prone position sessions: a prospective cohort study. *Ann Intensive Care* 2020;10(1):66.

16. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty Years of Research in ARDS.Respiratory Mechanics in Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine* 2017;196(7):822–833.

17. Douglas IS, Rosenthal CA, Swanson DD, et al. Safety and Outcomes of Prolonged Usual Care Prone Position Mechanical Ventilation to Treat Acute Coronavirus Disease 2019 Hypoxemic Respiratory Failure. *Crit Care Med* 2021;49(3):490–502.

18. Walter T, Zucman N, Mullaert J, et al. Extended prone positioning duration for COVID-19-related ARDS: benefits and detriments. *Crit Care* 2022;26(1):208.

19. Parker EM, Bittner EA, Berra L, Pino RM. Efficiency of Prolonged Prone Positioning for Mechanically Ventilated Patients Infected with COVID-19. *J Clin Medicine* 2021;10(13):2969.

20. The Acute Respiratory Distress Syndrome Network. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *New Engl J Medicine* 2000;342(18):1301–1308.

21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377–381.

22. Harris PA, Taylor R, Minor BL, et al. The REDCap Consortium: Building an International Community of Software Platform Partners. *J Biomed Inform* 2019;95:103208.

23. Guérin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. *Intens Care Med* 2020;46(12):2385–2396.

24. Ziehr DR, Alladina J, Wolf ME, et al. Respiratory Physiology of Prone Positioning With and Without Inhaled Nitric Oxide Across the Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Severity Spectrum. *Critical Care Explor* 2021;3(6):e0471.

25. Guérin C. Prone positioning acute respiratory distress syndrome patients. *Ann Transl Medicine* 2017;5(14):289–289.

26. Cornejo RA, Díaz JC, Tobar EA, et al. Effects of Prone Positioning on Lung Protection in Patients with Acute Respiratory Distress Syndrome. *Am J Resp Crit Care* 2013;188(4):440–448.

27. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intens Care Med* 2010;36(4):585–599.

28. Lee JM, Bae W, Lee YJ, Cho Y-J. The Efficacy and Safety of Prone Positional Ventilation in Acute Respiratory Distress Syndrome. *Crit Care Med* 2014;42(5):1252–1262.

29. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intens Care Med* 2014;40(3):332–341.

30. Langer T, Brioni M, Guzzardella A, et al. Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients. *Crit Care* 2021;25(1):128.

31. Scaramuzzo G, Gamberini L, Tonetti T, et al. Sustained oxygenation improvement after first prone positioning is associated with liberation from mechanical ventilation and mortality in critically ill COVID-19 patients: a cohort study. *Ann Intensive Care* 2021;11(1):63.

32. Camporota L, Sanderson B, Chiumello D, et al. Prone Position in COVID-19 and -COVID-19 Acute Respiratory Distress Syndrome: An International Multicenter Observational Comparative Study. *Crit Care Med* 2022;50(4):633–643.

33. Albert RK, Keniston A, Baboi L, Ayzac L, Guérin C, Investigators P. Prone Position–induced Improvement in Gas Exchange Does Not Predict Improved Survival in the Acute Respiratory Distress Syndrome. *Am J Resp Crit Care* 2014;189(4):494–496.

34. Grasso S, Mascia L, Turco MD, et al. Effects of Recruiting Maneuvers in Patients with Acute Respiratory Distress Syndrome Ventilated with Protective Ventilatory Strategy. *Anesthesiology* 2002;96(4):795–802.

35. Patel BV, Haar S, Handslip R, et al. Natural history, trajectory, and management of mechanically ventilated COVID-19 patients in the United Kingdom. *Intens Care Med* 2021;47(5):549–565.

36. Rossi S, Palumbo MM, Sverzellati N, et al. Mechanisms of oxygenation responses to proning and recruitment in COVID-19 pneumonia. *Intens Care Med* 2022;48(1):56–66.

37. Briel M, Meade M, Mercat A, et al. Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: Systematic Review and Meta-analysis. *Jama* 2010;303(9):865 873.

38. Amato MBP, Meade MO, Slutsky AS, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. *The New England Journal of Medicine* 2015;372(8):747–55.

39. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *Jama* 2016;315(8):788–800.

40. Carbonell R, Urgelés S, Rodríguez A, et al. Mortality comparison between the first and second/third waves among 3,795 critical COVID-19 patients with pneumonia admitted to the ICU: A multicentre retrospective cohort study. *Lancet Regional Heal - Europe* 2021;11:100243.

