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

Orlando R. Perez-Nieto [1], Diego Escarraman-Martinez [2], Manuel A. Guerrero-Gutierrez [3], Eder I. Zamarron-Lopez [4], Javier Mancilla-Galindo [5,6], Ashuin Kammar-García [7], Miguel A. Martinez-Camacho [8], Ernesto Deloya-Tomás [1], Jesús S. Sanchez-Díaz [9], Luis A. Macías-García [10], Raúl Soriano-Orozco [11], Gabriel Cruz-Sánchez [12], José D. Salmeron-Gonzalez [13], Marco A. Toledo-Rivera [14], Ivette Mata-Maqueda [15], Luis A. Morgado-Villaseñor [16], Jenner J. Martinez-Mazariegos [17], Raymundo Flores Ramirez [18], Josue L. Medina-Estrada [19] and Silvio A. Ñamendys-Silva [3,20] on behalf of the APRONOX Group [21]

[1]Intensive Care Unit, Hospital General San Juan del Rio, Querétaro, Mexico. [2]Dept of Anaesthesia, Hospital de Especialidades Centro Médico Nacional "LaRaza", Mexico City, Mexico. [3]Dept of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico City, Mexico. [4]Intensive Care Unit, Hospital CEMAIN Tampico, Tamaulipas, Mexico. [5]Unidad de Investigación UNAM-INC, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico. [6]Respiratory Medicine, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico. [7]Emergency Dept, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico. [8]Intensive Care Unit, Hospital General de México, Mexico City, Mexico. [9]Intensive Care Unit, Hospital de Alta Especialidad IMSS "Adolfo Ruiz Cortines" Veracruz, Veracruz, Mexico. [10]Intensive Care Unit, Hospital Regional ISSSTE "Fernando Quiroz Gutiérrez", Mexico City, Mexico. [11]Intensive Care Unit, Hospital de Alta Especialidad T1 IMSS, León, Mexico. [12]Intensive Care Unit, Clínica Hospital Mérida ISSSTE, Yucatán, Mexico. [13]Intensive Care Unit, Hospital General "Miguel Silva", Morelia, Mexico. [14]Intensive Care Unit, Hospital SEDNA, Mexico City, Mexico. [15]Secretaría de Salud del Estado de Querétaro, Ethics and Research Committee, Mexico. [16]Intensive Care Unit, Hospital General de Zona IMSS No. 15 Reynosa, Tamaulipas, Mexico. [17]Intensive Care Unit, Hospital Vida Mejor ISSSTECH Tuxtla Gutiérrez, Chiapas, Mexico. [18]Intensive Care Unit, Hospital de Especialidades "5 de Mayo" ISSSTEP, Puebla, Mexico. [19]Intensive Care Unit, Hospital Regional No. 1 IMSS "Vicente Guerrero", Acapulco, Mexico. [20]Division of Pulmonary, Anaesthesia and Critical Care Medicine, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico. [21]A complete list of members of the APRONOX Group is provided in appendix 1 in the supplementary material.

Corresponding author: Orlando Perez-Nieto (orlando_rpn@hotmail.com)

Shareable abstract (@ERSpublications)
**Awake prone positioning in nonintubated hospitalised patients with COVID-19 was associated with a lower risk of intubation and mortality in the APRONOX multicentre observational study** https://bit.ly/3Atb92Z

**Cite this article as:** Perez-Nieto OR, Escarraman-Martinez D, Guerrero-Gutierrez MA, *et al*. Awake prone positioning and oxygen therapy in patients with COVID-19: the APRONOX study. *Eur Respir J* 2022; 59: 2100265 [DOI: 10.1183/13993003.00265-2021].



This article has an editorial commentary: https://doi.org/10.1183/13993003.02416-2021

Received: 28 Jan 2021
Accepted: 26 June 2021

## Abstract

***Background*** The awake prone positioning strategy for patients with acute respiratory distress syndrome is a safe, simple and cost-effective technique used to improve hypoxaemia. We aimed to evaluate intubation and mortality risk in patients with coronavirus disease 2019 (COVID-19) who underwent awake prone positioning during hospitalisation.

***Methods*** In this retrospective, multicentre observational study conducted between 1 May 2020 and 12 June 2020 in 27 hospitals in Mexico and Ecuador, nonintubated patients with COVID-19 managed with awake prone or awake 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.

