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Awake prone positioning and oxygen therapy in patients with COVID-19: The APRONOX study

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Awake prone positioning and oxygen therapy in patients with COVID-19: The APRONOX study

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ABSTRACT

The awake prone position (AP) strategy for patients with acute respiratory distress syndrome (ARDS) is a safe, simple, and cost-effective technique used to improve hypoxemia. We aimed to evaluate intubation and mortality risk in patients with coronavirus disease (COVID-19) who underwent AP during hospitalisation.

In this retrospective, multicentre observational study conducted between 1 May and 12 June 2020 in 27 hospitals in Mexico and Ecuador, non-intubated patients with COVID-19 managed with AP or supine positioning were included to evaluate intubation and mortality risk through logistic regression models; multivariable and centre adjustment, propensity score analyses, and E-values were calculated to limit confounding. This study was registered at https://clinicaltrials.gov/ct2/show/NCT04407468

827 non-intubated patients with COVID-19 in the AP (n=505) and supine (n=322) groups were included for analysis. Less patients in the AP group required endotracheal intubation (23.6% vs 40.4%) or died (20% vs 37.9%). AP was a protective factor for intubation even after multivariable adjustment (OR=0.39, 95%CI:0.28-0.56, p<0.0001, E-value=2.01), which prevailed after propensity score analysis (OR=0.32, 95%CI:0.21-0.49, p<0.0001, E-value=2.21), and mortality (adjusted OR=0.38, 95%CI:0.25-0.57, p<0.0001, E-value=1.98). The main variables associated with intubation amongst AP patients were increasing age, lower baseline SpO_2/FiO_2, and management with a non-rebreather mask.

AP in hospitalised non-intubated patients with COVID-19 is associated with a lower risk of intubation and mortality.

Keywords: Acute respiratory distress syndrome – ARDS – prone – COVID-19 – SARS-CoV-2 – oxygen – high-flow nasal cannula.

Take-home message: Awake prone positioning in non-intubated hospitalised patients with COVID-19 was associated with a lower risk of intubation and mortality in this multicentre observational study.

INTRODUCTION

The awake prone position (AP) in non-intubated patients with acute hypoxemic respiratory failure results in improved oxygenation, as demonstrated by an increase in arterial partial pressure of oxygen (PaO_2), peripheral arterial oxygen saturation (SpO_2), and PaO_2/inspired oxygen fraction (PaO_2/FiO_2), without deleterious effects on the level of partial arterial pressure of carbon dioxide ($PaCO_2$), pH, respiratory rate (RR), or haemodynamics [1, 2]. The physiological mechanism by which prone positioning is useful for ARDS is by increasing functional residual capacity, reducing dead space, reducing intrapulmonary shunts, increasing ventilation in areas dependent of gravity, and relieving the weight that the heart exerts over the lungs [3].

The coronavirus disease (COVID-19) pandemic has unleashed a high global demand for respiratory support, a reason why AP in non-intubated patients has become popular and clinical interest has rapidly increased. AP combined with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC) in patients with moderate to severe acute respiratory distress syndrome (ARDS) [4, 5] and COVID-19 [6–8] has been shown to be safe and may prevent intubation. One further advantage of AP is that it allows patients to interact with their family during hospitalisation, thereby favouring humanisation of healthcare [9]. Nonetheless, few observational studies have evaluated AP against control groups (i.e. awake supine patients managed with NIV or HFNC) with conflicting findings [10–12]. Thus, the utility of AP remains to be further elucidated in larger observational or randomised studies.

In this multicentre retrospective observational study, we sought to evaluate intubation and mortality risk in conscious patients with COVID-19 who underwent AP during hospitalisation.

METHODS

Study design

A multicentre retrospective cohort study was conducted with patients diagnosed with COVID-19 admitted to 27 hospitals in Mexico and Ecuador (Appendix 2) from the emergency department. The study was approved by the Health Services Research Committee of the State of Querétaro (registration number 1178/SESEQ-HGSJR/08-05-20) and all other participating centres. This study was prospectively registered in ClinicalTrials.gov (NCT04407468); STROBE recommendations were followed during the reporting of this study.

Study population and data collection

In each participating hospital centre, data collection was carried out by medical specialists in emergency medicine, respiratory medicine, anaesthesiology, and intensive care medicine, who collected information from patients' medical records. A separate group of physicians were appointed to review the data obtained and check for plausibility. In cases of doubt physicians in charge at each centre were contacted. All patients were followed-up during their entire in-hospital stay, until discharge or in-hospital death.

Patients were deidentified by assigning them a code. All patients admitted to the emergency department during the period between 1 May and 12 June 2020 who met the following criteria were considered for inclusion in the study: 1. Age $\geq$18 years; 2. Positive test for SARS-CoV-2 or imaging study compatible with COVID-19 (see section ahead); 3. clinical record available in accordance with the official Mexican standard NOM-004-SSA3-2012 (http://dof.gob.mx/nota_detalle_popup.php?codigo=5272787) or equivalent in Ecuador; and 4. Room-air peripheral arterial oxygen saturation (SpO_2) <94% upon admission to the emergency department, and 5. two or more of the following symptoms: eye pain, cough, fever, dyspnoea, headache, myalgia, arthralgia, or odynophagia.

Due to the differences in funding and infrastructure between centres, two criteria were employed to standardise COVID-19 diagnosis: 1. A positive RT-PCR test for SARS-CoV-2 from a respiratory tract sample; or 2. Chest computed tomography (CT) scan with a COVID-19 Reporting and Data System (CO-RADS) score $\geq$3 (Appendix 3) [13]. The latter imaging criterion was applied only for patients in whom RT-PCR was not performed.

Exclusion criteria included: 1. Patients who were voluntarily discharged; 2. patients referred to another hospital prior to outcome ascertainment, and 3. those with incomplete clinical records (insufficient information to calculate SpO2/FiO2 ratio, or when unable to ascertain if the patient was managed in a prone or supine position).

Data recorded were demographic (age, sex) and clinical variables including comorbidities (diabetes, systemic arterial hypertension, obesity, heart disease, lung disease, cancer, liver disease, chronic kidney disease), pre-prone SpO_2/FiO_2 ratio (SpO_2/FiO_2 ratios of 235 and 315 correlate with SpO_2/FiO_2 ratios of 200 and 300) [14], post-prone SpO_2/FiO_2 (within one hour after proning), time-to-initiation of prone positioning (defined as the time elapsed from hospital admission to first successful attempt in prone lasting $\geq$2 hours), total time in AP, type of care (emergency room, hospitalisation, or intensive care unit [ICU]), medications, supplemental oxygen delivery device used, need for orotracheal intubation, and lethal outcome. FiO_2 was calculated based on the type of supplemental oxygen delivery device employed: low-flow nasal cannula, high-flow nasal cannula or non-rebreather mask (Appendix 4) [15].

Exposures and outcomes

Awake, spontaneously breathing patients managed with non-invasive oxygen devices who were able to remain in the prone position for at least 2 continuous hours were considered as patients in the AP group (main exposure); those not meeting this criterion or in whom prone positioning was not attempted at all, were considered as the comparison group (awake supine). The primary outcome was successful orotracheal intubation for invasive mechanical ventilation and the secondary outcome was death during in-hospital follow-up. Factors associated with intubation amongst patients in the AP group were also evaluated.

The decision to place patients in the prone position and perform orotracheal intubation were based on individualised medical criteria and were not priorly defined or standardised. Patients were managed with low-flow nasal cannula, non-rebreather mask, or high-flow nasal cannula; other non-invasive ventilation devices were either not used or unavailable across all centres.

Sample size

Sample size was calculated to observe a 10% difference of the incidence of intubation based on that reported by Argenziano et al [16]. The calculated sample size was 309 subjects per group (Appendix 5). Convenience sampling for the original cohort was employed, with further propensity score-matched sampling performed to reduce bias.

Statistical analysis

The clinical and demographic characteristics of the patients were examined for all patients and for those in the AP or awake supine groups. Descriptive results for quantitative variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR), and frequencies with percentage (%) for qualitative variables. Asymmetry and kurtosis were calculated for quantitative variables. Quantitative comparisons were performed with the independent-samples t-test; qualitative comparisons were done with chi-squared, chi-squared of trend, or Fisher's exact test. Baseline and post-AP SpO_2/FiO_2 ratios were compared with the dependent-samples t-test. The PH-Covid19 mortality score was calculated as described in the original model development and validation study [17].

To reduce the risk of bias due to unbalanced groups, propensity score analysis was performed through a logistic regression model adjusted for age, sex, the presence of 3 or more comorbidities, baseline SpO_2/FiO_2 ratio, supplemental oxygen device, ICU attention, and treatment with systemic steroids, enoxaparin, tocilizumab, or ceftriaxone. Patients were matched in a 1:1 ratio according to the nearest-neighbour matching algorithm; changes in density functions are shown in Appendix 6. All inferential analyses were performed for all patients in the original cohort and for the propensity score-matched cohorts.