**Table 1. Demographics and characteristics of patients admitted to the ICU with COVID.**

| | Overall | Prolonged Prone | Intermittent Prone | *P* Value[e] |
|---|---|---|---|---|
| | (N = 267) | (N = 157) | (N = 110) | |
| **Demographics** | | | | |
| Age | 62 (51-72) | 63 (52-70) | 60 (51-74) | 0.991 |
| Male | 172 (64.4) | 103 (65.6) | 69 (62.7) | 0.724 |
| White | 148 (55.4) | 89 (56.7) | 59 (53.6) | 0.712 |
| Hispanic or Latino/a | 117 (46.8) | 70 (48.6) | 47 (44.3) | 0.589 |
| BMI, $kg/m^2$ | 29.8 (26.5-34.8) | 29.6 (26.7-34.5) | 30.1 (26.0-35.7) | 0.743 |
| CCI | 3 (1-5) | 3 (1-4) | 4 (2-5) | 0.145 |
| SAPS II[a] | 32 (25-41) | 33 (26-43) | 32 (24-39) | 0.299 |
| SOFA Score[a] | 6 (4-8) | 7 (4-8) | 6 (4-8) | 0.555 |
| $P_aO_2/F_IO_2$ on admission[b] | 157 (99-211) | 158 (105-211) | 149 (99-211) | 0.623 |
| Vasopressor Use within 24 hours of Admission[c] | 138 (52.5) | 88 (56.8) | 50 (46.3) | 0.122 |
| Days of COVID Symptoms[b] | 6 (4-9) | 7 (4-10) | 6 (3-7) | 0.004 |
| Covid Therapies | | | | |
| Remdesivir | 28 (10.5) | 16 (10.2) | 12 (10.9) | 1 |
| Anti-IL-6 | 51 (19.1) | 15 (9.6) | 36 (32.7) | <0.001 |
| Steroids | 68 (25.5) | 41 (26.1) | 27 (24.5) | 0.883 |
| Admission Hospital | | | | |
| MGH | 175 (65.5) | 126 (80.3) | 49 (44.5) | <0.001 |
| NWH | 27 (10.1) | 16 (10.2) | 11 (10.0) | |
| SH | 65 (24.3) | 15 (9.6) | 50 (45.5) | |
| | | | | |
| **Intubation Characteristics** | | | | |
| Time to Intubation, days | 1 (0-2) | 1 (0-2) | 1 (0-3) | 0.046 |
| Ventilator Mode | | | | |
| Volume Control | 254 (95.1) | 152 (96.8) | 102 (92.7) | 0.305 |
| Pressure Control | 10 (3.7) | 4 (2.5) | 6 (5.5) | |
| Pressure Support | 3 (1.1) | 1 (0.6) | 2 (1.8) | |
| Vt/kg IBW[d], mL/kg | 6.01 (5.84-6.27) | 6.00 (5.84-6.22) | 6.04 (5.79-6.35) | 0.397 |
| PEEP, $cmH_2O$ | 12 (10-14) | 12 (10-14) | 12 (10-14) | 0.276 |
| | | | | |
| **Additional ICU Therapies** | | | | |
| Paralysis | 91 (34.1) | 43 (27.4) | 48 (43.6) | 0.009 |
| Pulmonary Vasodilator | 85 (31.8) | 53 (33.8) | 32 (29.1) | 0.501 |
| ECMO | 14 (5.2) | 4 (2.5) | 10 (9.1) | 0.037 |
| Tracheostomy | 89 (33.3) | 61 (38.9) | 28 (25.5) | 0.031 |

Data missing for [a]3, [b]1, [c]4, [d]6 patients.
[e]2-tailed *P* value based on Pearson chi-square test for categorical data and Mann-Whitney U test for continuous data.

**Table 2. Characteristics and respiratory parameters of proning.**

| | Overall | Prolonged Prone | Intermittent Prone | *P* Value[j] |
|---|---|---|---|---|
| | (N = 267) | (N = 157) | (N = 110) | |
| **Characteristics of Proning** | | | | |
| # Pronation and Supination[k] Events | 2 (1-3) | 1 (1-2) | 3 (1-4) | <0.001 |
| Time to Proning, days | 2 (1-4) | 2 (1-4) | 2 (1-4) | 0.844 |
| Prone Duration (Total)[a,l], hours | 59.4 (34.3-102.5) | 67.8 (45.5-120.0) | 47.7 (19.4-79.9) | <0.001 |
| Prone Duration (first Session)[m], hours | 25 (17-46) | 40 (27-55) | 17 (14-20) | <0.001 |
| | | | | |
| **Respiratory Parameters[n]** | | | | |
| $P_aO_2/F_IO_2$[a] | | | | |
| Before Proning | 132 (103-162) | 138 (106-164) | 126 (96-159) | 0.298 |
| After Proning[o] | 212 (161-280) | 220 (162-278) | 204 (158-283) | 0.471 |
| Change With Proning | 79 (28-136) | 79 (28-139) | 80 (28-134) | 0.773 |
| PEEP[a], $cmH_2O$ | | | | |
| Before Proning | 12 (10-14) | 12 (10-14) | 12 (10-14) | 0.405 |
| After Proning[n] | 12 (11-15) | 13 (12-14) | 12 (11-15) | 0.849 |
| Driving Pressure, $cmH_2O$ | | | | |
| Before Proning[b] | 11.0 (9.5-13.0) | 11.0 (9.0-13.0) | 12.0 (10.0-14.0) | 0.088 |
| After Proning[c,n] | 11.0 (9.0-13.0) | 11.0 (9.0-13.0) | 11.0 (10.0-14.0) | 0.171 |
| Change With Proning[d] | 0.0 (-1.0-1.0) | 0.0 (-2.0-1.0) | 0.0 (-1.0-1.0) | 0.397 |
| Compliance, $mL/cmH_2O$ | | | | |
| Before Proning[e] | 32.3 (25.4-40.0) | 33.3 (26.2-41.7) | 30.8 (25.0-37.3) | 0.235 |
| After Proning[f,n] | 33.3 (26.1-40.0) | 33.0 (26.0-40.0) | 33.8 (26.9-39.4) | 0.678 |
| Change With Proning[g] | 0 (-3.9-4.0) | 0 (-4.1-4.9) | 0 (-2.7-3.1) | 0.561 |
| Ventilatory Ratio | | | | |
| Before Proning[d] | 1.53 (1.26-1.87) | 1.47 (1.26-1.82) | 1.59 (1.34-2.03) | 0.103 |
| After Proning[h,n] | 1.58 (1.32-1.93) | 1.55 (1.30-1.83) | 1.63 (1.36-2.06) | 0.170 |
| Change With Proning[j] | 0.00 (-0.12-0.12) | 0.00 (-0.11-0.09) | 0.00 (-0.12-0.19) | 0.574 |

