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Original Article

Predictors of prone position use in patients with COVID-19 acute respiratory distress syndrome in intensive care units: A cross-sectional study

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ABSTRACT

Background & Aim: Clinical recommendations for ventilation management in patients with COVID-19 acute respiratory distress syndrome suggest the use of prone position as complementary therapy, however, there is wide variability in its use. The purpose of this study is to identify the predictor factors for using the prone position for patients hospitalized in intensive care units with COVID-19 acute respiratory distress syndrome.
Methods & Materials: A Cross-sectional study was carried out, including adult patients with COVID-19 acute respiratory distress syndrome hospitalized in intensive care units of four hospitals in Colombia. A multiple logistic regression model was constructed in which the main outcome was the prone position in intensive care, and the independent variables included sociodemographic characteristics, history, health status, progress, and treatment.
Results: A total of 473 patients were included in this study; 59.8% (n=283) received prone position therapy within 24-96 hours of hospitalization in intensive care. Out of the total of eligible variables in the logistics-regression model, factors in favor of the prone position were PCR>10mg/L (OR=3.33), private healthcare network (OR=1.99), hypertension (OR=1,76), cough or dyspnea symptoms at intensive care admission (OR=2.69 and OR=1.91), oxygen saturation <90% (OR=1.84). Factors against the prone position were heart disease (OR=0.34), FiO2>50% (OR=0.32), and TP>13 seconds (OR=0.53).
Conclusion: Patients with COVID-19 acute respiratory distress syndrome with a higher probability of prone position in intensive care were those with PCR>10mg/L, cough, dyspnea, and private healthcare network. The predictors identified in this study could help standardize the prone position therapy.

Introduction

The World Health Organization, at the end of 2019, announced a new global outbreak of pneumonia caused by a virus belonging to the "coronavirus (CoV)" family, which led to the development of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This was detected for the first time in Wuhan, China, causing the disease through coronavirus 2019 (COVID-19) (1).

Studies of patients worldwide evidenced that at the onset of COVID-19, patients had symptoms associated with viral pneumonia, with progression of the severity of cases until becoming critical cases, requiring hospitalization in intensive care units (ICU) (2).

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Around 13.8% of infected patients were classified with severe pneumonia (dyspnoea, respiratory rate ≥30 breaths per minute, oxygen saturation ≤92%, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO2/FiO2] <300 mm Hg and increased pulmonary infiltrates >50% in 24-48 h); and about a 6.1% classified as critical cases (3).

It has been estimated that between 20 to 41% of patients with COVID-19 that advanced to critical cases developed, in a few days, shock in the beginning and severe acute respiratory distress syndrome (ARDS)(4), which is why they required admission to ICU for hemodynamic management of the shock, mechanical ventilation in presence, therapy antibiotics, and other rescue measures. The specific characteristics shown by some markers of multi-organ failure present changes in laboratory results, like lymphopenia, elevated liver enzymes, elevation of lactate dehydrogenase (LDH), high inflammatory markers (e.g., C-reactive protein [CRP], ferritin), elevated D-Dimer (>1 mcg/mL), elevated procalcitonin, elevated time of prothrombin (PT), high troponin, and high creatine phosphokinase (CPK) (5). Progression of COVID-19 was observed much more in patients with high risk for severe disease and death, like, for example, in individuals with age ≥ 60 years and patients with comorbidities, like hypertension, cardiovascular disease, chronic respiratory disease, diabetes, and patients with cancer (6).

Mechanical ventilation (MV) is a therapy administered to patients with ARDS, using lung protection strategies such as low tidal volume ventilation and plateau pressure <30 cm H2O in the supine position. However, in cases with refractory hypoxemia, it has been suggested to use MV in the prone position for a period (PP) as a "rescue" strategy, provided there is no contraindication (4,7). PP's benefits appear consistent in patients with ARDS of various etiologies, underlying lung disease, obesity, and COVID-19 (8,9).

PP is a non-invasive technique of repositioning a patient toward a PP from a supine-horizontal position used in ICUs. This procedure aims to optimize gas exchange by improving the ventilation-perfusion relationship. During the SARS-Cov-2 pandemic, the time remaining in PP was implemented with a duration of 12 to 16 hours. The execution must be performed by two people (nurses, physicians, or physiotherapists) who share the tasks of rotating the patient when they care for vascular access, orotracheal tube, and other devices (8).

Despite the current clinical practice guidelines and recommendations for COVID-19 patients deeming PP intervention as a complementary form of therapy (8-10), there is wide variability in percentage use in these patients (between 27% to 70%) worldwide (11-13); therefore, some candidate patients could lose the opportunity to receive this intervention and its benefits. The uncertainty about this practice of PP may be related to multiple factors determining its benefit. These factors may be those related to aspects of the patient [demographics, comorbidities, health status, complexity, complications], the practice of the intervention [time to onset, relationship to the onset of symptoms, use of MV or other types of ventilation, among others], administrative aspects [frequency of repositioning, necessary staff, repositioning process, complications of the procedure], clear criteria for the intervention (14, 15).

Given the paucity of evidence, this study was executed to identify the patient and care-related factors that predict PP initiation in patients hospitalized in ICU with COVID-19 ARDS. The findings of this study may contribute to improving the parameters of intervention in the ICU.

Methods

This cross-sectional study was conducted on adult patients diagnosed with COVID-19 who were hospitalized in ICU. Due

to the period in which the pandemic began in Colombia and the start date of this study, patients were enrolled retrospectively at three institutions and prospectively at one institution.

The study population included patients hospitalized in ICU with ARDS caused by COVID-19 throughout four high-complexity healthcare institutions in Colombia; 3 of them private and one public.

