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# Awake Prone Positioning in COVID-19 Hypoxemic Respiratory Failure: Exploratory Findings in a Single-center Retrospective Cohort Study

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## ABSTRACT

**Background:** Awake prone positioning has been widely used in patients with COVID-19 respiratory failure to avoid intubation despite limited evidence. Our objective was to evaluate if prone positioning is associated with a reduced intubation rate when compared to usual care.

**Methods:** This was a retrospective cohort study in the emergency department of a large quaternary hospital in Sao Paulo. We retrieved data from all admitted patients in need of oxygen supplementation (>3 L/min) and tachypnea (>24 ipm) from March 1 to April 30, 2020, excluding those who had any contraindication to the prone position or who had an immediate need for intubation. The primary endpoint was endotracheal intubation up to 15 days. Secondary outcomes included a 6-point clinical outcome ordinal scale, mechanical ventilation–free days, admission to the intensive care unit, and need of hemodialysis and of vasoactive drugs, all assessed at or up to 15 days. We analyzed unadjusted and adjusted effect estimates with Cox proportional hazards models, logistic regression, quantile regression, and sensitivity analyses using propensity score models.

**Results:** Of 925 suspected COVID-19 patients admitted off mechanical ventilation, 166 patients fulfilled inclusion and exclusion criteria: 57 were exposed to prone positioning and 109 to usual care. In the intervention group, 33 (58%) were intubated versus 53 (49%) in the control group. We observed no difference in intubation rates in the univariate analysis (hazard ratio = 1.21, 95% confidence interval [CI] = 0.78 to 1.88, p = 0.39) nor in the adjusted analysis (hazard ratio = 0.90, 95% CI = 0.55 to 1.49, p = 0.69). Results were robust to the sensitivity analyses.

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Secondary outcomes did not differ between groups.

**Conclusions:** Awake prone positioning was not associated with lower intubation rates. Caution is necessary before widespread adoption of this technique, pending results of clinical trials.

The COVID-19 pandemic presented a unique challenge for the health care systems.[1–4] One of the main problems posed by the pandemic is the shortage of resources. Although a small fraction of all infected patients will become critically ill, the sudden amount of critically ill patients overwhelmed whole health systems. Besides human resources, the scarcest resources are intensive care unit (ICU) beds and mechanical ventilators. It is essential, therefore, that we accurately recognize patients who truly need an ICU bed or mechanical ventilation and develop strategies to reduce the number of intubations without adding risks and worsening outcomes.[5]

One such strategy is awake prone positioning.[6] Prone positioning is a well-established strategy for mechanically ventilated patients with moderate to severe ($PaO_2$:$FiO_2$ ratio < 150 mmHg with PEEP ≥ 5 $cmH_2O$) acute respiratory distress syndrome (ARDS),[7–10] probably due to improved gas exchange, attenuated mechanical lung injury,[11] and improved cardiac output.[12] Reports on awake prone positioning for acute hypoxemic respiratory failure had been scarce until the pandemic,[13–15] but its use gained traction in recent reports.[6,16–20] Some of these demonstrated an improvement in oxygenation in patients under noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) and others claimed a lower intubation rate.[15–18] However, they did not compare awake prone positioning with usual care neither have they evaluated patient-centered clinical outcomes.

Therefore, we designed this retrospective cohort study to compare patients receiving oxygen through nasal cannulas, Venturi masks, or nonrebreathing masks who were exposed to prone positioning while awake to those who were not exposed. We assessed whether awake prone positioning would reduce the requirement for invasive mechanical ventilation in the following 15 days. We also evaluated other clinical outcomes and physiologic improvement with the maneuver.

## METHODS

### Study Design and Setting

We designed a retrospective cohort study to compare patients exposed to prone positioning with those who did not undergo prone positioning. Given the observational nature of the study, we tried to emulate a clinical trial with inclusion and exclusion criteria and we used the recommendations for causal inference from the editors of pulmonary, critical care and sleep journals.[21] The study complies with the STROBE guidance[22] and it was approved by the National Brazilian Research ethics committee (CONEP), which waived informed consent for this retrospective analysis (CAAE 30629620.1.0000.0008).

We conducted this study at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a quaternary, acute care hospital in São Paulo, where one of its institutes (Central Institute) became a referral center for severe and critical COVID-19 in the city of Sao Paulo. There were 400 ward beds and 300 ICU beds, and the emergency department (ED) was exclusively dedicated for the treatment of patients with confirmed or suspected SARS-CoV-2 pneumonia at the time of this study.

### Selection of Participants

The target study population comprised patients with acute hypoxemic respiratory failure who required more than low-flow oxygen to achieve oxygenation targets and with some degree of increased work of breathing (assessed through respiratory rate), for whom the intervention (described below) would probably lead to higher beneficial effects.