Data missing for [a]2, [b]68, [c]59, [d]95, [e]72, [f]63, [g]99, 95, [h]25, [i]106 patients.
[j]2-tailed *P* value based on Pearson chi-square test for categorical data and Mann-Whitney U test for continuous data.
[k]One event defined as a pair of pronation and then supination.
[l]Calculated as the time spent in the prone position excluding any time spent supine.
[m]Calculated for the first discrete pronation/supination episode.
[n]Measured and calculated at the time of the first PPV session.
[o]Collected within 6 hours of pronation.

**Table 3. Complications in Prone Position.**

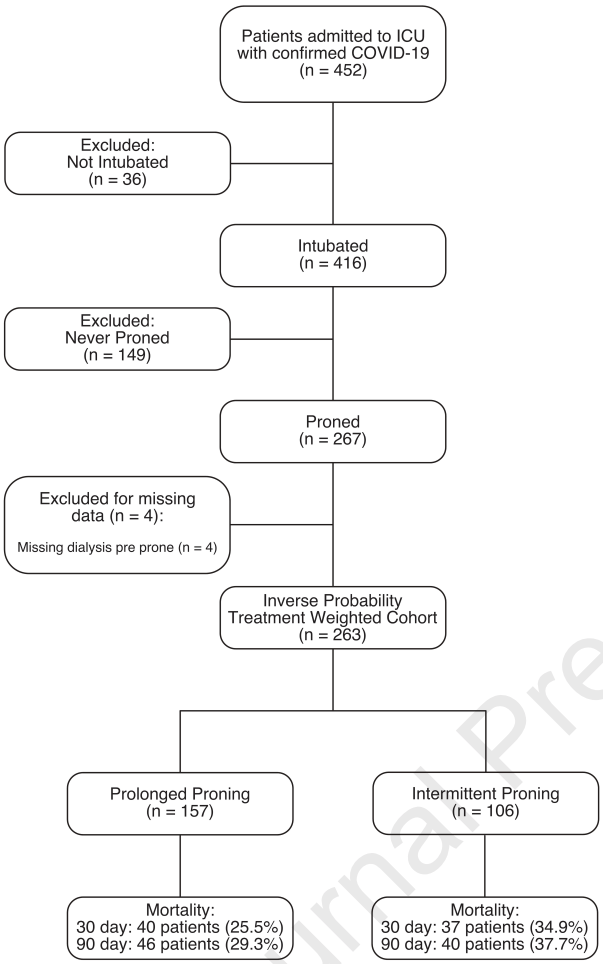
| | Overall | Prolonged Prone | Intermittent Prone | P-Value[a] |
|---|---|---|---|---|
| | (N = 267) | (N = 157) | (N = 110) | |
| Any Complication of Proning | 129 (48.3) | 73 (46.5) | 56 (50.9) | 0.558 |
| Early Cessation of Proning | 30 (23.3) | 13 (17.8) | 17 (30.4) | 0.144 |
| Arrhythmias | 6 (2.2) | 5 (3.2) | 1 (0.9) | 0.415 |
| Hypotension | 10 (3.7) | 2 (1.3) | 8 (7.3) | 0.027 |
| Loss of Vascular Access | 5 (1.9) | 1 (0.6) | 4 (3.6) | 0.187 |
| Chest Tube Displacement | 1 (0.4) | 0 (0.0) | 1 (0.9) | 0.858 |
| OG/NG Tube Displacement | 2 (0.7) | 0 (0.0) | 2 (1.8) | 0.330 |
| Accidental Extubation | 2 (0.7) | 2 (1.3) | 0 (0.0) | 0.640 |
| Endotracheal Tube Displacement | 9 (3.4) | 6 (3.8) | 3 (2.7) | 0.886 |
| Worsening Ventilator Mechanics | 8 (3.0) | 5 (3.2) | 3 (2.7) | 1 |
| Facial Edema | 31 (11.6) | 24 (15.3) | 7 (6.4) | 0.041 |
| Pressure Injuries | 78 (29.2) | 48 (30.6) | 30 (27.3) | 0.655 |
| Conjunctival Hemorrhage | 1 (0.4) | 1 (0.6) | 0 (0.0) | 1 |
| Vomiting | 6 (2.2) | 1 (0.6) | 5 (4.5) | 0.089 |
| Oropharyngeal Injury | 7 (2.6) | 4 (2.5) | 3 (2.7) | 1 |
| Rhabdomyolysis | 2 (0.7) | 2 (1.3) | 0 (0.0) | 0.640 |