Distinct multivariable logistic regression analyses were performed to determine the risk of orotracheal intubation and mortality associated with AP. Variables included in the models were selected by the Enter method; adjustment variables were those which had a p value <0.1 in

univariate analyses which have been reported to be associated with higher (or lesser) risk for adverse events (age, sex [men], ICU attention, diabetes, systemic arterial hypertension, obesity, heart disease, cancer, chronic kidney disease), pre-prone SpO_2/FiO_2 ratio, supplemental oxygen delivery device, ceftriaxone, enoxaparin, tocilizumab, oseltamivir, and systemic steroids). A multivariable logistic regression model was subsequently created to determine the risk of intubation amongst patients who tolerated AP; the variables included in this model were selected with the Stepwise Forward method, including those with a $p<0.1$ in the final model. Odds ratios (OR) with their 95% confidence interval (95%CI) were calculated. The goodness of fit of the final models were evaluated with the Hosmer-Loemeshow statistic, and the discrimination of the model was determined by calculating the area under the curve (AUC). The risk of intubation amongst AP patients according to age and baseline SpO_2/FiO_2 ratio were graphed through the smoothing spline method.

Sub-analyses of intubation and mortality risk for patients who had a positive RT-PCR for SARS-CoV-2 (excluding patients in whom RT-PCR was not available but had a compatible CO-RADS study) were performed in the unmatched and propensity-score matched cohorts through logistic regression models; the size of effect was adjusted for the same variables as the main analyses.

E-values for the lower bound of the confidence intervals were calculated to determine the value at which an unmeasured confounding factor could potentially alter the observed effect of AP on the outcomes and drive them to a non-significant value [18]. Regression analyses were verified through residual analysis.

To determine the variability of the association between AP and intubation rates across different centres, multicentre adjustment was performed through generalized estimating equations (GEE); the centre with the lowest intubation rate throughout the entire study period was set as the reference. The main effect of every centre and AP were calculated in the same model, as well as their interaction within the model.

A systematic search of studies of AP was conducted; the search strategy and inclusion criteria for studies are provided in Appendix 7. Results of eligible studies were summarised alongside the propensity score-matched cohort of APRONOX through a random-effects model in a forest and funnel plot of the overall risk of intubation for patients in AP vs supine position.

Missing values were not imputed. A p-value <0.05 was used to define bilateral statistical significance. All analyses and graphs were created with the SPSS software v.21, R software v.3.4.2, and RevMan 5.3.

RESULTS

Out of 932 patients identified across all 27 hospital centres, 827 patients were ultimately included for analysis (Figure 1). Descriptive results for all patients are provided in Table 1. Amongst all 927 patients, 227 (27.4%) were female and mean age was 54.3 (SD:14.2) years, with most patients being in the 50 to 59-year category (25.3%). The most prevalent comorbidities were diabetes (38.1%) and hypertension (34.5%). Most patients were managed with low-flow nasal cannulas (48.6%). Out of 249 patients who underwent orotracheal intubation, 69.9% (n=174) died during in-hospital follow-up. In comparison, out of 578 patients who were not intubated, 8.0% (n=46) died (p<0.0001).

The characteristics of patients in the AP and supine groups, in both the unmatched and matched cohorts, are provided in Table 2. Patients managed in AP had a median time-to-initiation of prone positioning of 15.5 (IQR:8-48) hours. The median time spent in the prone position during the hospital stay (total time in prone) was 12 (IQR:8-24) hours. A lesser proportion of patients in the AP group required endotracheal intubation (23.6% vs 40.4%) or had a lethal outcome (19.8% vs 37.3%). After propensity score matching, these differences prevailed. The SpO_2/FiO_2 ratio in the AP group was statistically significantly higher after prone (217.42, SD: 81.9) compared with baseline values (182.39, SD: 81.91), with a mean difference of 35.03 (95%CI: 29.99-40.06, p<0.0001) units.

The results of univariable logistic regression models for orotracheal intubation risk are provided in Table 3, for both the unmatched and matched cohorts. The main risk factors identified were age, diabetes, arterial hypertension, obesity, heart disease, cancer, a baseline SpO_2/FiO_2 <100 or between 100 and 199, and management with a non-rebreather mask. AP was a protective factor for orotracheal intubation even after multivariable adjustment (Table 4) for confounding variables (Adjusted OR=0.35, 95%CI:0.24-0.52, p<0.0001, E-value=2.12), which prevailed after propensity score analysis (Adjusted OR=0.41, 95%CI:0.27-0.62, p<0.0001, E-value=1.86). Similarly, AP was a protective factor for mortality (Adjusted OR=0.38, 95%CI:0.26-0.55, p<0.0001, E-value=2.03, Goodness of fit: Hosmer-Lemeshow X^2=10.2, p=0.3 AUC=0.78, 95%CI:0.74-0.81, p<0.0001) even after multivariable adjustment in propensity score analyses (Adjusted OR=0.40, 95%CI:0.27-0.61, p<0.0001, E-value=1.88, Goodness of fit: Hosmer-Lemeshow X^2=7.81, p=0.4 AUC=0.78, 95%CI:0.74-0.82, p<0.0001). Lower intubation and mortality risks for AP prevailed after sub-analyses of patients with a confirmatory SARS-CoV-2 RT-PCR (excluding those in whom molecular testing was not performed) (Appendix 8).

After adjusting for centre through GEE, 9 centres had an effect over the risk of intubation. Despite this, AP continued to be associated with lower intubation risk (OR: 0.22, 95%CI: 0.15-0.34, p<0.0001); the interaction between centre and AP was non-significant for all the centres.

The main variables associated with intubation amongst AP patients were increasing age (OR=1.02, 95%CI: 1.01-1.04, p=0.005), SpO_2/FiO_2 <100 (OR=2.78, 95%CI: 1.35-5.72, p=0.005), SpO_2/FiO_2 100-199 (OR=2.18, 95%CI: 1.31-3.64, p=0.003), and management with a non-rebreather mask (OR=2.17, 95%CI: 1.34-3.49, p=0.002), Goodness of fit: Hosmer-Lemeshow X^2=10.52, p=0.2; AUC=0.70, 95%CI:0.64-0.74, p<0.0001. The distribution of risk for increases in age and baseline SpO_2/FiO_2 are shown in Figure 2.

After the search of the literature, 99 records were retrieved, of which only 9 studies [10–12, 19–24] were observational comparison-group studies including both AP and supine patients, with sufficient information to calculate the overall risk of intubation, which are summarised alongside the APRONOX study in Figure 3; the funnel plot is provided as Appendix 9.

DISCUSSION

In this multicentre observational study, we aimed to evaluate the association between awake prone positioning and orotracheal intubation, as well as predictors of intubation amongst AP patients, and mortality in hospitalised patients with COVID-19. Even after multivariable adjustment and propensity score analyses, prone positioning in non-intubated patients was associated with lower intubation and mortality risk.

Patients in our cohort were younger (mean age 53.4 years) than those in other studies (56.0-65.8) [10–12]; hospitalised patients with COVID-19 in Mexico have been reported to be young [25]. The prevalence of comorbidities in our study is similar to that reported in a population-based sample of Mexican patients hospitalised with COVID-19, although diabetes was more common in our study (38.1% vs 29.2%), whereas obesity (14.4% vs 22.5%) and heart disease (2.1% vs 4.4%) were less frequent [25].

The total time spent in the prone position during in-hospital stay in our study was 12 (IQR:8-24) hours, which is considerable compared to a recent pilot randomised study which reported that self-proning patients spent only 1.6 (95%CI: 0.2-3.1) hours in the prone position in a 72-hour evaluation period [26]. Daily time spent in the prone position has been reported to be highly variable, with only 43% of patients achieving a daily dose of $\geq$6 hours in AP [27].

The overall intubation rate in the APRONOX cohort was higher (30.1%) than that reported for hospitalised patients with COVID-19 in Mexico City (20.2%) [25]; however, limited access to beds with ventilators in Mexico has been reported [28]. Intubation rates for patients in the unmatched AP (23.6%) and supine (40.4%) cohorts fall within those reported in previous studies (10–58% and 27.7–49%, respectively) [10–12]. AP in our study was associated with decreased intubation risk even after multivariable adjustment in both the unmatched and propensity-score matched cohorts, with an E-value of 2.01 and 2.21, respectively, which reflects that in order to drive this association to be non-significant, an unmeasured risk factor should have a lower-limit confidence interval that at least doubles the risk of the outcome between both groups. Out of all comorbidities, only diabetes and heart disease were associated with increased

intubation risk after multivariable adjustment, however, diabetes was no longer a risk factor after propensity score analysis. A higher baseline SpO_2/FiO_2 was associated with reduced intubation risk. The mortality rate reported in our study was 19.8%, comparable to 23.4% [12] and 27% [10] in other studies.

Regarding variables associated to intubation amongst AP patients, age, low SpO_2/FiO_2, and the use of a non-rebreather mask were the main variables associated. The distribution of risk for quantitative values of age show that the risk of intubation after AP is higher with increasing ages, whereas higher baseline SpO_2/FiO_2 have the lowest risks.