The inclusion criteria were as follows: 1) age > 18 years old, 2) confirmed or suspected COVID-19, 3) spontaneous breathing (i.e., not on invasive mechanical ventilation), 4) respiratory rate ≥ 24 ipm, and 5) using supplemental oxygen with a flow rate ≥ 3 L/min. The patients had to have a positive RT-PCR for SARS-CoV-2 from analysis of nasopharyngeal, oropharyngeal swab, or tracheal secretion specimens and/or suggestive clinical findings and typical lung CT scan.

Exclusion criteria were as follows: 1) patients intubated in other hospitals and referred to the HCFMUSP or patients intubated within 1 hour of arrival to the ED; 2) hemodynamic instability (defined as mean arterial pressure [MAP] < 65mm Hg and use of vasopressors to achieve MAP > 65 mm Hg); 3) recent abdominal surgery; 4) acute hypercapnic

respiratory failure; 5) unstable fractures; 6) pregnancy; or 7) other contraindication to the prone position, as judged by the treating physician and documented in the medical record. Patients with a discussion of limitation of organ support (do-not-intubate order) were also excluded. Patients who declined to undergo awake prone positioning were not excluded from the cohort and were included in the control group.

## Interventions

The primary intervention of this study was awake prone positioning. In the beginning of the preparedness for receiving patients with COVID-19–related respiratory failure, we observed that awake prone positioning was a possible strategy to avoid intubation in patients without contraindications (as described above) or who didn't have an immediate need for intubation. Therefore, some of the attending physicians, which included some of the authors of this report, used this strategy in the ED. Since there was no specific recommendation regarding awake prone positioning from the hospital protocol development group, other physicians did not use this strategy in their usual care. Awake prone positioning was deployed considering the following:

1. Patients with an immediate need for intubation were never considered for the intervention (see exclusion criteria above);
2. Intervention itself: patients were asked to stay in the prone position for at least 4 hours in their first session, when they were closely observed by clinicians, nurses, and respiratory therapists; for those who demonstrated some improvement in their oxygenation, respiratory rate, both, or their comfort, patients were stimulated twice daily to maintain awake prone positioning sessions;
3. Patients who required invasive mechanical ventilation at any time point were intubated regardless of their study group according to the same recommendations.

The recommendations to consider invasive mechanical ventilation were the following: 1) evidence of increased respiratory effort and work of breathing (assessed not only through increased respiratory rate, but from the patient subjective reporting of dyspnea and objective signs of high inspiratory efforts such as use of accessory muscles); 2) requirement for high-flow oxygen on a nonrebreather mask with progressive worsening; and 3) decreased level of consciousness, hemodynamic instability, cardiac arrest, or other indication for intubation unrelated to respiratory failure itself. The decision to intubate was always made by an attending emergency medicine physician and did not involve arbitrary cutoffs of oxygen requirements or respiratory rate.

Patients who were actively repositioning themselves with no medical advice were not included in the intervention group. Lateral positioning was not considered as awake prone positioning as well. Time spent on prone position was registered on their charts. In both groups, oxygen flow rate was titrated to achieve a $SpO_2$ target of 90% to 95%.

## Data Collection and Measurements

We reviewed the medical records of all patients admitted to our ED during the study period (March 1 to April 30, 2020). All data were extracted manually from the electronic medical records. The data obtained included patients' demographics, vital signs, laboratory results, radiologic examinations, antecedent characteristics and current diagnosis, clinical notes, discharge information, ventilator use data, oxygen use device and flow rate, and whether the patient was submitted to awake prone positioning or not. For the exploratory physiologic data of effect of prone positioning on oxygenation, vital signs (respiratory rate, peripheral oxygen saturation, heart rate, systolic arterial pressure), and oxygen flow rate before and after proning (between 30 minutes and 4 hours, while in prone position) were extracted from charts, when available. We followed most recommended steps to assure the quality of data abstraction from medical records in retrospective studies:[23] 1) all data collectors were trained on definition of variables, 2) we developed standardized abstraction forms with variables definition, 3) case selection was done by the two first authors independently (EMHP and FSV), 4) a meeting with all collectors was done prior to any data collection, and 5) data collection was monitored and reviewed by the first authors.