The population included patients admitted to the ICU from March to December of 2020 with ARDS diagnosed based on the Berlin definition criteria (16), caused by COVID-19, followed by the hospitals during the pandemic time (Table 1).

Table 1. The Berlin acute respiratory distress syndrome criteria

Time	**Acute onset (less than seven days) after a known or new clinical injury**		
Radiological features	Bilateral opacities on chest X-ray or CT scan-not fully explained by pleural effusion, atelectasis, or pulmonary nodules.		
Origin of edema	Ventilatory failure that is not fully explained by heart failure or fluid overload. If there are no acute respiratory distress syndrome risk factors, objective studies will be required to rule out hydrostatic edema.		
Oxygenation (With PEEP or CPAP≥ 5cm H2O)	Mild 200mmHg<PaO2/ FiO2≤300mmHg	Moderate 100 mmHg<PaO2/ FiO2≤200mmHg	Severe PaO2/FiO2≤100 mmHg

Rx= radiography; CT= Computerized axial tomography; PEEP= positive end-expiratory pressure; CPAP: continuous positive airway pressure; PaO2: arterial oxygen pressure; FiO2: fraction of inspired oxygen.

The following inclusion criteria were also taken into account: 1) Patients having a defined positive diagnosis for ARDS by SARS-CoV-2 obtained through a reverse transcription-polymerase chain reaction test from a nasopharyngeal sample who require admission to ICU due to their severe or critical state or other existing test; or 2) Patients with SARS with suspicious diagnosis for SARS-CoV-2 whose results were still not available (but will be documented), but required ICU; and 3 Adults ≥18 years of age. Patients who did not receive care in an ICU for any reason (hospitalization transfer to other centers or death in the first 4-6 hours of being in an ICU) were excluded.

The primary outcome of this study was the administration of PP therapy in the ICU (Considered as a dichotomous variable). As predictors were considered, the following variables data regarding admission date to ICU and demographic variables such as age, sex, working status, rural or urban origin, socioeconomic status, and level of security health. Also, there were considered variables such as medical history [i.e., hypertension, respiratory system disease, chronic obstructive pulmonary disease COPD, obesity, diabetes mellitus, peripheral vascular disease, acute myocardial infarction], and others like surgical, toxicological [i.e., ex-smoker] and pharmacological [Antihypertensive, Antiarrhythmic, Beta-blockers, Anticoagulants, into others]. Epidemiological variables related to COVID-19 [symptoms and date of onset of symptoms such as fever, cough, fatigue, dyspnea] and variables related to admission to ICU [place of referral, laboratories, respiratory devices] were included.

To identify eligible patients, the statistical office provided the list of patients with COVID-19 hospitalized in the ICU (Using the ICD-10 codes) at the institutions in which the study was conducted retrospectively. In contrast, ICU nurses informed study staff each time a patient with COVID-19 was admitted at the institution where the study was conducted prospectively.

The information was obtained from the clinical patient's charts as the primary source. If there was no relevant data in the medical record, the information was gathered directly

from the patient through an interview (conscious patients) or via phone contact with their relatives (unconscious patients). The information regarding each patient was collected from entering the ICU up to the patient's discharge by health recovery or death. Nursing leaders in each institution were contacted, invited, and trained to recruit the patients and collect the information in electronic case report forms- CRFs (Appendix 1). CRFs contained various sections, including information about the center, the patients [demographic aspects, admission clinical signs, treatment, clinical evolution, complications upon discharge], and nursing care. All the terms of the CRFs were defined to standardize the information and variables in each center. The database was centralized in the coordinator center in an online platform. A coordinator of the study performed verification of data for completeness to ensure the validity of the information. At least two monitoring sessions were implemented to follow up on the data quality registered in the study platform. Back-up copies were programmed of data in charge of the group responsible.

The G-Power software was used to calculate the sample size using the following assumptions: a power level of 0.90, an alpha level of 0.05, a probability of an event under the hypothesis null of 0.2 (Assuming that the minimum frequency of PP reported in the literature is around 20%), and an effect size (Odds ratio) of 1.5 for multiple logistic regression. Therefore, the estimated sample size required was 409 participants. The sample was selected from consecutive sampling in the period previously described. A total of 473 patients were finally recruited, anticipating possible biases due to missing data.

The description of the sociodemographic characteristics, clinical characteristics (comorbidities), signs and symptoms of COVID-19, and the characteristics on admission to ICU were made for the general population according to their distribution using counts/percentages for categorical variables and means (standard deviation) or medians (interquartile range) for continuous variables. In addition, descriptive statistics were calculated for these independent variables according to the status of the outcome, presenting the distribution in two groups: pronated and non-pronated patients. The description of the primary outcome included the distribution by patient's characteristics, by hour of occurrence, and the proportion of patients that received or did not receive PP therapy. Subsequently, some continuous variables, such as hemodynamic variables and laboratories, were categorized according to the standard clinical criteria commonly used to ease the quantitative variable's interpretation. Chi-squared or exact Fisher statistics and the student's t-test or Mann Whitney's statistics (according to the data distribution for the discrete and continuous variables, respectively) were used to test the relationships between independent variables (patient and care characteristics) and PP (primary outcome). Also, the size of the effect for each variable was estimated using unadjusted OR with its 95% confidence interval.