AP has been presented as one the most cost-effective strategies to treat patients with COVID-19. In countries with limited oxygen delivery devices, and a shortage of ventilators, AP could be used to avoid intubating patients with COVID-19 [29]. Nonetheless, conflicting evidence from observational studies for AP exists.

The supine position alters pulmonary function in patients with respiratory insufficiency due to the gravitational differences between dependent and non-dependent regions, resulting in a more negative pleural pressure (Ppl), increasing transpulmonary pressure (TPP) in non-dependent areas (more distension), and producing the opposite effect in dependent areas where Ppl is less negative and TPP is lower (less distension). Ventilation in the prone position causes even distribution of TPP, favouring uniform ventilation [30]. Approximately 45 years ago, prone positioning was shown to increase oxygenation in patients with respiratory insufficiency, primarily by improving the ventilation-perfusion ratio (V/Q) [31].

Prone positioning has been evaluated in hospitalised patients with respiratory failure due to COVID-19, having observed improvements in SpO_2 and PaO_2, decreased respiratory rate (RR), decreased need for intubation and possible reductions in mortality, in addition to being cost-free [8, 32–35]. As summarised in Figure 4, only three other studies to date have evaluated intubation risk among AP compared with AS. While Ferando et al. and Padrão et al. found no differences in intubation risk, Jagan et al found reduced intubation risk in AP patients [10–12]. The APRONOX study is the largest study to date evaluating the effect of AP on intubation risk.

Regarding oxygenation modality, the use of a non-rebreather mask was associated with greater risk of intubation amongst all patients and within AP patients, whereas other oxygenation devices were not. There is documented evidence of the correlation between the oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio and the partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio, with the advantage that the SpO_2/FiO_2 ratio only relies on a pulse oximeter, with no need to perform a blood gas test, thereby highlighting the value of validated cost-effective strategies [14].

Our study has the following limitations: 1) O_2 delivery devices were not standardised to a unique device, 2) the number of hours of AP varied between hospitals and patients, 3) no standardised criteria were established to consider intubation in patients requiring mechanical ventilation, 4) we were unable to asses which patients had do-not-intubate orders or other reasons for not performing intubation, 5) availability of laboratory studies was limited across centres and were thus not collected and analysed, 6) not all patients with a CO-RADS score $\geq$3 ultimately have a positive RT-PCR test [13]; this limitation was partially addressed by sub-analysing patients with a positive SARS-CoV-2 RT-PCR, 7) a measure of oxygenation comparable to post-prone SpO_2/FiO_2 in AP patients was not collected for patients in the supine group, and 8) the length of stay of patients was not collected.

The strengths of our research include: 1) this is the largest study evaluating AP to date; 2) the large number of hospitals included; and 3) the fact that various O_2 delivery devices were employed–may reflect that the benefits of AP are not necessarily unique to NIV or HFNC devices, which are costlier and not always available.

AP in spontaneously breathing patients with acute hypoxemic respiratory insufficiency may be a justifiable treatment modality, given the improvements in oxygenation and its physiological benefits, but the decision to intubate is based on the clinician's best judgement and intubation should not be delayed if under consideration. Close clinical evaluation of patients is key to avoid poor outcomes. Studies of AP are challenging and randomised controlled trials are warranted to

fully elucidate its usefulness since this is an easy to administer, safe, and reproducible intervention [36].

CONCLUSION

Prone positioning in awake hospitalised patients with COVID-19 is associated with a lower risk of intubation and mortality.

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Data availability: All data that support the findings of this study will be available from the corresponding author upon reasonable request.

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REFERENCES

1. Valter C, Christensen AM, Tollund C, SchØnemann NK. Response to the prone position in spontaneously breathing patients with hypoxemic respiratory failure. *Acta Anaesthesiol Scand* 2003; 47: 416–418.
2. Scaravilli V, Grasselli G, Castagna L, Zanella A, Isgrò S, Lucchini A, Patroniti N, Bellani G, Pesenti A. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. *J Crit Care* 2015; 30: 1390–1394.
3. Bower G, He H. Protocol for awake prone positioning in COVID-19 patients: to do it earlier, easier, and longer. *Crit Care* 2020; 24: 371.
4. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care* 2020; 24: 28.
5. Pérez-Nieto OR, Guerrero-Gutiérrez MA, Deloya-Tomas E, Ñamendys-Silva SA. Prone positioning combined with high-flow nasal cannula in severe noninfectious ARDS. *Crit Care* 2020; 24: 114.
6. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care* 2020; 10: 33.
7. Caputo ND, Strayer RJ, Levitan R. Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Acad Emerg Med* 2020; 27: 375–378.
8. Thompson AE, Ranard BL, Wei Y, Jelic S. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure. *JAMA Intern Med* 2020; 180: 1537.
9. Slessarev M, Cheng J, Ondrejicka M, Arntfield R. Patient self-proning with high-flow nasal cannula improves oxygenation in COVID-19 pneumonia. *Can J Anesth* 2020; 67: 1288–1290.
10. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, Ramasco F, Monedero P, Maseda E, Tamayo G, Hernández-Sanz ML, Mercadal J, Martín-Grande A, Kacmarek RM, Villar J, Suárez-Sipmann F. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: A

multicenter, adjusted cohort study. *Crit Care* 2020; 24: 1–11.

11. Padrão EMH, Valente FS, Besen BAMP, Rahhal H, Mesquita PS, de Alencar JCG, da Costa MGP, Wanderley APB, Emerenciano DL, Bortoleto FM, Fortes JCL, Marques B, de Souza SFB, Marchini JFM, Neto RAB, de Souza HP. Awake Prone Positioning in COVID-19 Hypoxemic Respiratory Failure: Exploratory Findings in a Single-center Retrospective Cohort Study. *Acad Emerg Med* 2020; 27: 1249–1259.
12. Jagan N, Morrow LE, Walters RW, Klein LP, Wallen TJ, Chung J, Plambeck RW. The POSITIONED Study: Prone Positioning in Nonventilated Coronavirus Disease 2019 Patients—A Retrospective Analysis. *Crit Care Explor* 2020; 2: e0229.
13. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M, COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. *Radiology* 2020; 296: E97–E104.
14. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, National Institutes of Health, National Heart, Lung and BIAN. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest* 2007; 132: 410–417.
15. Parke RL, Eastwood GM, McGuinness SP, George Institute for Global Health, Australian and New Zealand Intensive Care Society Clinical Trials Group. Oxygen therapy in non-intubated adult intensive care patients: a point prevalence study. *Crit Care Resusc* 2013; 15: 287–293.
16. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, Chang BP, Chau KH, Choi JJ, Gavin N, Goyal P, Mills AM, Patel AA, Romney M-LS, Safford MM, Schluger NW, Sengupta S, Sobieszczyk ME, Zucker JE, Asadourian PA, Bell FM, Boyd R, Cohen MF, Colquhoun MI, Colville LA, de Jonge JH, Dershowitz LB, Dey SA, Eiseman KA, Girvin ZP, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ* 2020; 369: m1996.
17. Mancilla-Galindo J, Vera-Zertuche JM, Navarro-Cruz AR, Segura-Badilla O, Reyes-Velázquez G, Tepepa-López FJ, Aguilar-Alonso P, Vidal-Mayo J de J, Kammar-García A. Development and validation of the patient history COVID-19 (PH-Covid19) scoring

system: a multivariable prediction model of death in Mexican patients with COVID-19. *Epidemiol Infect* 2020; 148: e286.

18. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web Site and R Package for Computing E-values. *Epidemiology* 2018; 29: e45–e47.
19. Prud'homme E, Trigui Y, Elharrar X, Gaune M, Loundou A, Lehingue S, Boyer A, Lefebvre L, Dols A, Chanez P, Papazian L, Forel J. Effect of Prone Positioning on the respiratory support of non-intubated patients with COVID-19 and acute hypoxemic respiratory failure: A retrospective matching cohort study. *Chest* American College of Chest Physicians; 2021; .
20. Belkhouja K, Alzahrani S, Al-Shalhoub N, Negm T, Darwish M, Pathan MW, Lone MM, Omer S, Al-Sharif H. Feasibility and efficacy of prone position combined with CPAP in COVID-19 patients with acute hypoxemic respiratory failure. *Intensive Care Med Exp* 2020; 8: 73.
21. Fazzini B, Fowler AJ, Zolfaghari P. Effectiveness of prone position in spontaneously breathing patients with COVID-19: A prospective cohort study. *J Intensive Care Soc* 2021; : 2–5.
22. Tonelli R, Pisani L, Tabbì L, Comellini V, Prediletto I, Fantini R, Marchioni A, Andrisani D, Gozzi F, Bruzzi G, Manicardi L, Busani S, Mussini C, Castaniere I, Bassi I, Carpano M, Tagariello F, Corsi G, d'Amico R, Girardis M, Nava S, Clini E. Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: A retrospective multicenter cohort study. *Pulmonology* Sociedade Portuguesa de Pneumologia; 2021; .
23. Alsharif H, Belkhouja K. 267: Feasibility and Efficacy of Prone Position Combined With CPAP in COVID-19 Patients With AHRF. *Crit Care Med* 2021; 49.
24. Barker J, Pan D, Koeckerling D, Baldwin AJ, West R. Effect of serial awake prone positioning on oxygenation in patients admitted to intensive care with COVID-19. *Postgrad Med J* 2021; : postgradmedj-2020-139631.
25. Mancilla-Galindo J, Kammar-García A, Martínez-Esteban A, Meza-Comparán A-K, Mancilla-Ramírez J, Galindo-Sevilla N. COVID-19 patients with increasing age experience differential time to initial medical care and severity of symptoms. *Cambridge Open Engag* 2021; : 10.33774/coe-2021-sjbcf.