## Outcomes

The primary outcome was orotracheal intubation up to 15 days after inclusion. The inclusion date was determined by the first prone positioning session (in the awake prone positioning group) or after fulfillment of inclusion criteria in the first 48 hours of hospitalization in the ED, in the case of the control group. Secondary outcomes included days alive and free of mechanical ventilation at 15 days; a 6-point ordinal

scale at 15 days (1 = alive and discharged; 2 = hospitalized, no oxygen use; 3 = hospitalized, using low-flow oxygen; 4 = hospitalized, using NIV or HFNC; 5 = hospitalized, using invasive mechanical ventilation IMV; and 6 = dead); need for dialysis up to 15 days; need for vasoactive drugs up to 15 days; and ICU admission up to 15 days. Physiologic improvement (respiratory rate, $SpO_2$, $SpO_2/FiO_2$ ratio, ROX index,[24] heart rate, systolic arterial pressure, and shock index) was also evaluated before and after proning (immediately before and 30 minutes to 4 hours after). To calculate $SpO_2/FiO_2$ ratio, we estimated $FiO_2$ as previously described: for patients using nasal cannula, 0.21 for room air + 0.03 per liter; for nonrebreather mask, 0.21 for room air + 0.04 per liter; and for Venturi masks, as displayed in the valve.[25] We also evaluated adverse events, prone positioning session duration, and response to prone positioning (defined as a 10% increase in $SpO_2/FiO_2$ ratio or 10% decrease in respiratory rate).

## Data Analysis

The sample size estimated for this study was around 55 patients in the "intervention" group with an event rate (intubation through 15 days) of 50% and at least the same number of patients in the control group with an absolute increase in risk of intubation of 20%. The event rate was estimated from the authors' acquired experience during the pandemic course. This would allow the inclusion of four to six covariates in a regression model to account for confounding by indication without overfitting the data.

Continuous data were described as means and standard deviations (SDs) when distribution is normal and medians and 25th/75th percentiles for nonnormally distributed data. Categorical variables are described as number of events and proportions (%). T-tests were used to compare variables with normal distribution; Wilcoxon rank-sum tests, for comparisons of nonnormally distributed continuous variables; and Fisher exact tests, for comparisons of categorical variables. For the primary outcome analysis, we present a Kaplan-Meier survival plot and a log-rank test for the univariate analysis, along with an unadjusted Cox model. We then fit a multivariable Cox model adjusting for age, $SpO_2/FiO_2$ ratio, respiratory rate, obesity status according to our causal assumptions (variables related with the decision to undergo awake prone positioning or possibly related to the outcome, regardless of statistical criteria) and the recently described 4C score.[26] The 4C score was recently derived and validated and it includes the following variables: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation on room air, Glasgow coma scale, serum urea, and C-reactive protein levels. It is included in this analysis because of the desired property of a compound score that allows statistical adjustment with fewer degrees of freedom. We evaluated the proportional hazards assumption with Schöenfeld residuals and log–log plots. As sensitivity analyses to this primary analysis model, we developed a propensity score (including age, $SpO_2/FiO_2$ ratio, respiratory rate, obesity status, and the 4C score), with four different analyses: 1) propensity score adjustment (in the Cox model), 2) propensity score matching analysis, 3) inverse probability of treatment weighting (IPTW) analysis, and 4) doubly robust estimation with IPTW for the treatment choice model and the same covariates for the outcome model. For the propensity score estimation, we evaluated the positivity assumption with overlap histograms and the balance achieved with standardized differences (Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14160/full). Effect estimates from the Cox models are presented as hazard ratios; from the propensity score analyses, as average treatment effects.

For the secondary analyses, the proportional odds assumption (assessed through the score test) did not hold for the ordinal scale, and we estimated risk ratios from a multinomial logistic regression analysis with hospital discharge as the base outcome adjusting for age, $SpO_2/FiO_2$ ratio, respiratory rate, and obesity status. Mechanical ventilation–free days are presented as median difference with the Hodges-Lehman estimator (univariate analysis). We used quantile regression at the median with 1,000 bootstrap replications[27] to provide adjusted estimates of this nonnormally distributed continuous outcome because linear regression assumptions (homoscedasticity) did not hold. ICU admission, use of vasopressors, and need for dialysis are presented as unadjusted univariate analyses. For the before–after analyses, we used the nonparametric Wilcoxon signed-rank test. Effect estimates are presented with 95% confidence intervals (CIs). p-values $< 0.05$ were considered statistically significant. We did not adjust for multiple comparisons. For the primary outcome analyses, there were no missing data in covariates included in the models. For secondary and physiologic analyses, we analyzed data on a complete

case scenario. All analyses were done in Stata/SE 16.0. Propensity score models were done with the psmatch2 user-written command and the "teffects" suite of Stata commands.