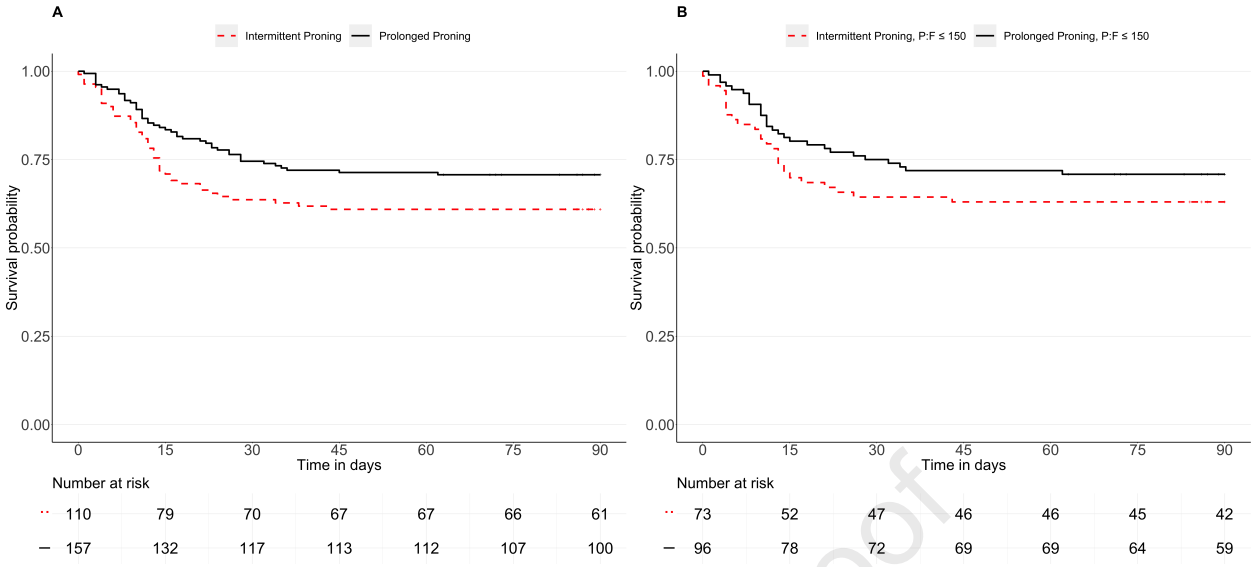
[a]2-tailed *P* value based on Pearson chi-square test.

**Figure Legends**

**Figure 1. Study flow diagram.**

**Figure 2. Kaplan-Meier Plot of the Probability of Survival from Time of Proning to 90 days.** (A) in the entire cohort, and (B) in patients with $P_aO_2/F_IO_2 \leq 150$ at time of pronation.