26. Johnson SA, Horton DJ, Fuller MJ, Yee J, Aliyev N, Boltax JP, Chambers JH, Lanspa MJ. Patient-Directed Prone Positioning in Awake Patients with COVID-19 Requiring Hospitalization (PAPR). *Ann Am Thorac Soc* 2021; 0: 2–11.
27. Jayakumar D, Ramachandran, DNB P, Rabindrarajan, DNB E, Vijayaraghavan, MD BKT, Ramakrishnan, AB N, Venkataraman, AB R. Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection—A Multicenter Feasibility Randomized Controlled Trial. *J Intensive Care Med* 2021; .
28. Fowler Z, Moeller E, Roa L, Castañeda-Alcántara ID, Uribe-Leitz T, Meara JG, Cervantes-Trejo A. Projected impact of COVID-19 mitigation strategies on hospital services in the Mexico City Metropolitan Area. Lazzeri C, editor. *PLoS One* 2020; 15: e0241954.
29. Touchon F, Trigui Y, Prud'homme E, Lefebvre L, Giraud A, Dols A, Martinez S, Bernardi M, Begne C, Granier P, Chanez P, Forel J, Papazian L, Elharrar X. Awake prone positioning for hypoxaemic respiratory failure: past, COVID-19 and perspectives. *Eur Respir Rev* 2021; 30: 210022.
30. Guérin C. Prone Positioning. In: Chiumello D, editor. *Acute Respir Distress Syndr* Cham: Springer International Publishing; 2017. p. 73–84.
31. Bryan AC. Comments of a Devil's Advocate. *Am Rev Respir Dis* 1974; 110: 143–144.
32. Elharrar X, Trigui Y, Dols A-M, Touchon F, Martinez S, Prud'homme E, Papazian L. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. *JAMA* 2020; 323: 2336.
33. Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, Zangrillo A. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. *JAMA* 2020; 323: 2338.
34. Telias I, Katira BH, Brochard L. Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19? *JAMA* 2020; 323: 2265.
35. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, Scala R, Malerba M, Carlucci A, Negri EA, Spoladore G, Arcaro G, Tillio PA, Lastoria C, Schifino G, Tabbì L, Guidelli L, Guaraldi G, Ranieri VM, Clini E, Nava S. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related

pneumonia. *Eur Respir J* 2020; 56: 2002130.

36. Taylor SP, Bundy H, Smith WM, Skavroneck S, Taylor B, Kowalkowski MA. Awake-Prone Positioning Strategy for Non-Intubated Hypoxic Patients with COVID-19: A Pilot Trial with Embedded Implementation Evaluation. *Ann Am Thorac Soc* 2020; : AnnalsATS.202009-1164OC.
37. Project COVID-19 Open Access. Living Evidence on COVID-19 [Internet]. 2020.Available from: https://ispmbern.github.io/covid-19/living-review/.

Table 1 Demographic and clinical characteristics at hospital admission and outcomes of patients in the APRONOX cohort

Demographic variables	
Age, years	54.3 (14.2)
Age categories, n (%)	
<20	1 (0.1)
20-29	29 (3.5)
30-39	101 (12.2)
40-49	194 (23.5)
50-59	209 (25.3)
60-69	162 (19.6)
≥70, n	131 (15.8)
Sex	
Women, n (%)	227 (27.4)
Men, n (%)	600 (72.6)
Type of care	
ICU	142 (17.2)
Non-ICU	685 (82.8)
Clinical variables	
Diabetes, n (%)	315 (38.1)
Systemic arterial hypertension, n (%)	285 (34.5)
Obesity, n (%)	119 (14.4)
Heart disease, n (%)	17 (2.1)
Lung disease, n (%)	41 (5)
Cancer, n (%)	10 (1.2)
Liver disease, n (%)	5 (0.6)
Chronic kidney disease, n (%)	35 (4.2)
PH-Covid19 Mortality Risk Score**	8.7 (3.6)
Pharmacological treatments	
Hydroxychloroquine	237 (28.7)
Chloroquine	114 (13.8)
Azithromycin	549 (66.4)
Ceftriaxone	370 (44.7)
Lopinavir-Ritonavir	81 (9.8)
Enoxaparin	319 (38.6)
Tocilizumab	47 (5.7)
Oseltamivir	130 (15.7)
Steroid (systemic)	153 (18.5)
Ivermectin	57 (6.9)
Baseline SpO_2/FiO_2 ratio**	189.5 (81.6)

Awake prone, n (%)* **	505 (61.1)
Awake supine, n (%)	322 (38.9)
Supplemental oxygen delivery device	
Low-flow nasal cannula, n (%)	402 (48.6)
High-flow nasal cannula, n (%)	83 (10)
Non-rebreather mask, n (%)	342 (41.4)
Outcomes, n (%)	
Intubation, n (%)	249 (30.1)
Mortality, n (%)	220 (26.6)
Failure to the prone****, n (%)	119 (23.6)*

*Percentage calculated out of all awake prone-positioned patients.
**These variables were determined at hospital admission.
***Median time-to-initiation of prone: 15.5 (IQR:8-48) hours
****Defined as patients who were successfully managed in the awake prone position but required orotracheal intubation anytime during follow-up.
FiO_2: Inspired oxygen fraction; SpO_2: peripheral arterial oxygen saturation.

Table 2. Comparison of demographic and clinical characteristics at hospital admission and outcomes of patients in the awake prone and supine groups in both the unmatched and propensity score-matched cohorts.

	Unmatched			**Matched**		
	Awake supine (n = 322)	**Awake prone (n = 505)**	**p-value**	**Awake supine (n = 311)**	**Awake prone (n = 311)**	**p-value**
Demographic variables						
Age, years	55.8 (14.5)	53.4 (13.9)	0.02	55.6 (14.5)	54.9 (14.1)	0.5
Women	92 (28.6)	135 (26.7)	0.6	86 (27.7)	79 (25.4)	0.5
Men	230 (71.4)	370 (73.3)		225 (72.3)	232 (74.6)	
Diagnostic criterion						
RT-PCR positive	294 (91.3)	440 (87.1)	0.06	282 (90.7)	289 (92.9)	0.3
CO-RADS 3-5*	28 (8.7)	65 (12.9)		29 (9.3)	22 (7.1)	
Type of care						
ICU	75 (23.3)	67 (13.3)	<0.0001	73 (23.5)	60 (19.3)	0.2
Non-ICU	247 (76.7)	438 (86.7)		238 (76.5)	251 (80.7)	
Clinical variables						
Diabetes	121 (37.6)	194 (38.4)	0.8	117 (37.6)	119 (38.3)	0.9
Systemic arterial hypertension	119 (37)	166 (32.9)	0.2	114 (36.7)	102 (32.8)	0.4
Obesity	45 (14)	74 (14.7)	0.8	45 (14.5)	39 (12.5)	0.6
Heart disease	4 (1.2)	13 (2.6)	0.2	4 (1.3)	8 (2.6)	0.4
Lung disease	17 (5.3)	24 (4.8)	0.7	16 (5.1)	17 (5.5)	0.9
Cancer	8 (2.5)	2 (0.4)	0.02	7 (2.3)	1 (0.3)	0.07
Liver disease	3 (0.9)	2 (0.4)	0.4	3 (1.0)	1 (0.3)	0.6
Chronic kidney disease	12 (3.7)	23 (4.6)	0.6	12 (3.9)	13 (4.2)	0.8
SpO_2/FiO_2 ratio**	201.1 (89.8)	182.4 (75.4)	0.002	201.1 (88.8)	195.9 (77.9)	0.4
PH-Covid19 Mortality Risk Score**	8.9 (3.6)	8.6 (3.5)	0.1	8.9 (3.6)	8.9 (3.5)	0.8
Pharmacological treatments						

