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Original Research

Characterization of patients with COVID-19-related ARDS before the prone position: prospective cohort study

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Abstract

Background: The general characteristics and ventilator-related variables of patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 infection who have undergone invasive mechanical ventilation (MV) remain unclear, especially those who need a prone position (PP). **Aim**: To characterize the clinical, demographical, and ventilatory variables of patients on MV with COVID-19-related ARDS, evolving to PP. **Methods**: This study was an observational prospective cohort investigation of COVID-19 patients undergoing invasive MV. PP and non-prone groups were compared using Student's t, Mann-Whitney U, chi-square, or Fisher's exact tests. Binary logistic regression was used to identify predictor variables. Statistical significance was set at $p < 0.05$. The study design was approved by the Research Ethics Committee. **Results**: The clinical and demographical characteristics of patients requiring PP were: age (63.4 ± 12.4 years), predicted body weight (57.3 ± 11.0 kg), SAPS 3 47.5 (41-55), SOFA 3 (2-6), comorbidities, days until intubation (1.2 ± 2.2 days), and death in the ICU (52.4%); these characteristics were similar to those who remained in supine position. A total of 42 (65.6%) subjects needed PP, especially females. There were no differences between PP and non-prone groups in respiratory system compliance (C_{rs}) [(30.0 (24.6-35.3)], driving pressure (ΔP) (14.2 ± 3.9 cm H_2O) and plateau pressure (Pplateau) (23.9 ± 4.7 cmH_2O). The PP group had lower initial PaO_2/FIO_2 ratio values (130.5 ± 58.1 vs 187.5 ± 59.1, $p < 0,05$). C_{rs} was not a significant predictor of PP (OR 1.702; CI 95% 0.962 – 1.131). **Conclusions**: Most patients required PP, especially females aged over 60. These patients frequently use neuromuscular blockers and had a longer hospital stay. Upon admission to the ICU, the C_{rs}, Pplateau, and ΔP values of these patients were similar to those who did not require PP; PaO_2/FiO_2 ratio characterized patients who needed PP.

Keywords: COVID-19; SARS-CoV-2; Artificial Respiration; Prone Position; Respiratory Distress Syndrome.

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How can the results of this study be used in clinical practice?

- Patients requiring prone position frequently use neuromuscular blockers and had a longer hospital stay.
- Upon admission to the intensive care unit, the Crs, Pplateau, and ΔP values of these patients were similar to those who did not require.
- PaO_2/FiO_2 ratio characterized patients who needed prone position.

Introduction

In 2019, a new coronavirus (SARS-CoV-2) was identified as the cause of several cases of pneumonia in Wuhan, a city in Hubei province, China[1]. Symptoms developed within 11.5 days in 97.5% of the infected cases; the average incubation period was 5.1 days[2]. Infection with SARS-CoV-2 results in COVID-19 infection, a disease with a fatality rate of 1-3%, which is associated with the development of acute respiratory distress syndrome (ARDS)[3,4].

Some ventilator strategies are associated with better outcomes in ARDS, particularly the lung-protective and the prone position (PP) strategies[5,6]. Some authors report that lungs injured by COVID-19 could have normal values of respiratory system compliance (C_{rs}). Therefore, a tidal volume (Vt) of 7-8 mL/kg of predicted body weight (PBW) can reduce the risk of hypoventilation-induced resorption atelectasis without a significant increase in the risk of ventilator-induced lung injury (VILI)[7]. However, according to Goligher et al.[8], there is not enough evidence to suggest that the standard approach for treating ARDS should be changed considering the COVID-19 pandemic.

ARDS is a common manifestation of the SARS-CoV-2 infection, with a few characteristics that differentiate it from its other forms[9]. The clinical, demographic, and ventilator variables of patients with COVID-19-related ARDS who have undergone invasive mechanical ventilation (MV) are not fully established in the literature, especially among those who are treated in PP. Whether these aspects are different in patients who need to be placed in PP are also unclear[10]. According to Krause et al.[11], it is essential to identify factors associated with mortality in this population, as well as their characteristics that can assist in intensive clinical management and yield better outcomes.

Therefore, the objective of the present study was to characterize the clinical, demographical, and ventilatory variables of patients who underwent MV with COVID-19-related ARDS in need of PP as part of their treatment.

Methods

Study design and ethical aspects

This was a prospective observational single-center cohort study including data collected from an intensive care unit exclusive for patients with COVID-19 infection. The present study was approved by the Research Ethics Committee on April 1st, 2020, submitted by the institution of origin Universidade Federal de Juiz de Fora - UFJF and approved by FHEMIG / DIGEPE/ Department of the Research Support Center.