***Results*** 827 nonintubated patients with COVID-19 in the awake prone (n=505) and awake supine (n=322) groups were included for analysis. Fewer patients in the awake prone group required endotracheal intubation (23.6% *versus* 40.4%) or died (19.8% *versus* 37.3%). Awake prone positioning was a protective factor for intubation even after multivariable adjustment (OR 0.35, 95% CI 0.24–0.52; p<0.0001, E=2.12), which prevailed after propensity score analysis (OR 0.41, 95% CI 0.27–0.62; p<0.0001, E=1.86) and mortality (adjusted OR 0.38, 95% CI 0.26–0.55; p<0.0001, E=2.03). The main variables associated with intubation among awake prone patients were increasing age, lower baseline peripheral arterial oxygen saturation/inspiratory oxygen fraction ratio ($P_{aO_2}/F_{IO_2}$) and management with a nonrebreather mask.

***Conclusions*** Awake prone positioning in hospitalised nonintubated patients with COVID-19 is associated with a lower risk of intubation and mortality.

## Introduction

The awake prone position in nonintubated patients with acute hypoxaemic respiratory failure results in improved oxygenation, as demonstrated by an increase in arterial oxygen tension ($P_{aO_2}$), peripheral arterial oxygen saturation ($S_{pO_2}$) and $P_{aO_2}$/inspiratory oxygen fraction ratio ($P_{aO_2}/F_{IO_2}$), without deleterious effects on the level of arterial carbon dioxide tension ($P_{aCO_2}$), pH, respiratory rate or haemodynamics [1, 2]. The physiological mechanism by which prone positioning is useful for acute respiratory distress syndrome (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 2019 (COVID-19) pandemic has unleashed a high global demand for respiratory support, a reason why awake prone positioning in nonintubated patients has become popular and clinical interest has rapidly increased. Awake prone positioning combined with noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) in patients with moderate to severe ARDS [4, 5] and COVID-19 [6–8] has been shown to be safe and may prevent intubation. One further advantage of the awake prone position is that it allows patients to interact with their family during hospitalisation, thereby favouring humanisation of healthcare [9]. Nonetheless, few observational studies have evaluated awake prone positioning against control groups (*i.e.* awake supine patients managed with NIV or HFNC), with conflicting findings [10–12]. Thus, the utility of awake prone positioning 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 awake prone positioning 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 in the supplementary material) from the emergency department. The study was approved by the Health Services Research Committee of the State of Querétaro (1178/SESEQ-HGSJR/08-05-20) and all other participating centres. This study was prospectively registered at ClinicalTrials.gov with identifier number NCT04407468. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) 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 was 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 de-identified by assigning them a code. All patients admitted to the emergency department during the period between 1 May 2020 and 12 June 2020 who met the following criteria were considered for inclusion in the study: 1) age $\geqslant$18 years, 2) positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or imaging study compatible with COVID-19, 3) clinical record available in accordance with the official Mexican standard (NOM-004-SSA3-2012) or equivalent in Ecuador, 4) room air $S_{pO_2}$ <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 reverse transcriptase-PCR (RT-PCR) test for SARS-CoV-2 from a respiratory tract sample or 2) chest computed tomography scan with a COVID-19 Reporting and Data System (CO-RADS) score 3–5 (appendix 3 in the supplementary material) [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 $S_{pO_2}/F_{IO_2}$ or when unable to ascertain if the patient was managed in a prone or supine position).

Data recorded were demographic (age and sex) and clinical variables, including comorbidities (diabetes, systemic arterial hypertension, obesity, heart disease, lung disease, cancer, liver disease and chronic kidney disease), pre-prone $S_{pO_2}/F_{IO_2}$ ($S_{pO_2}/F_{IO_2}$ ratios of 235 and 315 correlate with $P_{aO_2}/F_{IO_2}$ ratios of 200 and 300, respectively) [14], post-prone $S_{pO_2}/F_{IO_2}$ (within 1 h after proning), time to initiation of prone positioning (defined as the time elapsed from hospital admission to first successful attempt in prone lasting ⩾2 h), total time in the awake prone position, type of care (emergency room, hospitalisation or intensive care unit (ICU)), medications, supplemental oxygen delivery device used, need for orotracheal intubation and lethal outcome. $F_{IO_2}$ was calculated based on the type of supplemental oxygen delivery device employed: low-flow nasal cannula (LFNC), HFNC or nonrebreather mask (appendix 4 in the supplementary material) [15].

### *Exposures and outcomes*

Awake, spontaneously breathing patients managed with noninvasive oxygen devices who were able to remain in the prone position for at least 2 h continuously were considered as patients in the awake prone 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 among patients in the awake prone group were also evaluated.