Hydroxychloroquine	122 (37.9)	115 (22.8)	<0.0001	119 (38.3)	93 (29.9)	0.03
Chloroquine	49 (15.2)	65 (12.9)	0.3	48 (15.4)	50 (16.1)	0.9
Azithromycin	220 (68.3)	329 (65.1)	0.4	214 (68.8)	224 (72.0)	0.4
Ceftriaxone	139 (43.2)	231 (45.7)	0.5	133 (42.8)	130 (41.8)	0.8
Lopinavir-Ritonavir	44 (13.7)	37 (7.3)	0.003	42 (13.5)	26 (8.4)	0.04
Enoxaparin	96 (29.8)	223 (44.2)	<0.0001	90 (28.9)	82 (26.4)	0.5
Tocilizumab	22 (6.8)	25 (5.0)	0.3	21 (6.8)	20 (6.4)	0.9
Oseltamivir	69 (21.4)	61 (12.1)	<0.0001	67 (21.5)	38 (12.2)	0.002
Steroid (systemic)	69 (21.4)	84 (16.6)	0.08	67 (21.5)	74 (23.8)	0.5
Ivermectin	15 (4.7)	42 (8.3)	0.04	15 (4.8)	34 (10.9)	0.005
Supplemental oxygen delivery device**						
Low-flow nasal cannula	149 (46.3)	253 (50.1)	0.3	145 (46.6)	145 (46.6)	0.9
High-flow nasal cannula	22 (6.8)	61 (12.1)	0.01	22 (7.1)	33 (10.6)	0.1
Non-rebreather mask	151 (46.9)	190 (37.6)	0.008	144 (46.3)	132 (42.4)	0.3
Outcomes						
Intubation	130 (40.4)	119 (23.6)	<0.0001	123 (39.5)	77 (24.8)	<0.0001
Mortality	120 (37.3)	100 (19.8)	<0.0001	113 (36.3)	66 (21.2)	<0.0001

* RT-PCR was not performed in these patients.

** These variables were determined during hospital admission.

CO-RADS: COVID-19 Reporting and Data System; FiO_2: Inspired oxygen fraction; RT-PCR: Reverse transcriptase polymerase chain reaction; SpO_2: peripheral arterial oxygen saturation.

Table 3. Results of univariable logistic regression analyses of orotracheal intubation risk in patients with awake prone positioning.

	Unmatched		**Matched**	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Awake prone	0.46 (0.34-0.62)	<0.0001	0.50 (0.36-0.71)	<0.0001
Demographic variables				
Age, years	1.02 (1.004-1.03)	0.007	1.01 (1.002-1.03)	0.02
Sex (Men)	0.91 (0.70-1.37)	0.9	1.12 (0.77-1.65)	0.6
Type of care				
ICU	0.63 (0.41-0.96)	0.03	0.61 (0.39-0.94)	0.03
Clinical variables				
Diabetes	1.70 (1.26-2.30)	0.001	1.80 (1.28-2.54)	0.001
Systemic arterial hypertension	1.61 (1.19-2.19)	0.002	1.40 (0.99-1.99)	0.06
Obesity	2.01 (1.35-2.99)	0.001	2.69 (1.69-4.29)	<0.0001
Heart disease	3.41 (1.28-9.07)	0.01	4.35 (1.29-14.64)	0.02
Lung disease	1.36 (0.71-2.62)	0.4	1.39 (0.68-2.87)	0.4
Cancer	9.56 (2.02-45.35)	0.004	15.27 (1.87-124.96)	0.01
Liver disease	3.51 (0.58-21.15)	0.2	2.12 (0.29-15.17)	0.5
Chronic kidney disease	1.39 (0.69-2.81)	0.4	1.43 (0.63-3.24)	0.4
Baseline SpO_2/FiO_2 ratio				
<100	5.69 (3.48-9.31)	<0.0001	7.44 (4.18-13.24)	<0.0001
100-199	3.69 (2.57-5.29)	<0.0001	4.26 (2.86-6.33)	<0.0001
≥200	Reference		Reference	
Pharmacological treatments				
Hydroxychloroquine	1.08 (0.78-1.49)	0.7	1.13 (0.79-1.61)	0.5
Chloroquine	0.81 (0.52-1.26)	0.3	0.77 (0.48-1.25)	0.3
Azithromycin	1.05 (0.76-1.43)	0.8	0.94 (0.65-1.35)	0.7
Ceftriaxone	0.82 (0.61-1.11)	0.2	0.72 (0.51-1.02)	0.07
Lopinavir-Ritonavir	0.45 (0.25-0.83)	0.01	0.51 (0.28-0.95)	0.03
Enoxaparin	0.84 (0.62-1.15)	0.3	0.88 (0.61-1.29)	0.5
Tocilizumab	0.53 (0.25-1.12)	0.09	0.58 (0.27-1.23)	0.2
Oseltamivir	0.79 (0.52-1.21)	0.3	0.82 (0.52-1.29)	0.4
Steroid (systemic)	0.53 (0.35-0.81)	0.004	0.47 (0.30-0.74)	0.001
Ivermectin	0.89 (0.49-1.64)	0.7	1.03 (0.55-1.91)	0.9
Supplemental oxygen delivery device				
Low-flow nasal cannula	0.27 (0.19-0.38)	<0.0001	0.28 (0.19-0.41)	<0.0001
High-flow nasal cannula	0.77 (0.46-1.29)	0.3	0.77 (0.42-1.44)	0.4

Non-rebreather mask	3.94 (2.88-5.39)	<0.0001	3.75 (2.63-5.35)	<0.0001

95%CI: 95% confidence interval; FiO_2: Inspired oxygen fraction; ICU: Intensive Care Unit; OR: odds ratio; SpO_2: peripheral arterial oxygen saturation.

Table 4. Results of multivariable logistic regression analyses of orotracheal intubation risk in patients with awake prone positioning, adjusted by confounding variables.

	Unmatched*		**Matched****	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Awake prone	0.35 (0.24-0.52)	<0.0001	0.41 (0.27-0.62)	<0.0001
Age, years	1.01 (0.99-1.02)	0.4	1.01 (0.99-1.02)	0.6
Sex (Men)	1.15 (0.77-1.72)	0.5	1.26 (0.79-2.02)	0.3
ICU	0.52 (0.31-0.89)	0.01	0.50 (0.29-0.86)	0.01
Diabetes	1.50 (1.03-2.19)	0.03	1.66 (1.08-2.55)	0.02
Systemic arterial hypertension	1.23 (0.84-1.81)	0.3	0.95 (0.61-1.48)	0.8
Obesity	1.39 (0.86-2.28)	0.18	1.47 (0.81-2.65)	0.2
Heart disease	6.82 (2.13-21.78)	0.001	13.79 (3.31-57.61)	<0.0001
Cancer	7.41 (0.96-57.39)	0.06	12.58 (0.81-196.11)	0.07
Chronic kidney disease	1.11 (0.46-2.69)	0.8	1.29 (0.43-3.92)	0.7
Ceftriaxone	0.91 (0.63-1.31)	0.6	0.82 (0.53-1.25)	0.4
Enoxaparin	0.79 (0.54-1.16)	0.2	0.85 (0.53-1.36)	0.5
Tocilizumab	0.56 (0.22-1.38)	0.2	0.58 (0.22-1.53)	0.3
Oseltamivir	0.59 (0.35-1.02)	0.06	0.68 (0.37-1.24)	0.2
Steroid (systemic)	0.62 (0.38-1.03)	0.06	0.57 (0.34-0.97)	0.04
Baseline SpO_2/FiO_2 ratio	0.99 (0.98-0.99)	<0.0001	0.99 (0.98-0.99)	<0.0001
Low-flow nasal cannula	-	-	-	-
High-flow nasal cannula	0.99 (0.53-1.88)	0.9	1.19 (0.51-2.45)	0.8
Non-rebreather mask	2.70 (1.82-4.01)	<0.0001	2.49 (1.56-3.99)	<0.0001

*Goodness of fit: Hosmer-Lemeshow X^2=2.79, p=0.9; AUC=0.79, 95%CI:0.77-0.83, p<0.0001.

**Goodness of fit: Hosmer-Lemeshow X^2=10.95, p=0.2; AUC=0.82, 95%CI:0.79-0.85, p<0.0001.

95%CI: 95% confidence interval; AUC: area under de curve; FiO_2: Inspired oxygen fraction; OR: odds ratio; SpO_2: peripheral arterial oxygen saturation.

Figure 1. Flow diagram of participants included in the APRONOX cohort.

Figure 2. Risk of intubation amongst patients in the awake prone positioning group, according to age (A) and baseline SpO_2/FiO_2 (B)*.