The following step consisted of performing a multiple logistics regression model to identify the prediction power of the independent variables on the PP therapy. For the construction of this model, a backward step-by-step process was followed, initially with a complete principal effects model, while evaluating the behavior of the reduced model. All variables that met the criteria of significance statistical $p<0.20$ in the bivariate analysis (test the relationships between independent variables and PP) were selected to enter the initial regression model (complete principal effects model). In each step of the reduction, the variable with a minor contribution to the model was excluded until the final model. The adjusted OR for the final model was presented with its 95% confidence

interval. A priori alpha level of <0.05 was considered statistically significant. The model's fitness was evaluated through a likelihood ratio test, the Homer-Lemeshow, and the Bayesian criterion index of information. The percentage of correctly classified data by the model was also evaluated. Every analysis was processed and developed using the Stata software 12.0.

The study was submitted to the Research and Ethics Committee in the four participating institutions. The ethics committees approved this study on 13 May 2020 (record 24) in institution 1, on 21 May 2020 (record 18) in institution 2, and on 19 June 2020 (record 06) in institution 3. Permission was requested from the Ethics Committee in each of these institutions to review retrospectively the information in the clinical records of patients diagnosed with ARDS caused by COVID-19 and hospitalized in the ICU. Regarding institution 4, the ethics committee approved the conduct of the study prospectively as of 26 June 2020 (record 22). Consequently, at the time of admission to the ICU, after the investigator of each center explained the study and resolved any doubts, each patient (or their respective relatives) who agreed to participate prospectively in this study signed a printed consent form.

The electronic CRFs from each patient were anonymized by using an identification code. The access to the central database was limited to two people for monitoring and analysis. Formats from each center and each patient were archived to support the good practices of bioethics.

Results

Between 1 March and 15 December 2020, 4426 adult patients were hospitalized with COVID-19 within the four participant hospitals. Among these patients, 13.3% (n=587) were admitted to an ICU with ARDS caused by COVID-19. Therefore, a total of 473 patients (80.6%) with ARDS caused by COVID-19 were included in this study; 59.8% were under PP (n=283). In general, PP therapy began in the patients within the first 24-96 hours (average of two days) from entering the ICU, with an average intervention duration of 7 days (Interquartile range IQR 4 to 13). This therapy was administered in 16 hours per day cycles (IQR 16 to 24). Four nurses carried out the specific PP for the 28.3% of patients, three nurses for the 54.1%, two nurses for the 13.4%, and one for the remaining 3.2% of the patients.

Most patients were male (70%, n=331) with a median age of 63.6 years (IQR 53.4 to 73.1) and with low-middle socioeconomic stratum (66.2%, n=313). The gender, age, and socioeconomic stratum distribution did not have statistically significant differences among patients under PP and those who were not. 83.3% of patients in PP belonged to the private (contributive) national healthcare network, while the percentage of patients without PP patients was 76.3% (p=0.002) (Table 2).

Table 2. Comparison of patient sociodemographic characteristics between prone position and without prone position at ICU

Characteristics	Total (n= 473)	Prone position at the ICU		P-value
		Yes (n= 283)	No (n= 190)	
Sex, n (%)				
Male	331 (70.0)	203 (71.3)	128 (67.4)	0.310*
Female	142 (30.0)	80 (28.7)	62 (32.6)	
Age years, median (IQR)	63.6 (53.4- 73.1)	63.9 (53.9- 73.1)	63.5 (50.6- 73.3)	0.624**
Area of origin, n (%)				
Urban	424 (84.6)	256 (90.5)	168 (88.4)	0.350***
Rural	31 (6.6)	15 (5.3)	16 (8.4)	
Missing values	18 (3.8)	12 (4.2)	6 (3.2)	
Socioeconomic stratum, n (%)				
1-3	313 (66.2)	194 (68.6)	119 (62.6)	0.003*
4-6	52 (11.0)	38 (13.4)	14 (7.4)	
Missing values	108 (22.8)	51 (18.0)	57 (30.0)	

Social security, n (%)				
Contributive	378 (79.9)	233 (82.3)	145 (76.3)	0.002***
Subsidized	60 (12.6)	26 (9.2)	34 (17.9)	
Linked/uninsured	9 (1.9)	8 (2.8)	1 (0.5)	
Prepaid	13 (2.8)	11 (3.9)	2 (1.1)	
Missing values	13 (2.8)	5 (1.8)	8 (4.2)	

IQR: Interquartile range, *Chi-square test, **Mann Whitney's test, ***Fisher's exact test

Table 3. Comparison of clinical characteristics between prone position and without prone position patients at ICU