## RESULTS

### Characteristics of Study Subjects

Of 925 patients admitted to the ED not receiving mechanical ventilation from March 1 to April 30, 2020, as suspected COVID-19 cases, 690 patients did not fulfill inclusion criteria due to admission respiratory rate ≤ 24 or oxygen flow rate ≤ 3 L/min, 37 patients due to high suspicion of alternative diagnoses, and seven patients due to missing data. Twenty-five patients were excluded due to contraindications to prone positioning (three pregnant women, 19 palliative care patients who had do-not-intubate orders, one with recent major abdominal surgery, one with hemodynamic instability, and one with acute intense pain that would make prone positioning impossible). A total of 166 patients were included, of which 57 were exposed to prone positioning and 109 patients who could have been eligible to prone positioning were included in the control group (Figure 1).

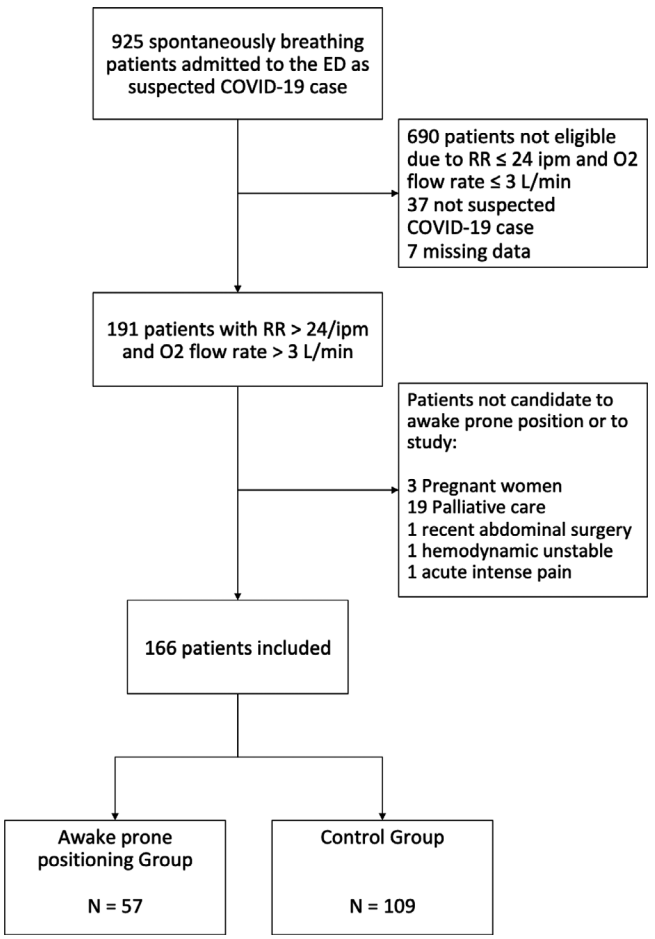


**Figure 1.** Flowchart of study participants.

Table 1 presents baseline characteristics between those exposed and not exposed to prone positioning. Overall, the groups were comparable and represent a cohort with acute hypoxemic respiratory failure with a low burden of extrapulmonary organ dysfunctions. The exceptions were age and $SpO_2/FiO_2$ ratio, which were lower, while respiratory rate was higher in the prone positioning group.

### Clinical Outcomes

In the primary outcome analysis, 33 of 57 patients (58%) exposed to prone positioning were intubated through 15 days compared to 53 of 109 control patients (49%; univariate hazard ratio = 1.21, 95% CI = 0.78 to 1.88, p = 0.39). Figure 2 presents the unadjusted Kaplan-Meier plot of time from inclusion in the study until intubation. In the multivariable Cox analysis accounting for age, obesity status, respiratory rate, $SpO_2/FiO_2$ ratio, and the 4C score, the point estimate changed direction, but results were still not statistically significant (adjusted hazard ratio = 0.89, 95% CI = 0.54 to 1.48, p = 0.67). The results were robust to the sensitivity analyses with different causal model assumptions (Table 2).

Table 3 presents the secondary outcomes analyses. We did not observe differences in 15-day outcomes between groups; mechanical ventilation–free days (through 15 days) did not differ (adjusted median difference = 2.4, 95% CI = −2.7 to 6.7, p = 0.40). Resource utilization did not differ either: need for dialysis (23% vs. 12%, p = 0.076), vasopressor utilization (47% vs. 39%, p = 0.32), and ICU bed utilization (82% vs. 72%, p = 0.183) did not present statistically significant differences.

Two patients used hydroxychloroquine for 1 day in the control group. Four patients used low-dose steroids in the control group before undergoing intubation. No patient used remdesivir, convalescent plasma, or other proposed pharmacologic intervention (except for antimicrobials when indicated) for the treatment of COVID-19 during the study period.