**Supplemental Material**

# Prolonged prone position ventilation is associated with reduced mortality in intubated COVID-19 patients

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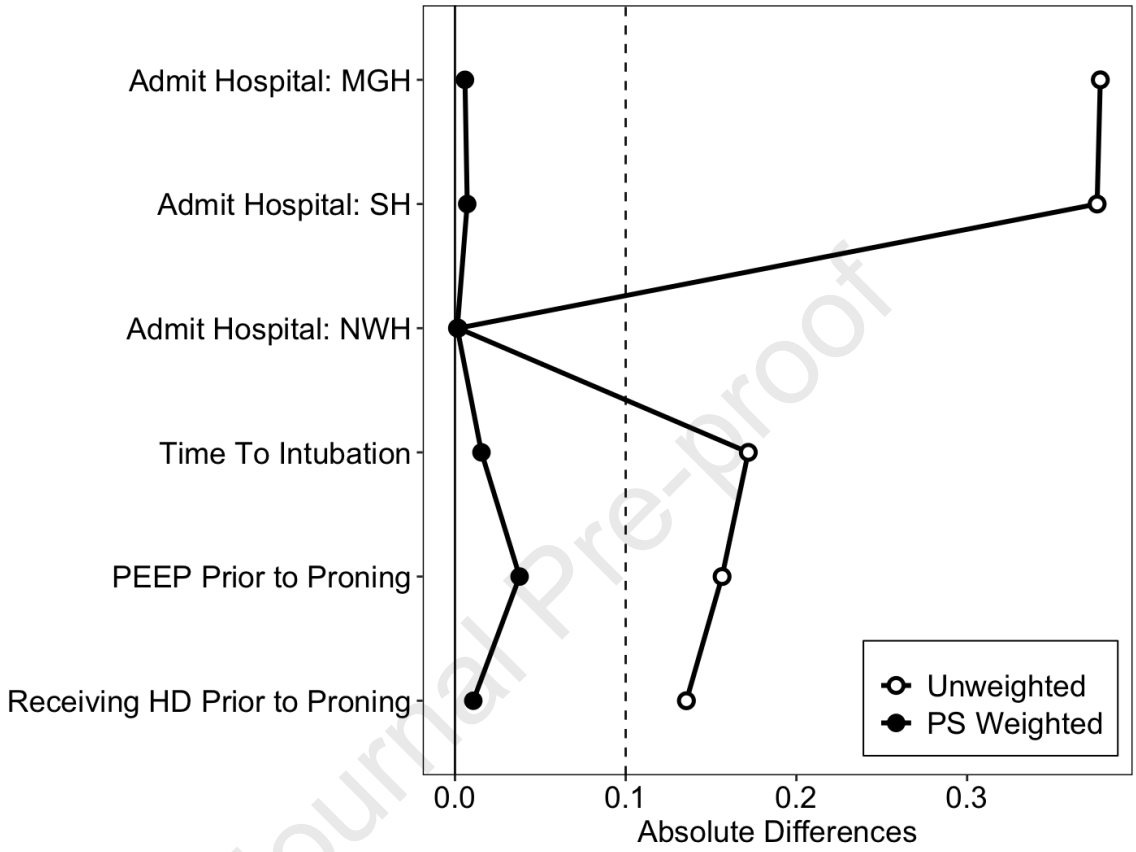
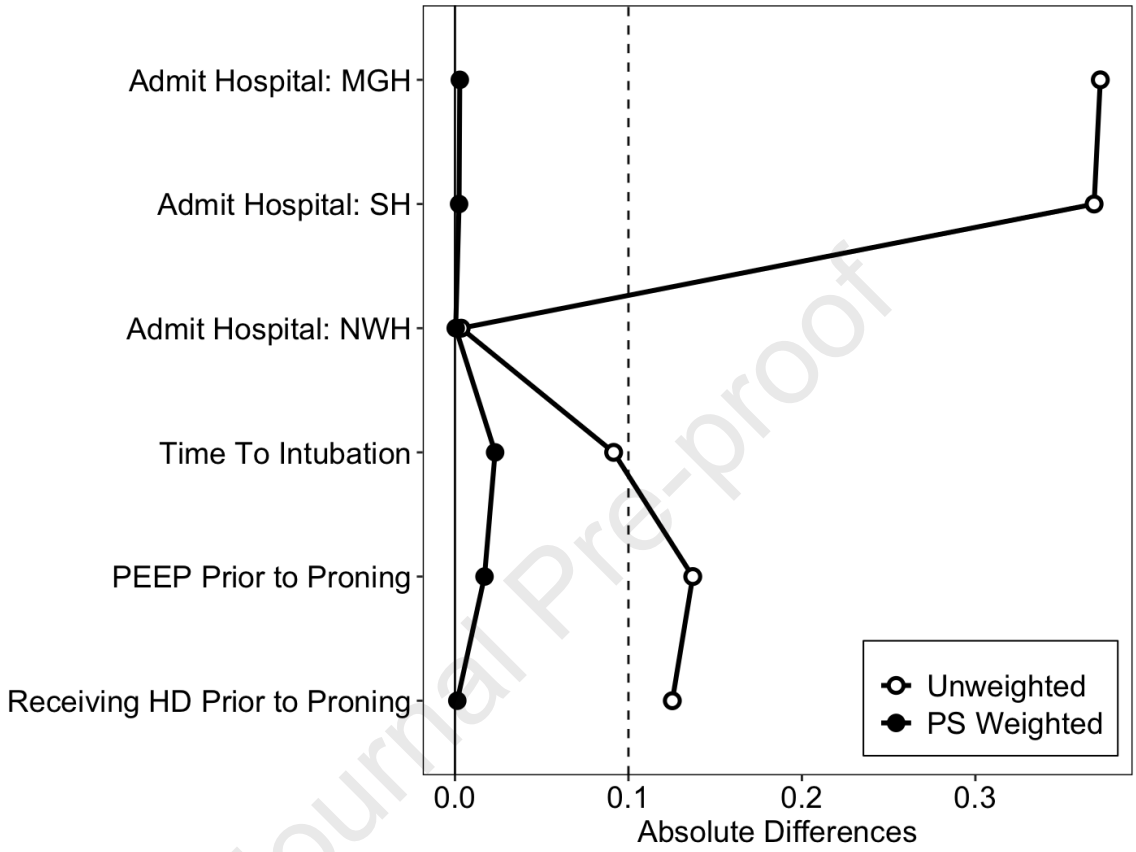
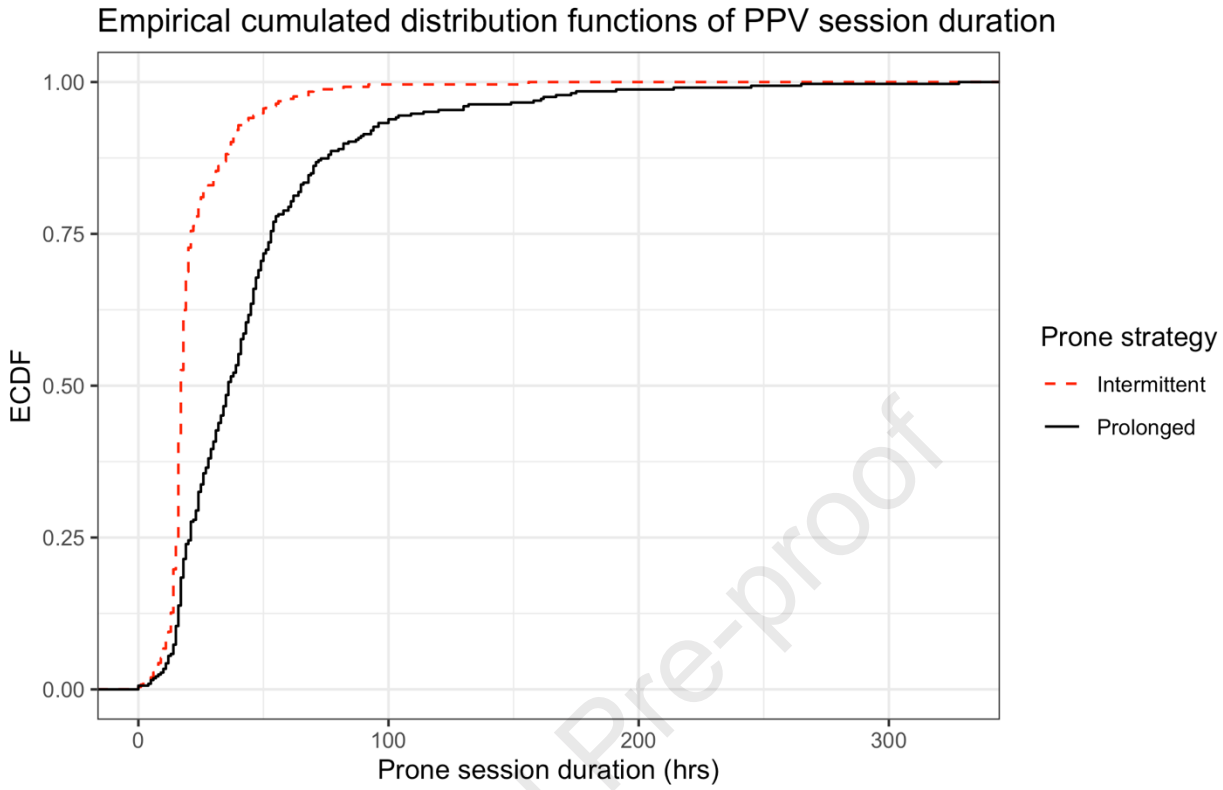
**e-Figure 1. Balance plot of propensity score variables in unweighted and after inverse probability treatment weighting in the overall cohort.** Absolute difference is given as standardized mean difference for continuous or distance variables and raw proportional differences for binary variables.