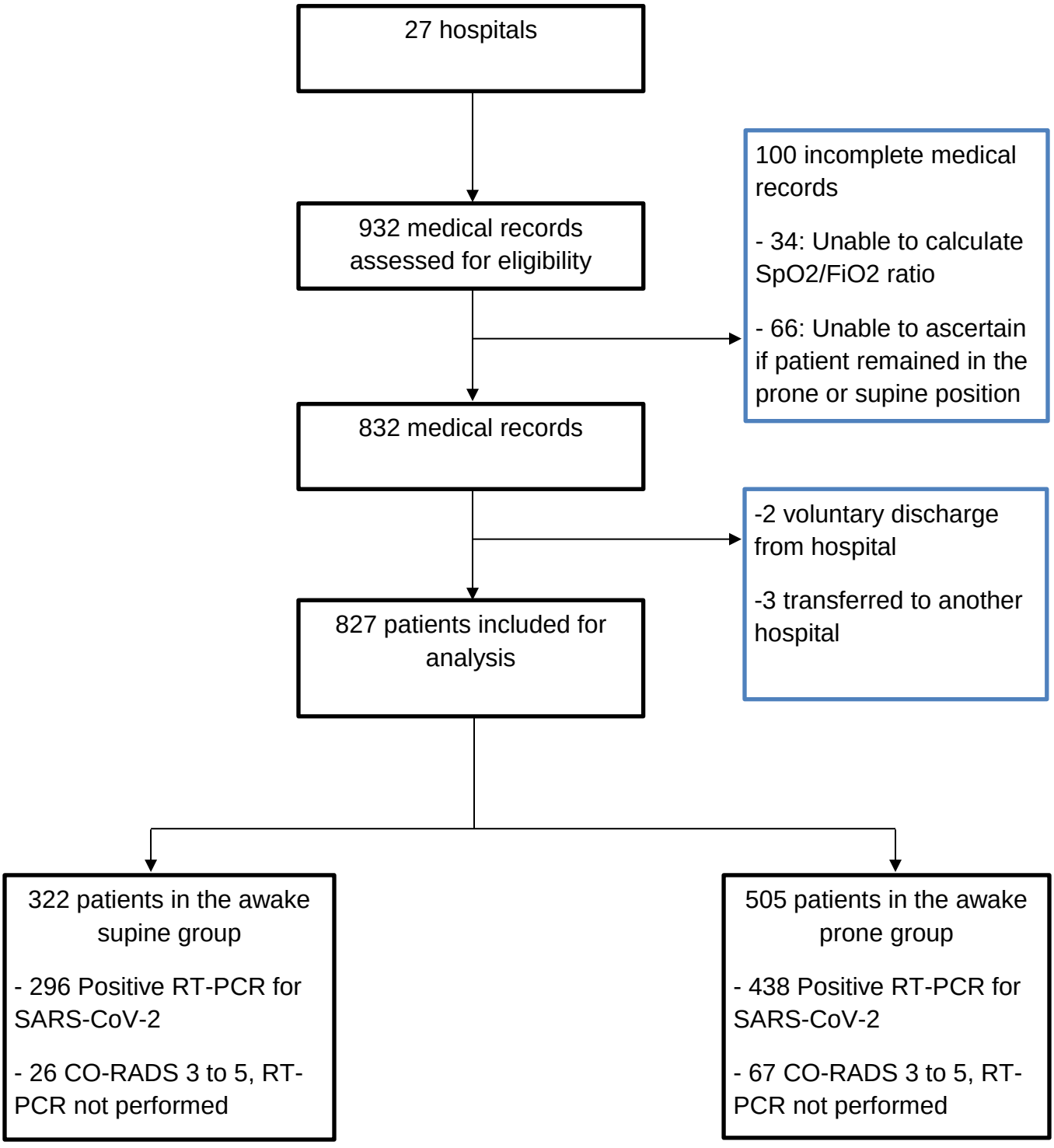
*For this analysis, baseline SpO_2/FiO_2 was studied as continuous variable, therefore, the range of odds ratios are different from others in the manuscript which consider baseline SpO_2/FiO_2 as a categorical variable and use a category of reference to compare other categories.

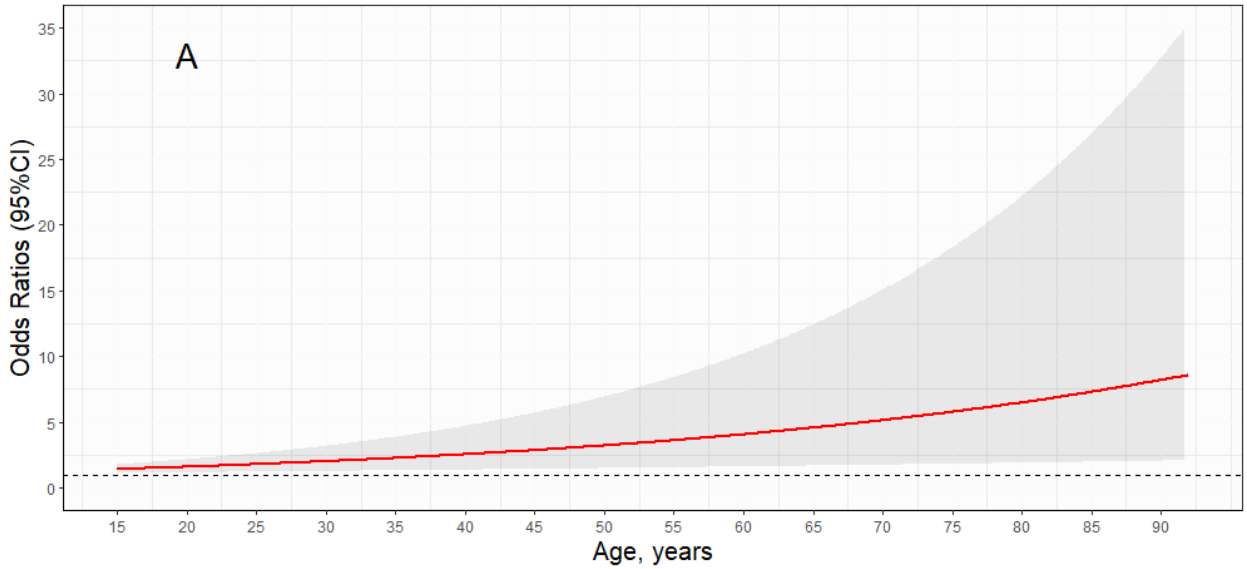
95%CI: 95% confidence intervals; FiO2: Inspired oxygen fraction; SpO2: peripheral arterial oxygen saturation

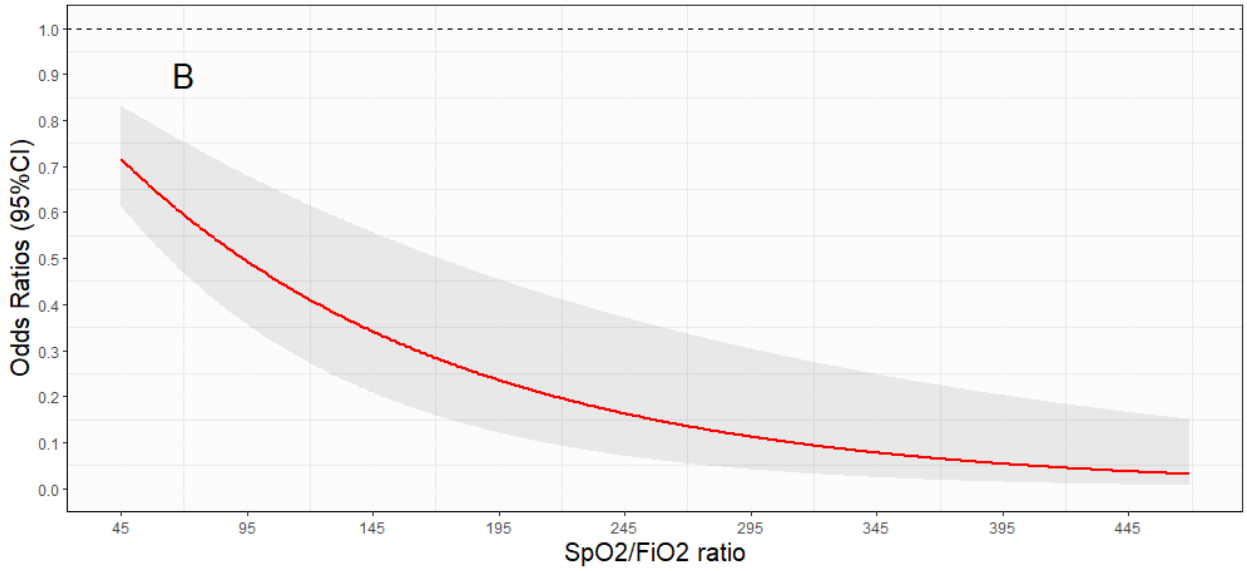
Figure 3. Forest plot of overall risk of orotracheal intubation in studies retrieved by the search strategy and the APRONOX cohort.

*Only patients in the propensity score-matched cohorts were included for the APRONOX study.