The decisions 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 LFNC, HFNC or a nonrebreather mask; other noninvasive 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 in the supplementary material). 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 awake prone or awake supine groups. Descriptive results are presented as mean with standard deviation or median (interquartile range (IQR)) for quantitative variables and frequencies (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 performed with the Chi-squared, Chi-squared of trend or Fisher's exact test. Baseline and post-awake prone positioning $S_{pO_2}/F_{IO_2}$ 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, presence of three or more comorbidities, baseline $S_{pO_2}/F_{IO_2}$, 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 in the supplementary material. 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 awake prone positioning. Variables included in the models were selected by the Enter method; adjustment variables were those which had $p<0.1$ in univariate analyses that have been reported to be associated with higher (or lower) risk for adverse events (age, sex (male), ICU attention, diabetes, systemic arterial hypertension, obesity, heart disease, cancer and chronic kidney disease), pre-prone $S_{pO_2}/F_{IO_2}$, 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 among patients who tolerated the awake prone position; the variables included in this model were selected with the Stepwise Forward method, including those with $p<0.1$ in the

final model. Odds ratios with their 95% confidence intervals were calculated. The goodness of fit of the final models was evaluated with the Hosmer–Lemeshow statistic and the discrimination of the model was determined by calculating the area under the curve (AUC). The risks of intubation among awake prone patients according to age and baseline $S_{pO_2}/F_{IO_2}$ were graphed through the smoothing spline method.

Subanalyses 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 who 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 awake prone positioning on the outcomes and drive them to a nonsignificant value [18]. Regression analyses were verified through residual analysis.

To determine the variability of the association between the awake prone position and intubation rates across different centres, multicentre adjustment was performed through generalised estimating equations; the centre with the lowest intubation rate throughout the entire study period was set as the reference. The main effects of every centre and awake prone positioning were calculated in the same model, as well as their interaction within the model.

A systematic search of studies of awake prone positioning was conducted; the search strategy and inclusion criteria for studies are provided in appendix 7 in the supplementary material. 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 the awake prone *versus* awake supine position.

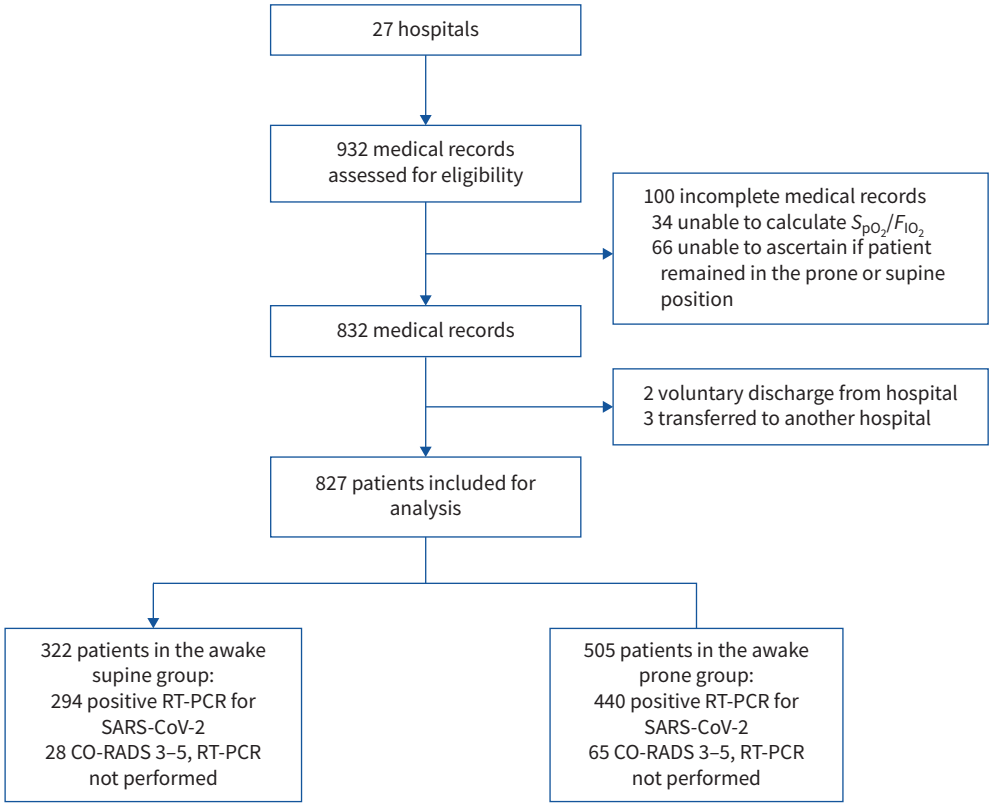


**FIGURE 1** Flow diagram of participants included in the APRONOX cohort. $S_{pO_2}$: peripheral arterial oxygen saturation; $F_{IO_2}$: inspiratory oxygen fraction; RT-PCR: reverse transcriptase-PCR; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CO-RADS: COVID-19 Reporting and Data System.