**e-Figure 2. Balance plot of propensity score variables in unweighted and after inverse probability treatment weighting in patients with $P_aO_2/F_IO_2 \leq 150$ prior to pronation.**
Absolute difference is given as standardized mean difference for continuous or distance variables and raw proportional differences for binary variables.



**e-Figure 3. Empirical cumulative distribution functions of PPV session duration.**



**e-Table 1. Demographics and characteristics of patients admitted to the ICU with COVID with $P_aO_2/F_IO_2 \leq 150$ at time of pronation.**

| | Overall (n = 169) | Prolonged Prone (n = 96) | Intermittent Prone (n = 73) | *P* Value[d] |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age | 62 (51-71) | 63 (51-69) | 60 (52-73) | 0.947 |
| Male | 104 (61.5) | 61 (63.5) | 43 (58.9) | 0.65 |
| White | 95 (56.2) | 55 (57.3) | 40 (54.8) | 0.867 |
| Hispanic or Latino/a | 75 (44.4) | 47 (52.2) | 28 (39.4) | 0.145 |
| BMI, $kg/m^2$ | 30.6 (26.8-35.7) | 30.1 (27.4-34.8) | 31.3 (26.6-37.1) | 0.669 |
| CCI | 3 (2-5) | 3 (1-5) | 4 (2-5) | 0.439 |
| SAPS II[a] | 32 (22-42) | 33 (22-44) | 32 (24-38) | 0.641 |
| SOFA Score[a] | 6 (4-8) | 6 (3-8) | 6 (4-7) | 0.890 |
| $P_aO_2/F_IO_2$[b] | 149 (93-211) | 151 (82-204) | 143 (94-220) | 0.985 |
| Vasopressor Use[b] | 78 (46.4) | 49 (51.0) | 29 (40.3) | 0.219 |
| Days of COVID Symptoms[b] | 6 (3-9) | 7 (4-11) | 6 (3-7) | 0.031 |
| Covid Therapies | | | | |
| Remdesivir | 21 (12.4) | 12 (12.5) | 9 (12.3) | 1 |
| Anti-IL-6 | 42 (24.9) | 14 (14.6) | 28 (38.4) | 0.001 |
| Steroids | 43 (25.4) | 25 (26.0) | 18 (24.7) | 0.979 |
| **Intubation Characteristics** | | | | |
| Time to Intubation, days | 1 (0-3) | 1 (0-3) | 1 (0-3) | 0.306 |
| Ventilator Mode | | | | 0.905 |
| Volume Control | 159 (94.1) | 91 (94.8) | 68 (93.2) | |
| Pressure Control | 8 (4.7) | 4 (4.2) | 4 (5.5) | |
| Pressure Support | 2 (1.2) | 1 (1.0) | 1 (1.4) | |
| Vt/kg IBW[c], mL/kg | 6.01 (5.82-6.27) | 6.00 (5.84-6.18) | 6.05 (5.73-6.35) | 0.605 |
| **Additional ICU Therapies** | | | | |
| Paralysis | 73 (43.2) | 36 (37.5) | 37 (50.7) | 0.119 |
| Pulmonary Vasodilator | 63 (37.3) | 37 (38.5) | 26 (35.6) | 0.819 |
| ECMO | 12 (7.1) | 3 (3.1) | 9 (12.3) | 0.045 |
| Tracheostomy | 51 (30.2) | 33 (34.4) | 18 (24.7) | 0.232 |

Data missing for [a]2, [b]1, [c]4 patients.