Clinical characteristics	Total (n= 473)	Prone position at ICU		P-value
		Yes (n= 283)	No (n= 190)	
Comorbidities, n (%)				
Hypertension				
Yes	243 (51.4)	157 (55.5)	86 (45.3)	0.028*
No	228 (48.2)	124 (43.8)	104 (54.7)	
Missing values	2 (0.4)	2 (0.7)	-	
Obesity				
Yes	119 (25.2)	82 (28.9)	37 (19.5)	0.003*
No	332 (70.2)	183 (64.7)	149 (78.4)	
Missing values	22 (4.6)	18 (6.4)	4 (2.1)	
Diabetes mellitus				
Yes	133 (28.1)	79 (27.9)	54 (28.4)	0.713*
No	338 (71.5)	202 (71.4)	136 (71.6)	
Missing values	2 (0.4)	2 (0.7)	-	
Cardiopathy				
Yes	46 (9.7)	23 (8.1)	23 (12.1)	0.227*
No	421 (89.0)	255 (90.1)	166 (87.4)	
Missing values	6 (1.3)	5 (1.8)	1 (0.5)	
Active cancer				
Yes	21 (4.4)	10 (3.5)	11 (5.8)	0.440*
No	445 (94.1)	268 (94.7)	177 (93.2)	
Missing values	7 (1.5)	5 (1.8)	2 (1.0)	
COPD				
Yes	31 (6.6)	16 (5.7)	15 (7.9)	0.288*
No	435 (91.9)	261 (92.2)	174 (91.6)	
Missing values	7 (1.5)	6 (2.1)	1 (0.5)	
Current habits, n (%)				
Smoker				
Yes	36 (7.6)	17 (6.0)	19 (10.0)	0.261**
No	406 (85.8)	248 (87.6)	158 (83.2)	
Missing values	31 (6.6)	18 (6.4)	13 (6.8)	
Alcohol drinker				
Yes	15 (3.2)	13 (4.6)	2 (1.0)	0.084*
No	424 (89.6)	251 (88.7)	173 (91.1)	
Missing values	34 (7.2)	19 (6.7)	15 (7.9)	
User of psychoactive substances				
Yes	3 (0.7)	-	3 (1.7)	0.140*
No	432 (91.3)	260 (91.9)	172 (90.5)	
Missing values	38 (8.0)	23 (8.1)	15 (7.9)	
Pharmacological history, n (%)				
Antihypertensives				
Yes	228 (48.2)	147 (51.9)	81 (42.6)	0.040*
No	242 (51.2)	133 (47.0)	109 (57.4)	
Missing values	3 (0.6)	3 (1.1)	-	
Beta-blockers				
Yes	82 (17.3)	56 (19.8)	26 (13.7)	0.089*
No	384 (81.2)	221 (78.1)	163 (85.8)	
Missing values	7 (1.5)	6 (2.1)	1 (0.5)	
NSAIDs				
Yes	67 (14.2)	38 (13.4)	29 (15.3)	0.251*
No	398 (84.1)	238 (84.1)	160 (84.2)	
Missing values	8 (1.7)	7 (2.5)	1 (0.5)	
Hypoglycemic agents				
Yes	83 (17.5)	56 (19.8)	27 (14.2)	0.118**
No	390 (82.4)	227 (80.2)	163 (85.8)	

Inotropes				
Yes	7 (1.5)	6 (2.1)	1 (0.5)	0.346*
No	448 (94.7)	265 (93.7)	183 (96.3)	
Missing values	18 (3.8)	12 (4.2)	6 (3.2)	
Immunosuppressive drugs				
Yes	31 (6.6)	12 (4.2)	19 (10.0)	0.006*
No	431 (91.1)	261 (92.2)	170 (89.5)	
Missing values	11 (2.3)	10 (3.6)	1 (0.5)	

COPD- Chronic obstructive pulmonary disease; Obesity defined as body mass index >30; NSAIDs- Nonsteroidal anti-inflammatory drugs; *Fisher's exact test; **Chi-square test

Patients with PP had a higher prevalence of hypertension and obesity than patients who did not receive PP (55.5% versus 45.3% and 28.9% versus 19.5%, respectively). While cardiopathy was less frequent in patients with PP than in patients without PP (8.1% versus 12.1%), this difference was not statistically significant. Patients in PP with a history of antihypertensives than patients without PP were more common (51.9% versus 42.6%, p=0.040); in contrast, the use of immunosuppressive drugs was higher in patients who did not receive PP therapy (10.0% versus 4.2%; p=0.006) (Table 3).

Regarding the signs and symptoms related to COVID-19, there was an observed significantly higher prevalence of fever (72.4% vs. 59.5%), cough (85.2% vs. 69.5%), and dyspnea (87.9% vs. 65.8%) in PP in comparison to the patients who did not receive PP (Table 4).

Table 4. Comparison of signs and symptoms of COVID-19 between prone position and without prone position patients on admission to ICU

		Prone position at ICU		
Characteristics	**Total (n= 473)**	**Yes (n= 283)**	**No (n= 190)**	**P-value**
Signs/symptoms COVID-19, n (%)				
Fever				
Yes	318 (67.2)	205 (72.4)	113 (59.5)	0.005*
No	151 (31.9)	75 (26.5)	76 (40.0)	
Missing values	4 (0.9)	3 (1.1)	1 (0.5)	
Cough				
Yes	373 (78.9)	241 (85.2)	132 (69.5)	
No	98 (20.7)	40 (14.1)	58 (30.5)	
Missing values	2 (0.4)	2 (0.7)	-	
Fatigue				
Yes	227 (48.0)	140 (49.5)	87 (45.8)	0.659*
No	240 (50.7)	140 (49.5)	100 (52.6)	
Missing values	6 (1.3)	3 (1.0)	3 (1.6)	
Dyspnea				
Yes	374 (79.1)	249 (87.9)	125 (65.8)	<0.001*
No	98 (20.7)	33 (11.7)	65 (34.2)	
Missing values	1 (0.2)	1 (0.4)	-	
Nausea				
Yes	44 (9.3)	25 (8.8)	19 (10.0)	0.926*
No	422 (89.2)	254 (89.8)	168 (88.4)	
Missing values	7 (1.5)	4 (1.4)	3 (1.6)	
Myalgia				
Yes	169 (35.7)	100 (35.3)	69 (36.3)	0.976*
No	298 (63.0)	179 (63.3)	119 (62.6)	
Missing values	6 (1.3)	4 (1.4)	2 (1.1)	
Had fever on hospital admission				
Yes	98 (20.7)	67 (23.7)	31 (16.3)	0.073*
No	366 (77.4)	209 (73.8)	157 (82.6)	
Missing values	9 (1.9)	7 (2.5)	2 (1.1)	
Time days between the date of onset of symptoms and hospital admission, median (IQR)	7 (4- 8)	7 (4- 8)	6 (3- 8)	0.321**

IQR: Interquartile range; *Chi-square test; **Mann Whitney's test

Among the related characteristics when entering an ICU (Table 5), the median for oxygen saturation and FIO2 (inspired fraction of oxygen) was also significantly higher in the PP group of patients (90% vs. 91% and 70% vs. 50%, respectively). In contrast, other hemodynamic variables were that the prothrombin time and partial thromboplastin time had a lower median in patients in PP compared to those without PP (14.0 vs. 14.2 seconds and 30.1 vs. 30.2 seconds, respectively). The numbers for the polymerase chain reaction (PCR) were significantly higher in the PP group of patients than those without PP (72.8 vs. 17.4 mg/L).