Missing values were not imputed. $p<0.05$ was used to define bilateral statistical significance. All analyses and graphs were created with SPSS version 21 (IBM, Armonk, NY, USA), R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) and RevMan version 5.3 (Cochrane, London, UK).

**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 | |
| <20 years | 1 (0.1) |
| 20–29 years | 29 (3.5) |
| 30–39 years | 101 (12.2) |
| 40–49 years | 194 (23.5) |
| 50–59 years | 209 (25.3) |
| 60–69 years | 162 (19.6) |
| ⩾70 years | 131 (15.8) |
| Sex | |
| Female | 227 (27.4) |
| Male | 600 (72.6) |
| Type of care | |
| ICU | 142 (17.2) |
| Non-ICU | 685 (82.8) |
| **Clinical variables** | |
| Diabetes | 315 (38.1) |
| Systemic arterial hypertension | 285 (34.5) |
| Obesity | 119 (14.4) |
| Heart disease | 17 (2.1) |
| Lung disease | 41 (5) |
| Cancer | 10 (1.2) |
| Liver disease | 5 (0.6) |
| Chronic kidney disease | 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 $S_{pO_2}/F_{IO_2}$[#]** | 189.5±81.6 |
| **Awake prone[¶]** | 505 (61.1) |
| **Awake supine** | 322 (38.9) |
| **Supplemental oxygen delivery device** | |
| Low-flow nasal cannula | 402 (48.6) |
| High-flow nasal cannula | 83 (10) |
| Nonrebreather mask | 342 (41.4) |
| **Outcomes** | |
| Intubation | 249 (30.1) |
| Mortality | 220 (26.6) |
| Failure to the prone[+] | 119 (23.6)[§] |

Data are presented as mean±SD or n (%). ICU: intensive care unit; $S_{pO_2}$: peripheral arterial oxygen saturation; $F_{IO_2}$: inspiratory oxygen fraction. [#]: these variables were determined at hospital admission; [¶]: median (interquartile range) time to initiation of prone 15.5 (8–48) h; [+]: defined as patients who were successfully managed in the awake prone position but required orotracheal intubation anytime during follow-up; [§]: percentage calculated out of all awake prone-positioned patients.

## 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. Among all 827 patients, 227 (27.4%) were female and the mean±SD age was 54.3±14.2 years, with most patients being in the 50–59 years category (25.3%). The most prevalent comorbidities were diabetes (38.1%) and hypertension (34.5%). Most patients were managed with LFNC (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 awake prone and awake supine groups, in both the unmatched and matched cohorts, are provided in table 2. Patients managed in the awake prone position had a median

**TABLE 2** Comparison of demographic and clinical characteristics at hospital admission and outcomes of patients in the awake prone and awake 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 |
| Female | 92 (28.6) | 135 (26.7) | 0.6 | 86 (27.7) | 79 (25.4) | 0.5 |
| Male | 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 |
| $S_{pO_2}/F_{IO_2}$[¶] | 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 |
| Nonrebreather 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 |

Data are presented as mean±SD or n (%). RT-PCR: reverse transcriptase-PCR; CO-RADS: COVID-19 Reporting and Data System; ICU: intensive care unit; $S_{pO_2}$: peripheral arterial oxygen saturation; $F_{IO_2}$: inspiratory oxygen fraction. [#]: RT-PCR was not performed in these patients; [¶]: these variables were determined during hospital admission.

(IQR) time to initiation of prone positioning of 15.5 (8–48) h. The median (IQR) time spent in the prone position during the hospital stay (total time in prone) was 12 (8–24) h. A smaller proportion of patients in the awake prone group required endotracheal intubation (23.6% *versus* 40.4%) or had a lethal outcome (19.8% *versus* 37.3%). After propensity score matching, these differences prevailed. The mean±SD $S_{pO_2}/F_{IO_2}$ in the awake prone group was statistically significantly higher after prone (217.42±81.9) compared with baseline values (182.39±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, baseline $S_{pO_2}/F_{IO_2}$ <100 or 100–199 and management with a nonrebreather mask. Awake prone positioning 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=2.12), which prevailed after propensity score analysis (adjusted OR 0.41, 95% CI 0.27–0.62; p<0.0001, E=1.86). Similarly, awake prone positioning was a protective factor for mortality (adjusted OR 0.38, 95% CI 0.26–0.55; p<0.0001; E=2.03; goodness of fit: Hosmer–Lemeshow $\chi^2$=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=1.88; goodness of fit: Hosmer–Lemeshow $\chi^2$=7.81; p=0.4; AUC 0.78, 95% CI 0.74–0.82; p<0.0001). Lower intubation and mortality risks for awake prone

**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 (male) | 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 $S_{pO_2}/F_{IO_2}$** | | | | |
| <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 |
| Nonrebreather mask | 3.94 (2.88–5.39) | <0.0001 | 3.75 (2.63–5.35) | <0.0001 |

ICU: intensive care unit; $S_{pO_2}$: peripheral arterial oxygen saturation; $F_{IO_2}$: inspiratory oxygen fraction.