### Physiologic Outcomes, Tolerability, and Adverse Events

Among patients undergoing prone positioning, we observed an improvement in gas exchange as measured by improved before and after $SpO_2/FiO_2$ ratios. We also observed a reduction in respiratory rate and

Table 1
Baseline Characteristics

| Variable | All Patients, *N* = 166 | Prone, *n* = 57 | No Prone, *n* = 109 | p-value |
|---|---|---|---|---|
| Age (y) | 58.1 (±14.1) | 51.8 (±13) | 61.4 (±13.6) | <0.001 |
| Male sex | 112 (67) | 40 (70) | 72 (66) | 0.73 |
| Comorbidities | | | | |
| BMI > 30 | 89 (54) | 33 (58) | 56 (51) | 0.51 |
| Hypertension | 89 (54) | 27 (47) | 62 (57) | 0.26 |
| Diabetes | 58 (35) | 22 (39) | 36 (33) | 0.50 |
| Asthma/COPD | 7 (4) | 3 (5) | 4 (4) | 0.69 |
| Heart failure | 5 (3) | 1 (2) | 4 (4) | 0.66 |
| Dialysis | 3 (2) | 1 (2) | 2 (2) | >0.99 |
| Cancer | 7 (4) | 1 (2) | 6 (6) | 0.42 |
| Immunosuppression | 4 (2) | 2 (4) | 2 (2) | 0.61 |
| Smoker* | 54 (33) | 13 (23) | 41 (38) | 0.057 |
| NEWS | 9 [8, 10] | 9 [8, 9] | 9 [8, 10] | 0.57 |
| 4C score | 12 [9, 14] | 11 [8, 12] | 12 [10, 14] | <0.001 |
| Respiratory characteristics | | | | |
| Respiratory rate | 30 [28, 36] | 34 [30, 38] | 29 [28, 34] | <0.001 |
| Oxygen saturation | 92.5 [90, 94] | 92 [88, 93] | 93 [91, 95] | <0.001 |
| Oxygen delivery device | | | | 0.023 |
| Nasal cannula | 72 (44) | 19 (34) | 53 (49) | |
| Venturi mask | 17 (10) | 3 (5) | 14 (13) | |
| Non-rebreather mask | 76 (46) | 34 (61) | 42 (39) | |
| Oxygen flow rate (L/min) | 6 [5, 10] | 7 [5, 13.5] | 6 [5, 10] | 0.086 |
| $SpO_2/FiO_2$ ratio < 235 | 92 (55) | 36 (63) | 56 (51) | 0.188 |
| Symptom onset to inclusion (days) | 8 [6, 13] | 9 [7, 13] | 8 [6, 12] | 0.31 |
| Chest CT involvement | | | | 0.52 |
| <25% | 18/148 (12) | 4/50 (8) | 14/98 (14) | |
| 25%–50% | 51/148 (34) | 17/50 (34) | 34/98 (35) | |
| >50% | 79/148 (53) | 29/50 (58) | 50/98 (51) | |
| Laboratory values | | | | |
| Creatinine (mg/dL) | 0.83 [0.63, 1.02] | 0.76 [0.61, 0.92] | 0.85 [0.68, 1.03] | 0.06 |
| Leucocytes ($\times 10^9$/L) | 7.5 [5.7, 10.2] | 7.9 [5.9, 10.1] | 7.4 [5.5, 10.5] | 0.67 |
| Lymphocytes ($\times 10^9$/L) | 0.96 [0.61, 1.26] | 0.94 [0.69, 1.19] | 0.97 [0.57, 1.34] | 0.77 |
| Platelets ($\times 10^9$/L) | 212 [179, 269] | 227 [189, 287] | 210 [169, 262] | 0.25 |
| Urea | 31 [22, 44] | 29.5 [20, 38] | 33 [22, 44] | 0.058 |
| CRP | 164 [110, 226] | 146 [111, 231] | 165 [104, 224] | 0.79 |
| D-dimer | 1,169 [683, 1,700] | 979 [645, 1486] | 1199 [746, 1776] | 0.178 |
| LDH | 426 [344, 522] | 429 [365, 567] | 408 [330, 510] | 0.23 |

Data are reported as mean (±SD), *n* (%), or median [P25, P75].
BMI = body mass index; CRP = C-reactive protein; LDH = lactate dehydrogenase.
*Current or previous.

an improvement in ROX score, an overall noninvasive measure of improvement in gas exchange (Table 4). There were no detectable hemodynamic differences among groups as assessed by the shock index. We could classify 51% of patients as responders regarding $SpO_2/FiO_2$ ratios; 69%, as responders regarding respiratory rate; and 80%, as improving in either one of these criteria. Table 5 presents further characteristics of the prone positioning session. Among the 57 patients, only 50 had available information regarding the duration of the first prone positioning session. Twenty-nine patients (58%) tolerated prone positioning for more than 4 hours. Accidental removal of peripheral IV lines occurred in two patients and cardiac arrest due to hypoxemia during intubation occurred in one patient. This event was ascertained by