Table 5. Comparison of patients' characteristics on admission to ICU between prone position and without prone position

Patients' Characteristics of admission to ICU	Total (n= 473)	PP at ICU		P-value
		Yes (n= 283)	No (n= 190)	
Place of referral, n (%)				
Emergencies				
Yes	247 (52.2)	156 (55.1)	91 (47.9)	0.311*
No	215 (45.5)	121 (42.8)	94 (49.5)	
Missing values	11 (2.3)	6 (2.1)	5 (2.6)	
Hospitalization				
Yes	187 (39.5)	108 (38.2)	79 (41.6)	0.675**
No	275 (58.1)	169 (59.7)	106 (55.8)	
Missing values	11 (2.3)	6 (2.1)	5 (2.6)	
Respiratory variables, median (IQR)				
Oxygen saturation (%)	90 (89-94)	90 (87- 93)	91 (89- 95)	<0.001***
FiO2 (%)	70 (35-90)	70 (50- 90)	50 (28- 70)	<0.001***
Laboratories, median (IQR)				
Creatinine mg/dl	0.9 (0.76- 1.17)	0.9 (0.76- 1.20)	0.9 (0.77- 1.14)	0.268***
PT Seconds	14.1 (12.2- 15.1)	14 (11.6- 15.2)	14.2 (13.3- 15.8)	<0.001***
PTT Seconds	30.1 (28.5- 32.4)	30.1 (27.8- 31.8)	30.2 (29.6- 33.7)	0.006***
PCR mg/L	39.5 (10.3-150.8)	72.8 (16- 169.8)	17.4 (5.7 -107)	<0.001***
High flow oxygen devices, n (%)				
Non-rebreathing mask	238 (50.3)	159 (56.2)	79 (41.6)	<0.001*
Orotracheal tube	91 (19.2)	60 (21.2)	31 (16.3)	
Venturi	18 (3.8)	15 (5.3)	3 (1.6)	
Missing values	126 (26.6)	49 (17.3)	77 (40.5)	
Nasal oxygen cannula, n (%)				
Yes	88 (18.6)	32 (11.3)	56 (29.5)	<0.001**
No	385 (81.4)	251 (88.7)	134 (70.5)	

PT- Prothrombin time; PTT- Partial thromboplastin time; IQR- Interquartile range; *Fisher's exact test; ** Chi-square test; *** Mann Whitney's test

Table 6 displays a multivariate model to identify the independent predictors of PP. Out of the evaluated variables in 411 complete patient registers, 17 were candidates for the multivariate analysis, and nine were identified as independent predictors of receiving PP. Having insurance from the private healthcare network, hypertension, cough-related symptoms, and dyspnea when admitted into an ICU, SaO2<90%, and PCR>10mg/L were identified as predictors that increase the likelihood of receiving PP. From these factors, the strongest predictors were the PCR >10mg/L (OR= 3.33; 95CI%= 1.87- 5.91) and having a cough (OR= 2.69; 95CI%= 1.51- 4.81). Furthermore, cardiopathy, FiO2<50%, and TP>13 seconds were identified as predictors to reduce the likelihood of receiving PP therapy (Area under the curve=0.786).

Table 6. Predictors of prone position on multivariate model analysis

	Unadjusted		Adjusted		
Predictors	**OR**	**95%CI**	**OR**	**95%CI**	**P-value**
Contributive or prepaid social security	1.71	0.99- 2.95	1.99	1.05- 3.79	0.035
Comorbidities					
Hypertension	1.53	1.04- 2.25	1.76	1.10- 2.82	0.018
Obesity	1.80	1.13- 2.89	1.58	0.93- 2.67	0.088
Cardiopathy	0.65	0.34- 1.26	0.34	0.15- 0.77	0.010
Symptoms associated with COVID-19					
Cough	2.64	1.64- 4.29	2.69	1.51- 4.81	0.001
Dyspnea	3.92	2.39- 6.48	1.91	1.06- 3.42	0.031
Referred to ICU from the emergency department	1.33	0.90- 1.97	1.39	0.87- 2.20	0.166
Hemodynamic variables at ICU admission					
Oxygen saturation <90 %	1.86	1.22- 2.84	1.84	1.12- 3.02	0.015
FiO2 <50%	0.27	0.18- 0.42	0.32	0.19- 0.52	<0.001
Laboratories at the ICU entrance					
PT >13 seconds	0.44	0.28- 0.69	0.53	0.31- 0.93	0.027
PCR >10 mg/L	2.47	1.53- 3.99	3.33	1.87- 5.91	<0.001

Obesity is defined as body mass index >30; PT- prothrombin

Discussion

This study was the first to identify the characteristics that can predict PP practice in ARDS patients caused by COVID-19 hospitalized in ICUs. The factors that predict the PP in ARDS patients with COVID-19 in ICUs were having insurance from the private healthcare network, having high blood pressure, cough, or dyspnea, SaO2<90%, and PCR>10mg/L when being admitted into an ICU. The negative predictors for PP were cardiopathy, FiO2<50%, and TP>13 seconds.