**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 (male)** | 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 $S_{pO_2}/F_{IO_2}$** | 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 |
| **Nonrebreather mask** | 2.70 (1.82–4.01) | <0.0001 | 2.49 (1.56–3.99) | <0.0001 |

ICU: intensive care unit; $S_{pO_2}$: peripheral arterial oxygen saturation; $F_{IO_2}$: inspiratory oxygen fraction; AUC: area under the curve. [#]: goodness of fit: Hosmer–Lemeshow $\chi^2$=2.79; p=0.9; AUC 0.79 (95% CI 0.77–0.83); p<0.0001; [¶]: goodness of fit: Hosmer–Lemeshow $\chi^2$=10.95; p=0.2; AUC 0.82 (95% CI 0.79–0.85); p<0.0001.

positioning prevailed after subanalyses of patients with a confirmatory SARS-CoV-2 RT-PCR (excluding those in whom molecular testing was not performed) (appendix 8 in the supplementary material).

After adjusting for centre through generalised estimating equations, nine centres had an effect over the risk of intubation. Despite this, awake prone positioning 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 awake prone positioning was nonsignificant for all of the centres.

The main variables associated with intubation among awake prone patients were increasing age (OR 1.02, 95% CI 1.01–1.04; p=0.005), $S_{pO_2}/F_{IO_2}$ <100 (OR 2.78, 95% CI 1.35–5.72; p=0.005), $S_{pO_2}/F_{IO_2}$ 100–199 (OR 2.18, 95% CI 1.31–3.64; p=0.003) and management with a nonrebreather mask (OR 2.17, 95% CI 1.34–3.49; p=0.002; goodness of fit: Hosmer–Lemeshow $\chi^2$=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 $S_{pO_2}/F_{IO_2}$ is shown in figure 2a and b.

After the search of the literature, 99 records were retrieved, of which only nine studies [10–12, 19–24] were observational comparison-group studies including both awake prone and supine patients, with sufficient information to calculate the overall risk of intubation. These nine studies are summarised alongside the APRONOX study in figure 3 (the funnel plot is provided as appendix 9 in the supplementary material).

## 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 among awake prone patients and mortality in hospitalised patients with COVID-19. Even after multivariable adjustment and propensity score analyses, prone positioning in nonintubated 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 years) [10–12]; hospitalised patients with COVID-19 in Mexico have been reported to be young [25]. The prevalence of comorbidities in our study was 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%