Continuous variables are presented as median (IQR), categorical variables are presented as No. (%).

[d]2-tailed *P* value based on Pearson chi-square test for categorical data and Mann-Whitney U test for continuous data.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CCI, Charlson Comorbidity Index; $F_IO_2$, fraction inspired oxygen; IBW, ideal body weight; ICU, intensive care unit; LOS, length of stay; $P_aO_2$, arterial partial pressure of oxygen; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; Vt, tidal volume.

**e-Table 2. Demographics and admission characteristics of patients excluded from compared to patients included in the propensity score analysis.**

| | Overall (n = 267) | Excluded (n = 4) | Included (n = 263) | *P* Value[d] |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age | 62 (51-72) | 57 (51-63) | 62 (51-72) | 0.471 |
| Male | 172 (64.4) | 1 (25.0) | 171 (65.0) | 0.257 |
| White | 148 (55.4) | 2 (50.0) | 146 (55.5) | 1 |
| Hispanic or Latino/a | 117 (43.8) | 1 (25.0) | 116 (44.3) | 0.707 |
| BMI, $kg/m^2$ | 29.8 (26.5-34.8) | 27.0 (25.6-29.6) | 29.9 (26.6-34.9) | 0.334 |
| CCI | 3 (1-5) | 2 (1-3) | 3 (2-5) | 0.337 |
| SAPS II[a] | 32 (25-41) | 21 (19-54) | 32 (25-41) | 0.616 |
| SOFA Score[a] | 6 (4-8) | 2 (2-10) | 6 (4-8) | 0.488 |
| $P_aO_2/F_IO_2$[b] | 157 (99-211) | 168 (107-189) | 156 (100-211) | 0.766 |
| Vasopressor Use[c], | 138 (52.5) | 1 (25.0) | 137 (52.9) | 0.546 |
| Days of COVID Symptoms[b] | 6 (4-9) | 12 (9-13) | 6 (4-9) | 0.169 |
| Covid Therapies | | | | |
| Remdesivir | 28 (10.5) | 1 (25.0) | 27 (10.3) | 0.895 |
| Anti-IL-6 | 51 (19.1) | 1 (25.0) | 50 (19.1) | 1 |
| Steroids | 68 (25.5) | 0 (0.0) | 68 (25.9) | 0.549 |
| **Additional ICU Therapies** | | | | |
| Paralysis | 91 (34.1) | 3 (75.0) | 88 (33.5) | 0.227 |
| Pulmonary Vasodilator | 85 (31.8) | 2 (50.0) | 83 (31.6) | 0.806 |
| Tracheostomy | 89 (33.3) | 1 (25.0) | 88 (33.5) | 1 |

Data missing for [a]3, [b]1, [c]4 patients.

Continuous variables are presented as median (IQR), categorical variables are presented as No. (%).

[d]2-tailed *P* value based on Pearson chi-square test for categorical data and Mann-Whitney U test for continuous data.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CCI, Charlson Comorbidity Index; $F_IO_2$, fraction inspired oxygen; IBW, ideal body weight; $P_aO_2$, arterial partial pressure of oxygen; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; Vt, tidal volume.

**e-Table 3. Propensity score matching variables after inverse probability treatment weighting in the overall cohort.** Adjusted difference is given as standardized mean difference for continuous or distance variables and raw proportional differences for binary variables.

| Balance Measures | Type | Unadjusted Difference | Adjusted Difference |
|---|---|---|---|
| Propensity Score | Distance | 0.9711 | -0.0184 |
| Admission Hospital: Massachusetts General Hospital | Binary | 0.3780 | -0.0058 |
| Admission Hospital: Salem Hospital | Binary | -0.3762 | 0.0072 |
| Admission Hospital: Newton-Wellesley Hospital | Binary | -0.0019 | -0.0013 |
| Time to Intubation | Continuous | -0.1718 | -0.0155 |
| PEEP At Time of Proning | Continuous | -0.1565 | 0.0379 |
| On Dialysis at Time of Proning | Binary | 0.1356 | -0.0107 |

Abbreviations: NIPPV, non-invasive positive pressure ventilation; PEEP, positive end-expiratory pressure.

**e-Table 4. Propensity score matching variables after inverse probability treatment weighting in patients with $P_aO_2/F_IO_2 \leq 150$ prior to pronation.** Adjusted difference is given as standardized mean difference for continuous or distance variables and raw proportional differences for binary variables.

| Balance Measures | Type | Unadjusted Difference | Adjusted Difference |
|---|---|---|---|
| Propensity Score | Distance | 0.9143 | -0.0049 |
| Admission Hospital: Massachusetts General Hospital | Binary | 0.3720 | -0.0028 |
| Admission Hospital: Salem Hospital | Binary | -0.3685 | 0.0024 |
| Admission Hospital: Newton-Wellesley Hospital | Binary | -0.0036 | 0.0004 |
| Time to Intubation | Continuous | -0.0915 | -0.0231 |
| PEEP At Time of Proning | Continuous | -0.1371 | 0.0170 |
| On Dialysis at Time of Proning | Binary | 0.1253 | -0.0013 |

Abbreviations: NIPPV, non-invasive positive pressure ventilation; PEEP, positive end-expiratory pressure.