Approximately 3 out of 5 patients were in PP along with this study. This practice was like the one reported in Mexico and Ecuador in the APRONOX study (12) but superior to the observational study carried out in Argentina, in which 1 out of 3 patients were in PP (17).

Different from the study performed by Stilma W et al. (13), in which the distribution of hypertension records was similar among patients in PP and without PP ones who received invasive ventilation, in our study, these records were more frequent in the group of patients in PP. This result was deemed as an independent predictor for receiving complementary therapy. Hypertension is one of the more common comorbidities in COVID-19 hospitalized patients and is viewed along with ARDS as the main factor to which the risk of severity and mortality is associated with this disease (18,19); this could explain an indication to mobilize this group of patients with caregiver preference in our study.

On another note, some studies have reported heart rate decrease (<35 heartbeats per minute) as an associated PP complication; as a result, this therapy has been contraindicated for patients with hemodynamic instability (20). This recommendation agrees with the recent findings related to the practice of our caregivers included in this study, in which patients with heart disease tend to have a higher hemodynamic instability. These patients had approximately 70% less likelihood of receiving PP therapy.

Other characteristics that help forecast the severity and mortality of COVID-19 were also identified as independent predictors in PP therapy in our study. A systematic revision with meta-analysis showed that the appearance of symptoms such as dyspnea and cough could independently predict the severity of COVID-19 (mainly dyspnea, OR=3.70; 95IC%=1.83-7.46) (18); in our study, the presence of cough when entering the ICU was one of the strongest predictors of PP therapy. Regarding the laboratories, the increase in PCR is a known predictor of hospitalization, ARDS severity, and mortality by COVID-19 (21). This examination is recommended as part of the daily monitoring routine for patients with infection in the ICU (22), and it was monitored in all patients with COVID-19 in the four

participant medical centers. This practice may explain why PCR>10mg/L was identified here as the strongest predictor factor for the use of PP.

Ventilation parameters such as SaO2 and FiO2 were positive and negative predictors in our study. The World Health Organization suggests keeping oxygenation standards initially with one peripheral SaO2 >94% and ≥90% during oxygen maintenance (23). Therefore, the threshold of SaO2<90% is clinically known as an indicator to evaluate hypoxemia. This alert may suggest to the caregivers a need for PP to improve ventilation/perfusion. Furthermore, the algorithms for oxygenation defined the threshold for SaO2<85% as an alert for repositioning a patient to a supine position (11, 24). On the other hand, FiO2 is considered one of the defining criteria for determining the need for PP (11), so one recommendation is not to use PP in patients non-intubated with acute respiratory distress (as a strategy to delay the intubation) (9). This recommendation could explain why patients with FiO2<50% had a lesser probability of being in PP in our study.

In addition to the clinical determinants for the management of ventilation/perfusion in patients with ARDS, another predictor factor is associated with the private healthcare insurance network. In our country, the healthcare system is integrated by two coexistent networks. One is a private contributory regime covering all workers (including adult children) who contribute financially to the system. The other is a publicly subsidized regime, covering all vulnerable portions of the Colombian population with lower income through state funding (25). Prior studies have reported inequalities in the level of care, access, and services between healthcare regimes/networks, which mainly favor those who are part of the contributory/private network (25,26). During the COVID-19 pandemic, the specific private healthcare sub-networks and centers have had an overall higher coverage, better assistance opportunities, and better human resources to tend to healthcare needs (27, 28), which could be related to these private network-affiliated patients having higher chances of receiving complementary therapy such as PP.

Some setbacks and barriers related to nursing personnel availability, personal protection elements, training, and fear of complications associated with PP therapy, such as pressure ulcers, accidental extubating, loss of intravenous access, and others, have been presented as limitations for the use of PP therapy (14,15,29,30); however, these factors were not evaluated in this study. The knowledge about the predictors of PP of patients with ARDS caused by COVID-19 and the cumulated learning obtained during this pandemic may prepare the teams to establish protocols to standardize the use of this therapy. These protocols may include indications and eligibility criteria for the practice of PP in patients with ARDS in the ICU, allowing equal access to this therapy for all patients.

The strong points of this study include a large sample of ARDS patients due to COVID-19 in four complex medical centers/institutions in one developing country, all of which represent both the country's public and private healthcare services. The monitoring from entering hospitalization up to the moment of pronation allowed for a classification of included patients and a gathering of a considerable amount of information to evaluate the predictor factors obtained from the grouping variables (clinical characteristics and health condition, sociodemographic aspects) that may influence the practices carried out by healthcare professionals. Findings were consistent between retrospectively and prospectively recruited patients.

The limitations of this study included that approximately ⅔ of the information was gathered retrospectively, allowing for selection biases. Other limitations may be related to some COVID-19 diagnostic test confirmation delays for suspected cases or some failures related to

the discrimination capability of the PCR test used for COVID-19, avoiding including some false negatives for patients. Other limitations refer to some factors that could not be included in the prediction model because not all hospitals in their ICU include them as part of the patient evaluation. These are the case of variables like Barthel's index, SOFA score, or the presence of delirium. A final limitation relates to some organizational factors that may have affected the use of PP for these patients and were not included in this analysis. These factors were the academic level of nurses involved in ICU care, shifts, nursing time, nursing competency level, the weight of direct patient care, the amount of physical exertion, and re-training according to the complexity of care. Finally, the observations were limited to the practices of four participant healthcare institutions in a developing country, and the results must be evaluated carefully.