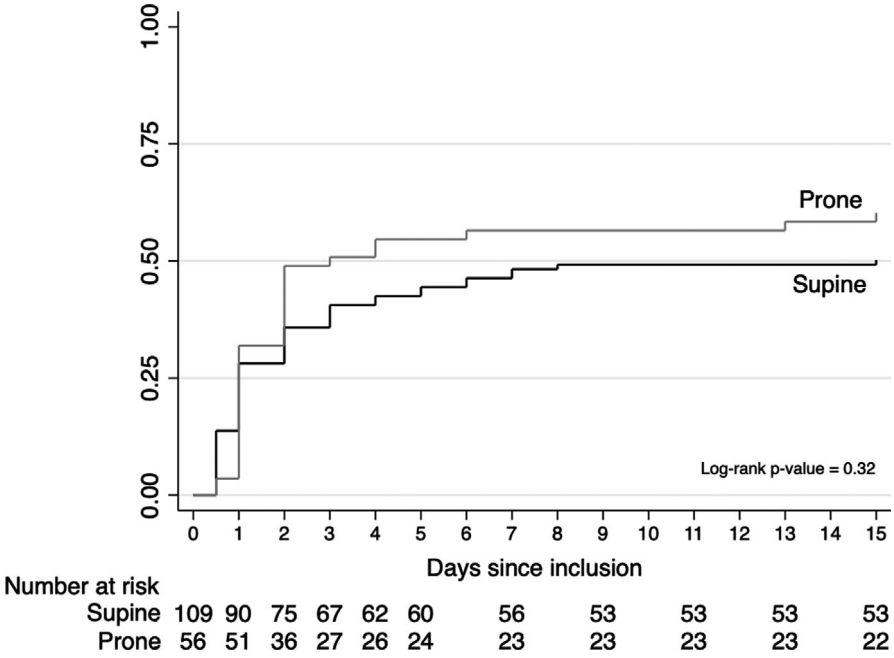


**Figure 2.** Kaplan-Meier failure plot of intubation through 15 days.

three of the authors (EMHP, FSV, and BAMPB) as not being related to the prone positioning session. The patient was on high-flow oxygen (15 L/min face mask) with respiratory distress, but good level of consciousness and hemodynamic stable. He underwent awake prone positioning for 15 minutes, but did not experience any amelioration and a decision to intubate was made. During the procedure, the patient presented with a difficult airway and crashed after three attempted intubations by the emergency medicine fellow and the attending physicians, with a return to spontaneous circulation after intubation during the cardiac arrest.

## DISCUSSION

In this retrospective cohort study with a control group, we observed a beneficial physiologic improvement in gas exchange with a greater than 50% rate of responders to awake prone positioning. Moreover, most patients tolerated more that 4 hours of prone positioning in their first session of prone positioning.

Table 2
Primary Outcome Analyses

| Analysis | Intubation | p-value |
|---|---|---|
| No events/no. of patients at risk (%) | | 0.33 |
| Prone | 33/57 (58%) | |
| Supine | 53/109 (49%) | |
| Univariate analysis, hazard ratio (95% CI) | 1.21 (0.78 to 1.88) | 0.39 |
| Multivariable analysis, hazard ratio (95% CI)* | 0.90 (0.55 to 1.49) | 0.69 |
| Propensity score analyses† | | |
| PS-adjusted, hazard ratio (95% CI) | 1.02 (0.63 to 1.64) | 0.93 |
| PS-matched (1:1), ATE (95% CI) | 0.053 (−0.17 to 0.28) | 0.64 |
| IPTW, ATE (95% CI) | 0.021 (−0.14 to 0.18) | 0.80 |
| Doubly robust estimator – ATE (95% CI)‡ | 0.01 (−0.17 to 0.17) | 0.99 |

ATE = average treatment effects; IPTW = inverse probability of treatment weighting; PS = propensity score.
*Adjusted for age, obesity status, $SpO_2/FiO_2$ ratio, respiratory rate, and the 4C score at inclusion.
†Propensity score included variables were age, obesity status, $SpO_2/FiO_2$ ratio, respiratory rate, and the 4C score at inclusion. Standardized differences were all lower than 10% after matching and weighting.
‡Variables included for regression adjustment in the doubly robust estimation were the same as the propensity score variables.