**e-Table 5. Sensitivity analysis of outcomes.** Outcome analysis was performed in the overall cohort and in patients with $P_aO_2/F_IO_2 \leq 150$ prior to pronation. Propensity scores were re-calculated for each group using a multivariable logistic regression model including admission hospital, time-to-intubation in days, positive end-expiratory pressure at time of intubation, need for dialysis at time of proning, $P_aO_2/F_IO_2$ prior to proning, age, sex, CCI, history of type 2 diabetes, history of chronic kidney disease, history of immunosuppression, SOFA score on admission, BMI, treatment with anti-IL-6 therapy, treatment with steroids, treatment with remdesivir, and treatment with paralysis. Inverse probability treatment weights were re-calculated and a univariable Weibull survival model was fitted.

| | **HR** | **95% CI** | ***P* value** |
|---|---|---|---|
| **Overall Cohort** | | | |
| 30-day mortality | 0.477 | 0.346-0.657 | < 0.001 |
| 90-day mortality | 0.617 | 0.460-0.826 | 0.001 |
| | | | |
| **$P_aO_2/F_IO_2 \leq 150$ at Proning** | | | |
| 30-day mortality | 0.469 | 0.311-0.709 | < 0.001 |
| 90-day mortality | 0.628 | 0.432-0.911 | 0.02 |

**e-Table 6. Length of stay and ventilator-free days in proned patients with COVID-19 broken down by survivors and non-survivors.** Non-survivors calculated at day 30 after pronation.

| | Overall (n = 267) | Prolonged Prone (n = 157) | | Intermittent Prone (n = 110) | | *P* Value[b] |
|---|---|---|---|---|---|---|
| | | Survivors (n = 117) | Non-Survivors (n = 40) | Survivors (n = 70) | Non-Survivors (n = 40) | |
| Hospital LOS[a] | 28 (18-40) | 35 (25-43) | 15 (11-22) | 35 (23-48) | 16 (11-18) | <0.001 |
| ICU LOS[a] | 20 (14-28) | 23 (17-34) | 14 (10-22) | 23 (17-38) | 13 (8-17) | <0.001 |
| Ventilator-free days at 28 days | 7 (0-12) | 10 (7-14) | 0 (0-0) | 9 (6-14) | 0 (0-0) | <0.001 |

Data missing for [a]1 patient.
Data presented as median (IQR).
[b]2-tailed *P* value based on Mann-Whitney U test.
Abbreviations: ICU, intensive care unit; LOS, length of stay.

**e-Table 7. Ventilator parameters before and after pronation.**

| | Overall (n = 267) | Prolonged Prone (n = 157) | Intermittent Prone (n = 110) | *P* Value[e] |
|---|---|---|---|---|
| **Prior to Pronation** | | | | |
| Ventilator Mode[a] | | | | 0.126 |
| Volume Control | 252 (95.1) | 152 (96.8) | 100 (92.6) | |
| Pressure Control | 12 (4.5) | 4 (2.5) | 8 (7.4) | |
| Other | 1 (0.4) | 1 (0.6) | 0 (0.0) | |
| Vt/kg IBW[b], mL/kg | 5.99 (5.72-6.21) | 5.97 (5.65-6.14) | 6.02 (5.86-6.27) | 0.023 |
| Plateau Pressure[c], $cmH_2O$ | 24 (21-26) | 23 (21-26) | 25 (22-27) | 0.026 |
| **After Pronation** | | | | |
| Ventilator Mode[a] | | | | 0.212 |
| Volume Control | 251 (94.7) | 151 (96.2) | 100 (92.6) | |
| Pressure Control | 13 (4.9) | 5 (3.2) | 8 (7.4) | |
| Other | 1 (0.4) | 1 (0.6) | 0 (0.0) | |
| Vt/kg IBW[†], mL/kg | 5.99 (5.72-6.18) | 5.98 (5.68-6.13) | 6.01 (5.90-6.27) | 0.042 |
| Plateau Pressure[d], $cmH_2O$ | 24 (22-27) | 24 (22-26) | 24 (22-27) | 0.314 |

Data missing for [a]2, [b]7, [c]80, [d]72 patients.
Continuous variables are presented as median (IQR), categorical variables are presented as No. (%).
[e]2-tailed *P* value based on Pearson chi-square test for categorical data and Mann-Whitney U test for continuous data.
Abbreviations: IBW, ideal body weight; Vt, tidal volume.

**e-Table 8. Analysis of associations with proning complications.** Multivariable conditional logistic regression was used to estimate the adjusted odds ratio (aOR).

| **Subgroup** | **aOR** | **95% CI** | ***P* Value** |
|---|---|---|---|
| Prone duration, hours | 1.009 | 1.004 – 1.014 | < 0.001 |
| Prone strategy[a] | 0.66 | 0.39 – 1.106 | 0.116 |
| Age | 0.99 | 0.97 – 1.02 | 0.610 |
| Sex | 0.98 | 0.57 – 1.68 | 0.931 |
| BMI | 1.007 | 0.97 – 1.04 | 0.713 |
| CCI | 1.08 | 0.92 – 1.26 | 0.345 |
| SOFA Score | 0.97 | 0.88 – 1.06 | 0.463 |

[a]Prone strategy defined as prolonged (> 24 hours) as compared to intermittent (daily supination)
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; SOFA, sequential organ failure assessment.