Conclusion

Among the patients with acute respiratory distress caused by COVID-19, having when entering an ICU, a PCR>10 mg/L, and symptoms such as cough or dyspnea, low oxygen saturation, a record of high blood pressure, and having insurance from the private healthcare network, increased the likelihood of receiving PP therapy during hospitalization in intensive care. The findings of this study can contribute to the improvement and standardization of PP as a complementary form of therapy in ARDS patients caused by COVID-19.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix 1. Case report forms

Study characteristics evolution treatments and care of adult patients hospitalized in the ICU with COVID-19

Date of completion of this instrument: Day: ____ Month: ____ Year: ____ **Reviewer** (initials)**: _____**

Institution: (CODE)_____ Patients code: COV-_____

Patient Social Security System: Affiliate__ Subsidy with ARS ___ Contributive___ Beneficiary___ Prepaid___ No Affiliate___

1. ADMISSION TO THE HOSPITAL AND DEMOGRAPHY									
Initials of Patient		**No Of ID**				**No CLINIC HISTORY**			
Hospital admission date	Day: ____ Month: ____ Year: _____ **Hour:** ____: ____ (Format of 24 hours)								
Origin:	Rural area		Urban area		Country/city		Departament		

Gender	Male		Female		Age (years completed)		Date of Birth	Day: ____ Month: ____ Year: ___

Civil Status	Do you live alone		Do live accompanied		

Ocupation	Are you Employee		Are you Independent Worker		Are you Retired		Are you Health worker	

Position in your family	Are you Resource Provider	Yes_ No_	Are you Head of the family	Yes_ No_	Do you Dependent on your family	Yes_ No_	Number of dependents:	Children: __ Adults: ___

Education Level	Primary		High school		Technical		College		Illiterate		Can read and write (without studies)
Socioeconomic Level 1-2-3-4-5-6											

2. BACKGROUND AND PATIENT'S HEALTH STATUS								
Pathological	Arterial hypertension	Yes ___ No __	Mellitus diabetes	Yes_ No _	AMI	Yes _ No __	Active cancer	Yes __ No __
	Respiratory system diseases	Yes ___ No___	Peripheral vascular disease	Yes_ No	CVA	Yes __ No __	Transient ischemic accident	Yes __ No __
	COPD (Only)	Yes ___ No___	HIV	Yes_ No_	Arrhythmias	Yes __ No __	Other Pathology (which)	Do not apply _
Vaccines do you have	Tuberculosis BCG	Yes___ No__	Measles, Rubella, Mumps	Yes_ No	Chickenpox	Yes __ No __	FLU	Yes_ _ No__
	Polio	Yes___ No__	yellow fever	Yes__ No_	Patient does not remember	Yes _ No _		
Had any of the above described illnesses?	Yes__ No__	If the answer is yes, what was all of the above?	Which? _____ If the answer is No, register Does not apply.		Do you remember any vaccines applied in the last 5 years? Which?	Yes__ No__		

Surgical	Number of surgeries you had		Number of surgeries you had		Does no apply _____

Toxicological	Ex-smoker	Yes_ No__	Ex-alcoholic	Yes _ No _	Ex-consumer of psychoactive substances	Yes __ No ___	Does no apply __

Pharmacological	Antihypertensive	Yes _ No__	Beta blockers	Yes _ No_	NAID	Yes _ No _	Antiarrhythmic	Yes_ No_
	Antianginal	Yes _ No__	Inotropic	Yes_ No_	Antilipemic	Yes_ No _	Diuretics	Yes_ No_
	Antiulcer	Yes _ No__	Anti-asthmatics	Yes __ No___	Anticoagulants	Yes _ No __	Immunosuppressants	Yes_ No_
Others	Yes ___ No ___							

Gynecological history	Total, pregnancies		N° of Births		caesarean sections		Abortion		Live births	
Currently pregnant	Yes__ No_		Gestation weeks	#_____	Does not apply ___					

Currently consuming toxic substances	Smoker		Yes ___ No __	Alcoholic	Yes___ No ___	Psychoactive substances	Yes ___ No___
Weight Kg		**Size**		**IMC=Kg/height²**			

2. EPIDEMIOLOGICAL DATA						
Infection exposure	3.1 Previous trips (14 days before)	Yes ___ No ___	3.2 Contact sick person	Yes___ No ___	3.3 Contact with patients at work	Yes___ No ___
	Confirmed diagnosis	Yes ___ No ___	COVID_19 Positive	Yes ___ No __	Date: confirmation	day__mm __y__
	Suspicious diagnosis	Yes ___ No ___	Pending result	Yes ___ No___		

2. SYMPTOMS					
Fever	Yes ___ No ___	Dyspnoea	Yes ___ No___	Diarrhea	Yes___ No ___
Cough	Yes ___ No ___	Sickness	Yes ___ No___	Pain when swallowing	Yes___ No ___
Fatigue	Yes ___ No ___	Myalgia	Yes ___ No___	Other. ¿which?	

2. INCUBATION PERIOD								
1. Did you have a fever on admission?	Yes ___ No___							
2. Specify the fever data according to the note in the medical record	<37.5		37.5-38		38.1-39		> 39	
Does not apply___								

2. DATA RELATED TO ENTRY AND EXIT TO THE HOSPITAL					
1.Date of onset of symptoms:	dd__mm__yy__	Date / time admission emergency		dd__mm__yy____	Hour: ___ (formato24 hours)
		General hospital admission date		dd__mm__yy____	Hour: ___ (Format 24 hours)
		Date of admission to ICU		dd__mm__yy____	Hour: _____ (Format 24 hours)
2.ICU discharge	Alive	Yes__No__		dd__mm__yy___ Hour: _____	Hour: (Format 2 hours)
	Dead	Yes__No__	Causes death on death note:_____	dd__mm__yy___ Hour: _____	Other:
3-Discharge to hospitalization	Dies in hospitalization	Yes__No__	Cause in death note:_____	dd__mm__yy___ Hour: _____	
4-Hospital discharge alive	Departure	Yes___No__		dd__mm__yy__ Hour: _____	Hour: ___ (format 24 hours)