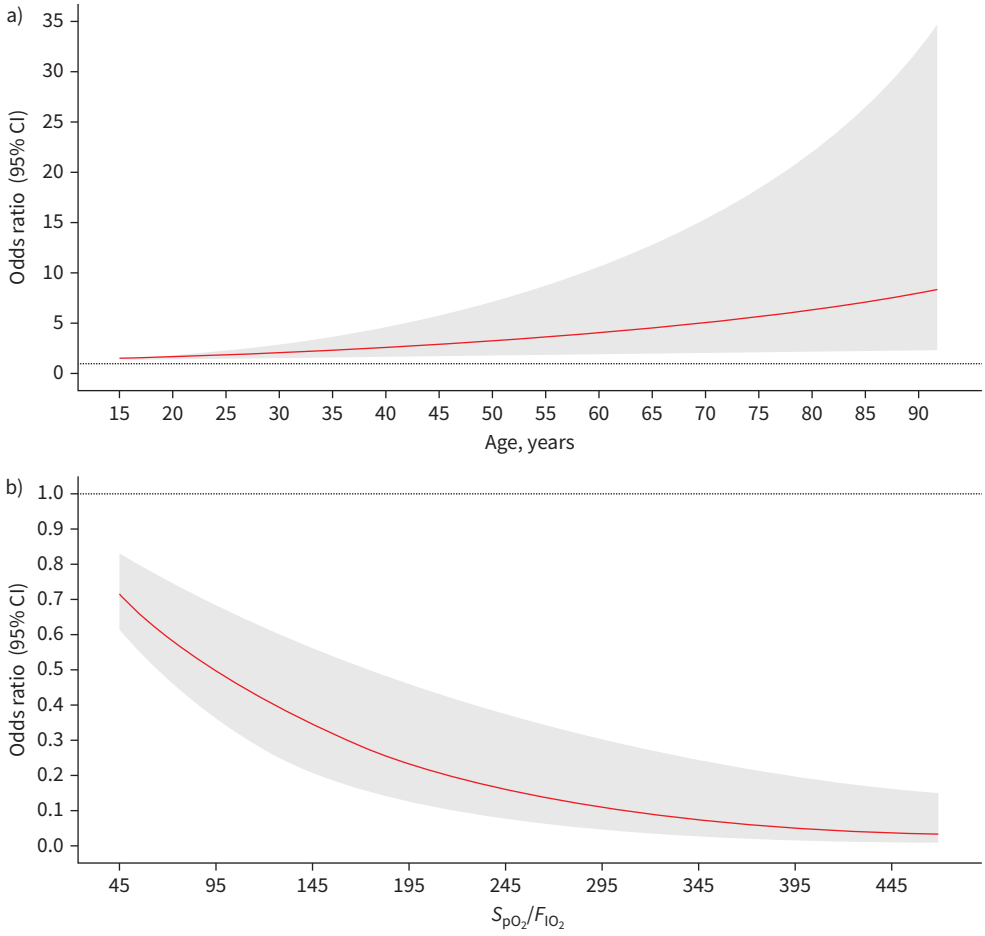


**FIGURE 2** Risk of intubation among patients in the awake prone group, according to a) age and b) baseline peripheral arterial oxygen saturation/inspiratory oxygen fraction ratio ($S_{pO_2}/F_{IO_2}$). For this analysis, baseline $S_{pO_2}/F_{IO_2}$ was studied as a continuous variable, therefore the range of odds ratios differs from others in the article which consider baseline $S_{pO_2}/F_{IO_2}$ as a categorical variable and use a category of reference to compare other categories.

| Study or subgroup | Awake prone Events | Total | Awake supine Events | Total | Weight, % | Odds ratio M-H, Random (95% CI) |
|---|---|---|---|---|---|---|
| Alsharif [23] | 2 | 31 | 12 | 48 | 6.2 | 0.21 (0.04–1.00) |
| APRONOX Group[#] | 77 | 311 | 123 | 311 | 18.0 | 0.50 (0.36–0.71) |
| Barker [24] | 6 | 10 | 5 | 10 | 5.3 | 1.50 (0.26–8.82) |
| Belkhouja [20] | 2 | 31 | 12 | 48 | 6.2 | 0.21 (0.04–1.00) |
| Fazzini [21] | 10 | 34 | 10 | 12 | 5.7 | 0.08 (0.02–0.45) |
| Ferrando [10] | 22 | 55 | 60 | 144 | 14.6 | 0.93 (0.50–1.76) |
| Jagan [12] | 4 | 40 | 18 | 65 | 9.0 | 0.29 (0.09–0.93) |
| Padrão [11] | 33 | 57 | 53 | 109 | 14.4 | 1.45 (0.76–2.77) |
| Prud'homme [19] | 7 | 48 | 8 | 48 | 9.5 | 0.85 (0.28–2.57) |
| Tonelli [22] | 7 | 38 | 30 | 76 | 11.1 | 0.35 (0.14–0.89) |
| Total (95% CI) | | 655 | | 871 | 100.0 | 0.53 (0.33–0.85) |
| Total events | 170 | | 331 | | | |

Heterogeneity: $\tau^2$=0.29; $\chi^2$=23.10, df=9 (p=0.006); $I^2$=61%
Test for overall effect: Z=2.64 (p=0.008)

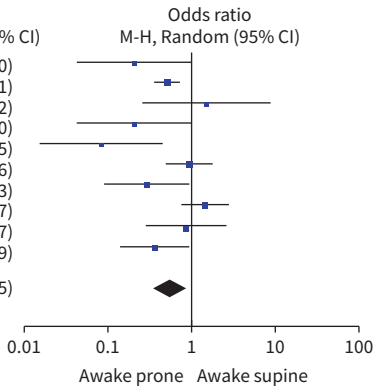


**FIGURE 3** Forest plot of overall risk of orotracheal intubation in studies retrieved by the search strategy (appendix 7 in the supplementary material) [37] and in the APRONOX cohort. [#]: only patients in the propensity score-matched cohorts were included for the APRONOX study. M-H, Random: Mantel–Haenszel random effects method.