Sample composition and study allocation

Initially, patients with suspected COVID-19 infection were admitted to the ICU of Hospital Regional Dr. João Penido - Hospital regional João Penido - HRJP of the Fundação Hospitalar do Estado de Minas Gerais - FHEMIG, in the city of Juiz de Fora - MG from May to November 2020, where they were tested and confirmed for SARS-CoV-2.

Patients with negative SARS-CoV-2 reverse-transcriptase-polymerase chain reaction (RT-PCR) reports were excluded and, among those with positive SARS-CoV-2 RT-PCR results, we included men and women aged > 18 years who had progressed to the MV support and were admitted in the intensive care unit (ICU); the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen (PaO_2/FiO_2) was ≤ 300. Patients who were intubated outside the ICU, those with MV time greater than 48 hours, advanced dementia, and/or who died less than 24 hours after admission, patients in palliative care, patients who did not require invasive MV, and patients suspected of brain death were excluded.

In the prone group, we included patients who had a PaO_2/FiO_2 ratio < 150 mmHg at some point, and those with no absolute contraindications to PP, such as severe acute arrhythmias, pelvic fractures, suspected increased intracranial pressure, unstable fractured vertebrae, and recent sternotomy or peritonectomy. The remaining patients (150 ≥ PaO_2/FiO_2 ratio ≤ 300) comprised the non-prone group.

Demographic variables

Data were obtained from the institution's official medical records system and transferred to an electronic database for further analysis. Demographic variables (sex, age, comorbidities, smoking, and use of medications), information on clinical signs and symptoms, and laboratory results were collected during admission to the ICU. Researchers continuously updated the study database on length of ICU stay, duration in hours of the first PP, length of ICU stay before PP, days of MV, days before MV, and other data.

Clinical variables

To objectively assess the extent and severity of organ dysfunction, the Sequential Organ Failure Assessment (SOFA) score was calculated on admission, for two more consecutive days, and on the day of orotracheal intubation.

The prognostic system used was the Simplified Acute Physiology Score 3 (SAPS 3), to establish a predictive index of mortality for patients admitted to intensive care units.

Coexisting medical conditions were obtained from the patients' medical records and clinical history. These were used to calculate the Charlson Comorbidity Index (Charlson Index).

Instrumental score calculations were performed by the physician responsible for the ICU stay duration and added to the study's database, along with information on the following laboratory tests of interest: C-reactive protein (mg/l), leukocytes (103/mm^3), lymphocytes (103/mm^3), lactate (U/l), creatine phosphokinase (U/l), lactate dehydrogenase (IU/l), D-dimer (ng/l), and ferritin (mcg/l) levels.

ARDS was diagnosed according to the Berlin definition[12].

Ventilatory variables

For the evaluation of respiratory mechanics, patients' synchronization with the mechanical ventilator was assessed using the pressure, flow, and volume curves. If patients had any condition preventing the correct calculation of these parameters, researchers were instructed to disregard the data and collect it later at an appropriate time. Three ICU professionals collected and adjusted all parameters and mechanic respiratory variables daily in the morning. Arterial blood gases were collected at the same time as mechanical ventilator parameters.

The invasive ventilatory strategy adopted was lung-protective ventilation, which consisted of initial adjustments of Vt between 4 and 6 mL/kg PBW, plateau pressure (Pplateau) ≤ 30 cmH_2O, initial positive end-expiratory pressure (PEEP) through PEEP table, maintenance of driving pressure $\Delta P < 15$ cmH_2O, and permissive hypercapnia guided by the pH levels of serial blood gases levels. Patients with a PaO_2/FiO_2 ratio < 150 cmH_2O were selected to receive PP treatment and maintain it for 16 hours.

The ventilatory variables collected and evaluated included: driving pressure (ΔP; cmH_2O); respiratory system compliance (C_{rs}; static complacency - mL/cmH_2O); tidal volume (Vt; mL); Vt/kg (mL/kg PBW); adjusted respiratory rate (RRa; breaths/min); total respiratory rate (RRt; breaths/min); positive end-expiratory pressure (PEEP; cmH_2O); peak pressure (Peak; cmH_2O); plateau pressure (Pplateau; cmH_2O); inspiratory time (Ti; s); fraction of inspired oxygen (FIO_2; %); partial pressure of arterial oxygen (PaO_2; mmHg); partial pressure of arterial carbon dioxide ($PaCO_2$; mmHg); PaO_2/FIO_2 (mmHg); bicarbonate (HCO_3; mEq/l), and arterial oxygen saturation (SaO_2; %).

Statistical analysis

Values are presented as mean and standard deviation, median (1st-3rd quartile), or percentage. Data normality and homogeneity of variance were verified using Kolmogorov-Smirnov and Levene tests, respectively.

The PP and non-prone groups were compared using Student's t or Mann-Whitney U tests for numerical variables, and chi-square or Fisher's exact test for categorical variables. To identify predictor variables, a binary logistic regression was performed, meeting the requirements of the absence of outliers and multicollinearity. Statistical significance was set at $p < 0.05$. All tests were performed using the IBM SPSS 20.0. (Armonk, NY).