Table 3
Secondary Outcomes

| Variable | Prone, *n* = 57 | Supine, *n* = 109 | Unadjusted Effect Estimate | Adjusted Effect Estimate |
|---|---|---|---|---|
| 15 days outcome ordinal scale* | | | | |
| 1 – Discharged alive | 23 (40) | 43 (39) | — | — |
| 2 – Hospitalized, no oxygen therapy | 5 (9) | 10 (9) | 0.93 (0.29, 3.06) p = 0.91 | 0.55 (0.14, 2.12) p = 0.39 |
| 3 – Hospitalized, oxygen therapy by mask or nasal cannula | 12 (21) | 13 (12) | 1.73 (0.68, 4.39) p = 0.25 | 2.62 (0.87, 7.86) p = 0.086 |
| 4 – Hospitalized, NIV or HFNC | 1 (2) | 5 (5) | 0.37 (0.04, 3.39) p = 0.38 | 0.26 (0.02, 3.3) p = 0.30 |
| 5 – Hospitalized, MV | 10 (18) | 16 (15) | 1.17 (0.46, 2.99) p = 0.75 | 1.05 (0.36, 3.07) p = 0.92 |
| 6 – Dead | 6 (11) | 22 (20) | 0.51 (0.18, 1.44) p = 0.202 | 0.50 (0.15, 1.65) p = 0.26 |
| Mechanical ventilation–free days† | 8 [2, 12] | 6 [0, 11] | 1 (0, 2) p = 0.26 | 2.4 (−2.7, 6.7) p = 0.40 |
| Other resource utilization during hospitalization | | | | |
| Dialysis | 13 (23) | 13 (12) | 1.91 (0.95, 3.85) p = 0.076 | — |
| Vasopressors | 27 (47) | 42 (39) | 1.23 (0.86, 1.77) p = 0.32 | — |
| ICU admission | 47 (82) | 79 (72) | 1.14 (0.96, 1.34) p = 0.183 | — |

Data are reported as *n* (%).
HFNC = high-flow nasal cannula; MV = mechanical ventilation; NIV = noninvasive ventilation.
*The ordinal scale was modeled as a multinomial logistic regression model with hospital discharge as the base outcome because the proportional odds assumption did not hold. Results are all presented as crude risk ratios and adjusted risk ratios accounting for age, $SpO_2/FiO_2$ ratio, respiratory rate, and obesity status.
†Results are presented as median differences with the Hodges-Lehmann estimator (crude estimate) and quantile regression at the median (adjusted estimate) with 1,000 bootstrap replications adjusted for age, $SpO_2/FiO_2$ ratio, and respiratory rate at inclusion.

Table 4
Vital Signs Before and After Proning in the Prone Group

| Variable | Before | After | p-value |
|---|---|---|---|
| Peripheral oxygen saturation, % | 92 [88, 93] | 94 [92, 96] | <0.001 |
| Complete data | 57/57 | 51/57 | |
| Respiratory rate, ipm | 34 [30, 38] | 29 [26, 32] | <0.001 |
| Complete data | 57/57 | 51/57 | |
| $SpO_2/FiO_2$ ratio | 196 [128, 254] | 224 [159, 307] | <0.001 |
| Complete data | 56/57 | 51/57 | |
| ROX index | 5.7 [3.9, 7.7] | 7.7 [5.4, 11] | <0.001 |
| Complete data | 56/57 | 51/57 | |
| Systolic arterial pressure, mm Hg | 127.5 [114, 140] | 125 [116, 136] | 0.43 |
| Complete data | 54/57 | 41/57 | |
| Heart rate, bpm | 94 [84, 101] | 90 [78, 100] | 0.026 |
| Complete data | 54/57 | 43/57 | |
| Shock index | 0.73 [0.63, 0.83] | 0.71 [0.61, 0.86] | 0.61 |
| Complete data | 54/57 | 40/57 | |

All data are presented as median [P25, P75].
Before–after comparisons were done with Wilcoxon signed-rank test.
ROX index = ratio of $SpO_2/FiO_2$ ratio to respiratory rate.
Shock index = ratio of heart rate to systolic arterial pressure.

However, in spite of responding to the maneuver and tolerating it, we could not observe a beneficial effect in the intubation rate through 15 days, whose avoidance would be the mediator of an increase in ventilator-free days, lower admission rates to the ICU, or a reduction in mortality, all of which were not observed in this

Table 5
Prone Positioning First Session Duration, Responders, and Reported Adverse Events

| Variable | |
|---|---|
| First session duration | |
| <1 hour | 3/50 (6%) |
| 1-2 hours | 7/50 (14%) |
| 2-3 hours | 6/50 (12%) |
| 3-4 hours | 5/50 (10%) |
| >4 hours | 29/50 (58%) |
| Proportion of responders | |
| 10% increase in $SpO_2/FiO_2$ ratio | 26/51 (51%) |
| 10% decrease in respiratory rate | 35/51 (69%) |
| Either one | 41/51 (80%) |
| Adverse events | |
| Accidental removal of peripheral IV lines | 2 |
| Back pain limiting prone positioning | 3 |

study. These results add to the recent literature on acute hypoxemic respiratory failure in COVID-19 patients in that previous reports only presented physiologic findings, and there were no comparisons with a control group of more patient-centered clinical outcomes.