*versus* 29.2%), whereas obesity (14.4% *versus* 22.5%) and heart disease (2.1% *versus* 4.4%) were less frequent [25].

The median (IQR) total time spent in the prone position during in-hospital stay in our study was 12 (8–24) h, which is considerable compared with a recent pilot randomised study which reported that self-proning patients spent only 1.6 (95% CI 0.2–3.1) h in the prone position in a 72-h 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 ⩾6 h in the awake prone position [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 awake prone (23.6%) and awake supine (40.4%) groups fall within those reported in previous studies (10–58% and 27.7–49%, respectively) [10–12]. Awake prone positioning 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 2.12 and 1.86, respectively, which reflects that in order to drive this association to be nonsignificant, 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 of the 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 $S_{pO_2}/F_{IO_2}$ 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 with intubation among awake prone patients, age, low $S_{pO_2}/F_{IO_2}$ and use of a nonrebreather mask were the main variables associated. The distribution of risk for quantitative values of age show that the risk of intubation after awake prone positioning is higher with increasing age, whereas higher baseline $S_{pO_2}/F_{IO_2}$ has the lowest risks.

Awake prone positioning 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, awake prone positioning could be used to avoid intubating patients with COVID-19 [29]. Nonetheless, conflicting evidence from observational studies for awake prone positioning exists.

The supine position alters pulmonary function in patients with respiratory insufficiency due to the gravitational differences between dependent and nondependent regions, resulting in a more negative pleural pressure, increasing transpulmonary pressure in nondependent areas (more distension), and producing the opposite effect in dependent areas where pleural pressure is less negative and transpulmonary pressure is lower (less distension). Ventilation in the prone position causes an even distribution of transpulmonary pressure, favouring uniform ventilation [30]. In 1974, prone positioning was shown to increase oxygenation in patients with respiratory insufficiency, primarily by improving the ventilation/perfusion ratio [31].

Prone positioning has been evaluated in hospitalised patients with respiratory failure due to COVID-19, having observed improvements in $S_{pO_2}$ and $P_{aO_2}$, decreased respiratory rate (respiratory rate), decreased need for intubation, and possible reductions in mortality, in addition to being cost-free [8, 32–35]. As summarised in figure 3, few other studies to date have evaluated intubation risk among awake prone compared with awake supine patients. While Ferrando *et al.* [10] and Padrão *et al.* [11] found no differences in intubation risk, Jagan *et al.* [12] found reduced intubation risk in awake prone patients. The APRONOX study is the largest observational study to date evaluating the effect of awake prone positioning on intubation risk.

Regarding oxygenation modality, the use of a nonrebreather mask was associated with greater risk of intubation among all patients and within awake prone patients, whereas other oxygenation devices were not. There is documented evidence of the correlation between $S_{pO_2}/F_{IO_2}$ and $P_{aO_2}/F_{IO_2}$, with the advantage that $S_{pO_2}/F_{IO_2}$ 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) oxygen delivery devices were not standardised to a unique device, 2) the number of hours of awake prone positioning varied between hospitals and patients, 3) no standardised criteria were established to consider intubation in patients requiring mechanical ventilation, 4) we were unable to assess which patients had “do not intubate” orders or other reasons for not

performing intubation, 5) availability of laboratory studies was limited across centres and these data were thus not collected and analysed, 6) not all patients with a CO-RADS score ⩾3 ultimately have a positive RT-PCR test [13] (this limitation was partially addressed by subanalysing patients with a positive SARS-CoV-2 RT-PCR), 7) a measure of oxygenation comparable to post-prone $S_{pO_2}/F_{IO_2}$ in awake prone patients was not collected for patients in the awake supine group, and 8) length of stay of patients was not collected.

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

Awake prone positioning in spontaneously breathing patients with acute hypoxaemic 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 awake prone positioning 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.

Acknowledgements: Healthcare workers treating COVID-19 patients: Edgard Díaz Soto, Jaziel López Pérez, José Antonio Meade Aguilar, Rubén Rodríguez Blanco, José Luis Patiño Pérez, Janisia Rodríguez Solís, Maribel Santosbeña Lagunes, Alberto Calvo Zúñiga, Manuel de Jesús Santaella Sibaja, Luis Iván Contreras Ley, María Alejandra Sicsik Aragón, Yessica Bernal Luna, Carlos Baez Ambriz, Yanira Jiménez Blancas, Alejandro Ayala Mata, Tania Gabriela Ramírez Lira, Iván Avalos Flores, Edwing Díaz Rodríguez, Roberto Robles Godínez, Eduardo Espino López, Hugo Francisco Díaz Ramírez, Concepción Mendoza Fragoso, Oliver Garaz Trujillo and Jesús Elías Paredes Flores. We thank the anonymous reviewers for their recommendations which allowed us to make significant improvements to our manuscript.