95%CI: 95% confidence intervals; M-H: Mantel-Haenszel


27 hospitals
932 medical records assessed for eligibility
100 incomplete medical records
- 34: Unable to calculate SpO2/FiO2 ratio
- 66: Unable to ascertain if patient remained in the prone or supine position
832 medical records
-2 voluntary discharge from hospital
-3 transferred to another hospital
827 patients included for analysis
322 patients in the awake supine group
- 296 Positive RT-PCR for SARS-CoV-2
- 26 CO-RADS 3 to 5, RT-PCR not performed
505 patients in the awake prone group
- 438 Positive RT-PCR for SARS-CoV-2
- 67 CO-RADS 3 to 5, RT-PCR not performed

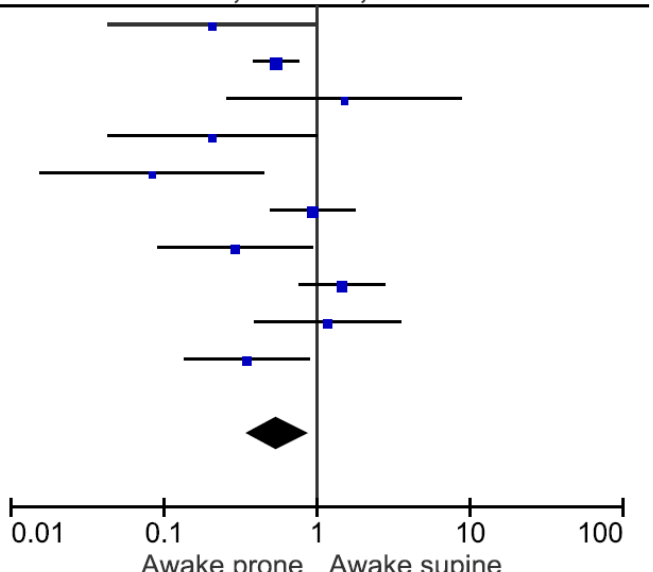

A
Odds Ratios (95%CI)
0
5
10
15
20
25
30
35
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Age, years


B
Odds Ratios (95%CI)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
45
95
145
195
245
295
345
395
445
SpO2/FiO2 ratio

Study or Subgroup	Awake prone Events	Total	Awake supine Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alsharif, et al. 2021	2	31	12	48	6.2%	0.21 [0.04, 1.00]
APRONOX Group*	81	311	123	311	17.9%	0.54 [0.38, 0.76]
Barker, et al. 2021	6	10	5	10	5.3%	1.50 [0.26, 8.82]
Belkhouja, et al. 2021	2	31	12	48	6.2%	0.21 [0.04, 1.00]
Fazzini, et al. 2021	10	34	10	12	5.7%	0.08 [0.02, 0.45]
Ferando, et al. 2020	22	55	60	144	14.6%	0.93 [0.50, 1.76]
Jagan, et al. 2020	4	40	18	65	9.0%	0.29 [0.09, 0.93]
Padrão, et al. 2020	33	57	53	109	14.4%	1.45 [0.76, 2.77]
Prud´homme, et al. 2021	8	48	7	48	9.6%	1.17 [0.39, 3.53]
Tonelli, et al. 2021	7	38	30	76	11.1%	0.35 [0.14, 0.89]
Total (95% CI)		**655**		**871**	**100.0%**	**0.55 [0.34, 0.89]**
Total events	175		330			

Heterogeneity: Tau² = 0.30; Chi² = 23.50, df = 9 (P = 0.005); I² = 62%

Test for overall effect: Z = 2.46 (P = 0.01)



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Appendix 2. List of hospitals participating in the study and physicians in charge

	Name of hospital	**Institution**	**State**	**Country**
1	Hospital de Beneficencia Española	Private	San Luis Potosi	Mexico
2	Centro Medico Luis Adolfo López Mateos	ISSSTE	Mexico City	Mexico
3	Centro Médico Nacional 20 de Noviembre	ISSSTE	Mexico City	Mexico
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8	Hospital General Dr. Enrique Cabrera	SSA	Mexico City	Mexico
9	Hospital Estatal de Atención COVID 19	SSA	Guanajuato	Mexico
10	Hospital Materno de Celaya	SSA	Guanajuato	Mexico
11	Hospital Juárez de México	SSA	Mexico City	Mexico
12	Hospital Santo Tomas	Private	Querétaro	Mexico
13	Hospital General Tuxtepec	SSA	Oaxaca	Mexico
14	Hospital SEDNA	Private	Mexico City	Mexico
15	Hospital General San Juan del Rio	SSA	Querétaro	Mexico
16	Hospital General de Zona No. 48 San Pedro Xalpa	IMSS	Mexico City	Mexico
17	Hospital General Fernando Quiroz Gutiérrez	ISSSTE	Mexico City	Mexico
18	Hospital General Tláhuac	SSA	Mexico City	Mexico
19	Hospital General SESEQ	SSA	Querétaro	Mexico
20	Hospital General Regional No. 1 Vicente Guerrero	IMSS	Guerrero	Mexico
21	Hospital General de Zona No. 1	IMSS	Mexico City	Mexico
22	Hospital General de Zona No. 71	IMSS	Veracruz	Mexico
23	Hospital General Regional No. 251	IMSS	Mexico City	Mexico
24	Hospital Manuel Ygnacio Monteros	IESS	Loja	Ecuador
25	Unidad Médica de Alta Especialidad “Adolfo Ruiz Cortines”	IMSS	Veracruz	Mexico
26	Hospital Comunitario de Ocuituco	SSA	Morelos	Mexico
27	Hospital Rural No. 1 San Felipe Ecatepec	IMSS	Chiapas	Mexico

* IMMS: Mexican Social Security Institute

* ISSSTE: Government Workers’ Social Security and Services Institute

* SSA: Secretariat of Health (*Secretaría de Salud*)

* IESS: Ecuadorian Social Security Institute

Appendix 3. Chest CT assessment using the CO-RADS* categorical assessments scheme to evaluate suspicion of COVID-19

Category	Level of COVID-19 suspicion	Chest CT findings
CO-RADS 1	Very low	Normal or non-infectious abnormalities
CO-RADS 2	Low	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indeterminate	Unclear whether COVID-19 is present
CO-RADS 4	High	Abnormalities suspicious for COVID-19
CO-RADS 5	Very high	Typical COVID-19
CO-RADS 6	Proven	RT-PCR + for SARS-CoV-2

*CO-RADS: COVID-19 Reporting and Data System.

Appendix 4. Calculation of FiO_2 based on type of supplemental oxygen delivery device used.

Oxygen therapy	Flow (L/min)	*FiO2 (%)
Nasal cannula	1 2 3 4 5 6	24 % 28 % 32 % 36 % 40 % 44 %
Non-rebreather mask	10-15	80-95 %
High-flow nasal cannula	Flows up to 60	*Up to 100%

* FiO_2: Fraction of inspired oxygen.

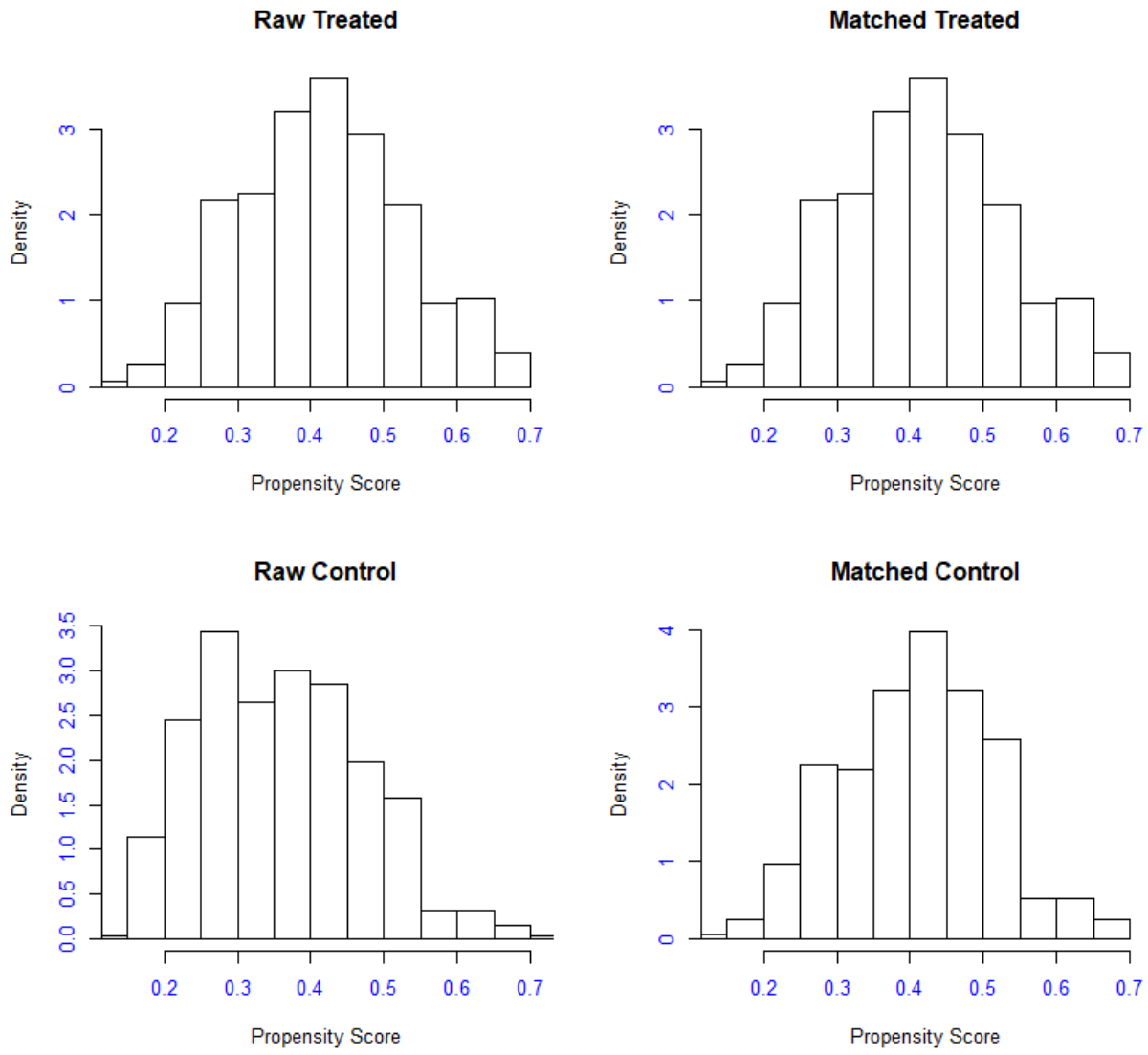
Appendix 5. Sample size calculation.