7- ENTRY TO ICU								
Diagnosis cause of ICU admission	Pneumonia	Yes_ No_	ARDS	Yes_ No_	Shock	Yes_ No_	Other. which	
Patient is referred from	Surgery	Yes_No_	Procedure		Yes__No__	Hospitalization Yes__No__		
Degree of severity of ARDS on admission (Clash. Berlin)	ARDS Mild		PaO2/FiO$_2$: between 200-300mmHg			PEEP: ≥5 cmH$_2$O		
	ARDS Moderate		PaO2/FiO$_2$: between 100-200mmHg			PEEP: ≥10 cmH$_2$O		
	ARDS Severe		PaO2/FiO$_2$: <100mmHg			PEEP: ≤18 cmH$_2$O		

Basic Monitoring (Complete information)	ICU admission	ICU discharge
BP Systolic (mmhg		
BP Diastolic (mmhg)		
Temperature (°C)		
Heart frequency (Lat. / min		
Breathing frequency		
Oxygen saturation (%)		
FiO2 (%)		
Score AOSF		
BARTHEL		
Delirium CAM-ICU		
Laboratories (Register Yes / No)		
Procalcitonin> 0.05 ng / mL		
Troponin I> 0.028 ng / L or> 28 pg / mL		
Creatinine> 1.2 mg / dl		
TP> 14 seconds		

TTP >36 seconds		
PCR>3mg/L		
Devices	High Flow Yes___ No____	which?
	Low Flow Yes___ No____	which?

8- MECHANICAL VENTILATION IN ICU				
Type of ventilation	Non- Invasive	Yes__ No__	If the answer is yes, indicate which	
	Invasive	Yes_ No__		
Si la respuesta es Sí, indique	Start: dd__mm__yy___ Hour: ___		Ending: dd__mm__yy__hora:___	
Ventilatory parameters (Gasimetry)	**Initials**		**For extubation**	
Oxygen saturation (%)				
FiO2 (%)				
PaO2				
PEEP				
Tidal volume	Oxygen saturation (%)			
Adjuvant intervention				
Did the patient require pronation?	Yes___ No___			
If the answer is yes, please indicate **Ventilator parameters**	Date of start: dd__mm__yy__Hour: __ **At the start of pronation therapy**		**At the end of pronation**	
Oxygen saturation (%)				
FiO2 (%)				
PEEP				
Does not apply___	Indicate does not apply if the patient did not require pronation.			
Number of hours per day _____	**End date**	dd__mm__yy__	**Reason for termination**	Resolution Yes_ No_ Na_
				Exit Yes_ No_ Na_
				Death Yes_ No_ Na_
	Number of nurses Pronate	1__ 2__ 3__ More of 3___	**Complications Of the Pronation**	Ulcers Totals #___ Site____ Ulcer Grade___ Yes_ No_ Na_
				Arrhythmias Yes_ No_ Na_
				Tube occlusion Yes_ No_ Na_

9-TREATMENT							
Antibiotics IV	Yes ___ No ___	Glucocorticoides sistémicos	Yes ___ No ___	Vasoactivos	Yes ___ No ___	Other	
Antivirals	Yes ___ No ___	Anticoagulante	Yes ___ No ___	Inotrópicos	Yes ___ No ___		
Antimalarials	Yes ___ No ___	Analgésicos	Yes ___ No ___	Broncodilatadores	Yes ___ No ___		
Medication infusion catheter	Total in ICU	#___	**TYPE**	**PICC**	Yes ___ No ___	Step with ultrasound scanner: Yes__ No__	Who performs the procedure? -Doctor -Nurse
				Central	Yes ___ No ___		Who performs the procedure? -Doctor -Nurse
				Peripheral	Yes ___ No ___	Step with ultrasound Yes__ No___	Who performs the procedure? -Doctor -Nurse -
Extracorporeal membrane for oxygenation	Yes_ No_	**Start date**	dd__mm__yy- Hour:__ Na___	Renal replacement therapy	Yes__ No__	Start Date	dd__mm__yy__ Hour:__ Na___
Enteral nutrition catheter	Yes__ No__	**Parenteral nutrition catheter**	Yes__ No__				

10- WELL-BEING-CARE INTERVENTIONS					
Bed position changes prevention of pressure ulcers	Yes__ No___	If yes, please indicate:	Frequency_____		
Early mobilization	Yes ___ No ___	Start date	dd_ mm_yy__hour:__ Na___		Walk? yes_No_
Hygiene: Bath in bed	Yes ___ No ___	Frequency/day	1_2_	Hour:	Na__
Oral hygiene	Yes ___ No ___	Frequency/day	1_2_	Hour:	Na__
Direct family communication	Yes__ No__	Telephone Video call Other, which one?	yes___No_	Frecuencia/day/ How many times	1__ 2_ more than 2__ Na__

11- COMPLICACIONES								
ICU	Septic shock	Yes __ No___	Myocarditis	Yes __ No___	Thromboembolism	Yes __ No___	renal failure	Yes ___ No___
	Serious ARDS	Yes __ No___	myocardial infarction	Yes __ No___	Disseminated intravascular coagulation	Yes __ No___	Pressure ulcers	Yes ___ No___
	Pneumonia	Yes ___ No___	Arrhythmia	Yes ___ No___	Delirium	Yes ___ No___		If yes, please indicate: Total____ Place ____
	Other:	which_						