Our results concur with the physiologic studies that demonstrated an improvement in $PaO_2/FiO_2$ ratio and a reasonable amount of responders to prone positioning:[16,17,19,20] we observed improvement of $SpO_2$, respiratory rate, $SpO_2/FiO_2$, and the ROX index—despite the fact that the ROX index was initially described for patients in HFNC,[24] we extrapolated the concept for patients in low-flow oxygen devices. Nevertheless, this improvement did not reduce the intubation rate neither had an impact on other outcomes. By contrast, this study reassures that prone positioning is probably safe, although some studies showed that delayed intubation may be harmful in other conditions.[28,29] Delaying intubation with awake prone positioning was also an initial concern of our group due to increased risk of intubation complications such as hypoxia and cardiac arrest, but it did not seem to be an issue in this cohort. Our study had only one reported cardiac arrest during intubation in the patients who were submitted to prone positioning, but it was not related to the prone positioning session itself. Given that this event is not common, larger studies would be necessary to confirm this finding.

Some explanations can be raised to explain the neutral results. First, it is possible that awake prone positioning can only improve oxygenation in the short term in some patients, without any real effect on clinical outcomes because one cannot assure lung-protective ventilation out of the mechanical ventilator. Another possibility is that it does not work when used in isolation and it must be combined with other methods of oxygen delivery associated with either reduced mortality or intubation rates.[30] For example, a small Chinese cohort showed that 11 (55%) patients with ARDS avoided intubation when using NIV or HFNC.[14] It is also possible that the duration of the prone positioning sessions may be important, although we achieved a higher than 50% tolerability for more than 4 hours. The PROSEVA trial showed statistically significant benefit with prone positioning in intubated patients and they were submitted to prone positioning for an average of 17 hours.[9,10] It is also possible that only a subset of patients, still to be characterized, can benefit from awake prone positioning. While we observed at least a 50% physiologic response to therapy, Sartini et al.[19] showed that 80% of the 15 patients submitted to prone positioning responded to the therapy,[19] while Elharrar et al.[17] showed that only six (25%) responded to the therapy. Finally, patient self-inflicted lung injury could have a role in limiting the beneficial effects of awake prone positioning, which could delay intubation—and more informed attempts of lung-protective ventilation—because improvements in oxygenation alter clinical reasoning for intubation.

Our study has some strengths. To allow for a stronger causal inference in an observational study, we developed explicit inclusion and exclusion criteria to refine the inclusion in the cohort. This resulted in only small imbalances in the overall cohort, which could be adjusted in multivariable analyses without major drawbacks regarding degrees of freedom. Furthermore, we present our primary outcome with different models and causal assumptions and results were robust to all sensitivity analyses. The event rate was reasonable and allowed us good interpretability of study results, which could lead to better generalization of our findings.

## LIMITATIONS

Our study also has several limitations. First, given the retrospective nature of the study, we do not have granular data on arterial blood gases analysis before and after the proning session, but the noninvasive data can be a good surrogate and a major strength of our

data is the focus on other clinical outcomes. Furthermore, blinding of data collection was not possible due to the nature of the intervention and inter-rater agreement was not done because of time constraint issues. However, the first authors reviewed all data collected to ensure data quality and both the intervention and the main outcomes are objective and not subject to information bias due to unblinding. Second, our sample size was at most reasonable to allow for some covariate adjustment, but our CIs cannot exclude a beneficial nor a negative effect on clinical outcomes. Third, we did not assess the effects of awake prone positioning with more advanced noninvasive methods of respiratory support. This represents the practice of our ED at the time and may hamper the generalizability to other centers, although these forms of respiratory support were scarce during the study period and dedicated to the intensive care units in our hospital. Fourth, there was no prestudy written awake prone positioning protocol to ensure that all patients would receive the exact same intervention. Nevertheless, this is the reason why we had a representative control group in this cohort to address this specific research question.

## CONCLUSION

In summary, the exposure to awake prone positioning in patients with suspected or confirmed COVID-19 with hypoxemic respiratory failure was not associated with reduced intubation rates in our cohort. However, the technique is associated with improved physiologic parameters and the confidence intervals could not exclude neither a beneficial nor a harmful effect of the therapy. Therefore, randomized clinical trials are required to assess the relative benefits and harms of awake prone positioning before widespread adoption of this technique.

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## Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14160/full

**Data Supplement S1.** Supplemental material.