This study is registered at ClinicalTrials.gov with identifier number NCT04407468. All data that support the findings of this study will be available from the corresponding author upon reasonable request.

Conflict of interest: None declared.

## References

1 Valter C, Christensen AM, Tollund C, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* Prone positioning combined with high-flow nasal cannula in severe noninfectious ARDS. *Crit Care* 2020; 24: 114.
6 Sun Q, Qiu H, Huang M, *et al.* 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, *et al.* Prone positioning in awake, nonintubated patients with COVID-19 hypoxemic respiratory failure. *JAMA Intern Med* 2020; 180: 1537–1539.
9 Slessarev M, Cheng J, Ondrejicka M, *et al.* Patient self-proning with high-flow nasal cannula improves oxygenation in COVID-19 pneumonia. *Can J Anaesth* 2020; 67: 1288–1290.

10 Ferrando C, Mellado-Artigas R, Gea A, *et al.* 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: 597.

11 Padrão EMH, Valente FS, Besen BAMP, *et al.* 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, *et al.* The POSITIONED study: prone positioning in nonventilated coronavirus disease 2019 patients – a retrospective analysis. *Crit Care Explor* 2020; 2: e0229.

14 Rice TW, Wheeler AP, Bernard GR, *et al.* Comparison of the $Spo_2/Fio_2$ ratio and the $Pao_2/Fio_2$ ratio in patients with acute lung injury or ARDS. *Chest* 2007; 132: 410–417.

15 Parke RL, Eastwood GM, McGuinness SP, *et al.* 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, *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, *et al.* 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, *et al.* Web site and R package for computing E-values. *Epidemiology* 2018; 29: e45–e47.

19 Prud'homme E, Trigui Y, Elharrar X, *et al.* 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* 2021; 160: 85–88.

20 Belkhouja K, Alzahrani S, Al-Shalhoub N, *et al.* 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; in press [https://doi.org/10.1177/1751143721996542].

22 Tonelli R, Pisani L, Tabbì L, *et al.* Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: a retrospective multicenter cohort study. *Pulmonology* 2021; in press [https://doi.org/10.1016/j.pulmoe.2021.03.002].

23 Alsharif H, Belkhouja K. Feasibility and efficacy of prone position combined with CPAP in COVID-19 patients with AHRF. *Crit Care Med* 2021; 49: 120.

24 Barker J, Pan D, Koeckerling D, *et al.* Effect of serial awake prone positioning on oxygenation in patients admitted to intensive care with COVID-19. *Postgrad Med J* 2021; in press [https://doi.org/10.1136/postgradmedj-2020-139631].

25 Mancilla-Galindo J, Kammar-García A, Martínez-Esteban A, *et al.* COVID-19 patients with increasing age experience differential time to initial medical care and severity of symptoms. *Cambridge Open Engag* 2021; preprint [https://doi.org/10.33774/coe-2021-sjbcf].

26 Johnson SA, Horton DJ, Fuller MJ, *et al.* Patient-directed prone positioning in awake patients with COVID-19 requiring hospitalization (PAPR). *Ann Am Thorac Soc* 2021; 18: 1424–1426.

27 Jayakumar D, Ramachandran P, Rabindrarajan E, *et al.* 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: 36: 918–924.

28 Fowler Z, Moeller E, Roa L, *et al.* Projected impact of COVID-19 mitigation strategies on hospital services in the Mexico City Metropolitan Area. *PLoS One* 2020; 15: e0241954.

29 Touchon F, Trigui Y, Prud'homme E, *et al.* 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, ed. Acute Respiratory Distress Syndrome. Cham, Springer, 2017; pp. 73–84.

31 Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a Devil's Advocate. *Am Rev Respir Dis* 1974; 110: 143–144.

32 Elharrar X, Trigui Y, Dols A-M, *et al.* Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020; 323: 2336–2338.

33 Sartini C, Tresoldi M, Scarpellini P, *et al.* Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA* 2020; 323: 2338–2340.

34 Telias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? *JAMA* 2020; 323: 2265–2267.

35 Franco C, Facciolongo N, Tonelli R, *et al.* 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, *et al.* Awake-prone positioning strategy for non-intubated hypoxic patients with COVID-19: a pilot trial with embedded implementation evaluation. *Ann Am Thorac Soc* 2021; 18: 1360–1368.
37 Project COVID-19 Open Access. Living Evidence on COVID-19. 2020. https://ispmbern.github.io/covid-19/living-review Date last accessed: 8 June 2021.