Sample size was calculated to determine the difference between two independent proportions with the formula:

$$\text{Subjects per group} = \frac{[Z_{\propto}\sqrt{[2P\ (1-P)]} + Z_{\beta}\sqrt{[P_1(1-P_1) + P_2\ (1-P_2)]}]^2}{(P_1 - P_2)^2}$$

Where $Z_{\propto}$ at 95% (two-sided) was 1.96; Z_{β} at 90%, was 1.282; P_1 was 0.23 for the number of patients with oxygen therapy who were intubated during in-hospital stay, according to Argenziano MG, et al. 2020. Considering a clinically significant reduction of 1'% in the incidence of orotracheal intubation, P_2 was estimated to be 0.13 for the number of patients in prone position intubated during in-hospital stay. P was the pondered measure of the two proportions, being equal to 0.18. Hence, the calculated sample size was 309 subjects per group. Calculations were performed with the G*Power v.3.1.9.7 software.

Appendix 6. Density functions before and after propensity score matching of patients in the awake prone (treated) and awake supine (control) cohorts.



Appendix 7. Search strategy

We searched MEDLINE and EMBASE through OVID, PubMed, BioRxiv and MedRxiv for research on COVID-19 published until 8 June 2021. We used the publicly available COVID-19 Living Evidence on COVID-19 dataset [32]. Search terms for the search strategy were: (‘severe acute respiratory syndrome coronavirus 2’ [supplementary concept] OR ‘COVID-19’ [supplementary concept] OR ‘coronavirus’ OR ‘HCoV’ OR ‘nCoV’ OR ‘2019 nCoV’ OR ‘covid’ OR ‘covid19’ OR ‘severe acute respiratory syndrome coronavirus 2’ OR ‘SARS-CoV-2’ OR ‘SARS-CoV 2’ OR ‘SARS coronavirus 2’) AND (prone) AND (awake). The following filters were applied for study design: case series, case-control study, cohort study, trial, other, or unclassified. Studies were chosen regardless of language, provided an abstract in English was available, and if the study included and clearly differentiated patients undergoing awake prone positioning from those in awake supine position, as well as intubation rates for both groups.

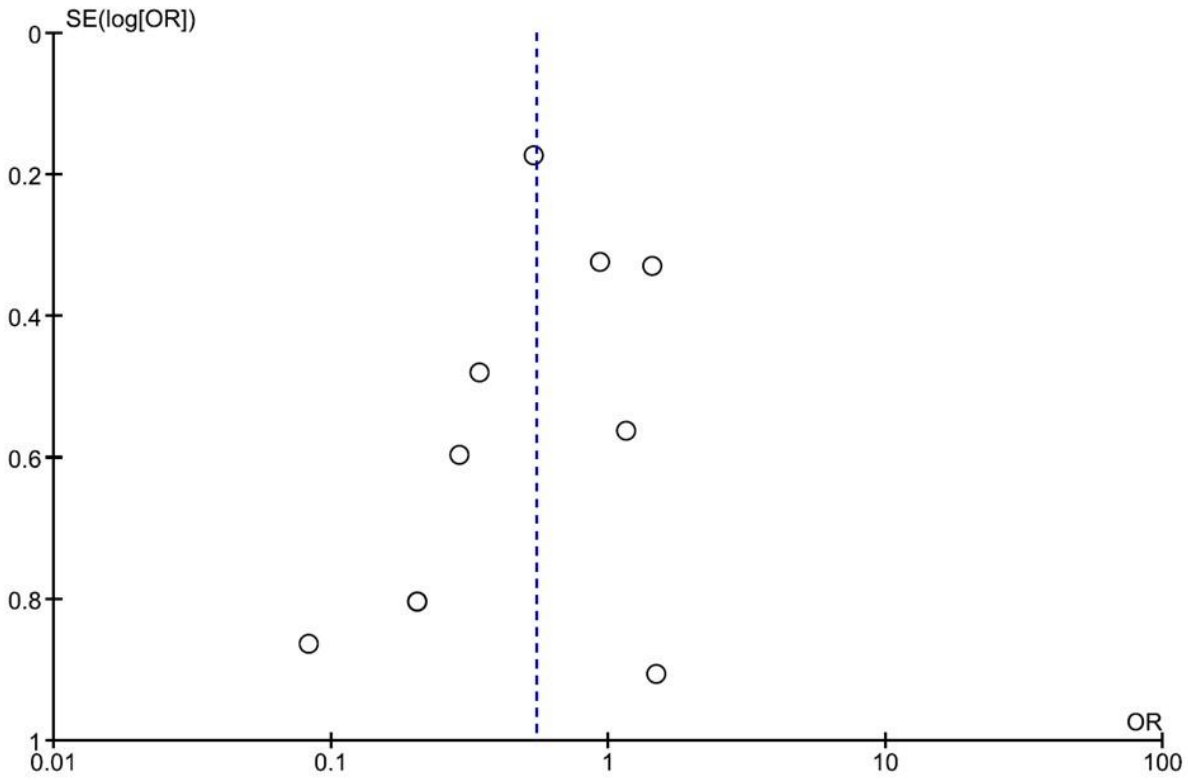
Appendix 8. Orotracheal intubation risk and mortality risk in patients with a positive SARS-CoV-2 test (excluding patients in whom diagnostic testing was not performed) managed with awake prone positioning, adjusted for confounding variables, in both the unmatched and the propensity-score matched cohort.

	Unmatched			**Matched**		
	OR (95% CI)	**p value**	**E-Value**	**OR (95% CI)**	**p value**	**E-Value**
Model for intubation[a]						
Awake prone	0.18 (0.12-0.28)	<0.0001	3.19	0.20 (0.12-0.32)	<0.0001	2.93
Model for mortality[b]						
Awake prone	0.23 (0.15-0.35)	<0.0001	2.77	0.23 (0.14-0.37)	<0.0001	2.67

a: Model adjusted for age, sex [men], ICU attention, diabetes, systemic arterial hypertension, obesity, heart disease, cancer, chronic kidney disease, pre-prone SpO_2/FiO_2 ratio, supplemental oxygen delivery device, ceftriaxone, enoxaparin, tocilizumab, oseltamivir, and systemic steroids. Goodness of fit: Hosmer-Lemeshow X^2=11.6, p=0.2 AUC=0.84, 95%CI:0.81-0.88, p<0.0001

b: Model adjusted for age, sex [men], ICU attention, diabetes, systemic arterial hypertension, obesity, heart disease, pre-prone SpO_2/FiO_2 ratio, supplemental oxygen delivery device, ceftriaxone, enoxaparin, tocilizumab, oseltamivir, and systemic steroids. Goodness of fit: Hosmer-Lemeshow X^2=12.7, p=0.1 AUC=0.80, 95%CI:0.77-0.84, p<0.0001

Appendix 9. Funnel Plot



Abbreviations

PaO_2: partial arterial pressure of oxygen, SpO_2: peripheral arterial oxygen saturation, PaO_2/FiO_2: arterial partial pressure of oxygen /fraction of inspired oxygen, $PaCO_2$: arterial partial pressure of carbon dioxide, RR: respiratory rate, NIV: non-invasive ventilation, HFNC: high-flow nasal cannula, ARDS: Acute respiratory distress syndrome, COVID-19: coronavirus disease, STROBE: Strengthening the Reporting of Observational studies in Epidemiology, AP: awake prone, CO-RADS: COVID-19 Reporting and Data System, IQR: interquartile range, SD: standard deviation, OR: odds ratio, CI: confidence interval, Ppl: pleural pressure, TPP: Transpulmonary pressure, V/Q: ventilation-perfusion.