Results

Figure 1 shows the flowchart of the study. A total of 64 eligible patients were included in this analysis.

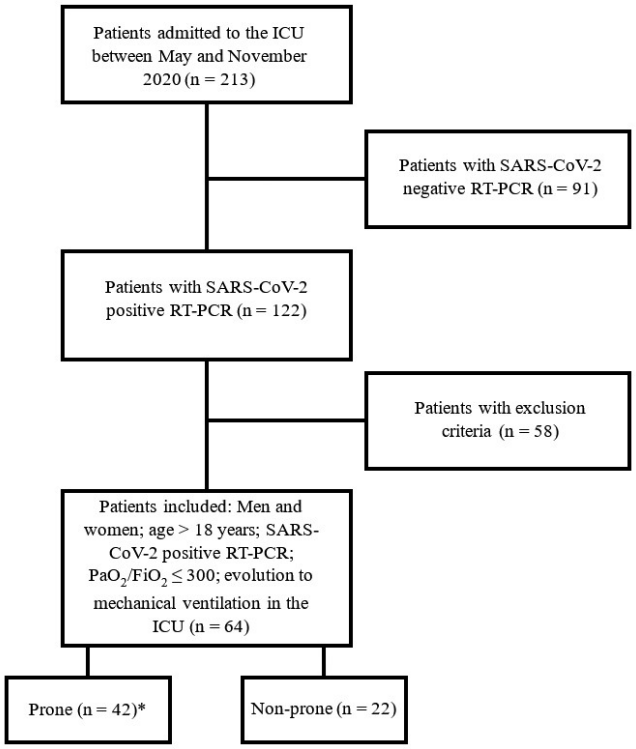

Figure 1. Flowchart of the study. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ICU: intensive care unit; RT-PCR: reverse-transcriptase polymerase chain reaction; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure (PaO_2) to fraction of inspired oxygen (FiO_2). *No patients had absolute contraindications to prone position.

Clinical and demographical variables

The study's sample consisted of 64 patients; there was an identical prevalence of men and women (50%), with no significant differences in age between the PP and non-prone groups. There was a higher proportion of women in the PP group (59.5%). The Charlson Comorbidity Index score was lower in the PP group ($p = 0.037$), 65.6% of the sample (42) met the criteria for PP and underwent the procedure. These patients frequently used neuromuscular blocking agents (95.2%), had longer ICU stays (18 [13-31] days), and had a higher duration of MV (19.3 ± 12.6 days) relative to the non-prone group; however, there was no significant differences in the proportion of deaths ($p = 0.389$).

The mortality rate of patients who had undergone invasive MV was 56.3%. Of the total number of patients (64), 44% were diagnosed with moderate ARDS (100 mmHg < PaO_2/FIO_2 ≤ 200 mmHg). In general, patients in the study progressed to the MV support within the first three days of hospitalization; this matched with the first PP session. Table 1 summarizes the different outcomes, baseline demographic variables, clinical and therapeutical characteristics of the total sample and of those in the non-prone and PP groups. Baseline data, severity scores, and laboratory tests were performed on the first day of hospitalization.

Ventilatory variables

The mean value of each ventilatory variable was obtained by collecting daily values for each patient over 28 days. With

Table 1. Demographical, clinical and baseline therapeutical characteristics of the studied sample (to be continued).

Variable	Total sample (n = 64, 100%)	Non-Prone (n = 22, 34%)	Prone (n = 42, 66%)	*p*
Age, years	64.5 ± 12.8	66.7 ± 13.5	63.4 ± 12.4	0.327
Sex, male., n (%)	32 (50.0)	15 (68.2)	17 (40.5)	0.035*
PBW, kg	59.2 ± 11.0	62.8 ± 10.2	57.3 ± 11.0	0.056
SAPS 3 admission	49 (42-58)	51 (45-66)	47.5 (41-55)	0.083
SOFA admission	3 (2-6)	4 (2-9)	3 (2-6)	0.083
Charlson Index	3 (2-5)	4.4 ± 2.5	3.1 ± 1.7	0.037*
Comorbidities, %				
Hypertension	43 (67.2)	16 (72.7)	27 (64.3)	0.495
Diabetes	28 (43.8)	8 (36.4)	20 (47.6)	0.389
Heart disease	11 (17.2)	4 (18.2)	7 (16.7)	0.879
Pneumopathy	6 (9.4)	2 (9.1)	4 (9.5)	0.955
Nephropathy	6 (9.4)	4 (18.2)	2 (4.8)	0.080
Hepatopathy	1 (1.6)	0 (0.0)	1 (2.4)	0.466
Cancer	4 (6.3)	2 (9.1)	2 (4.8)	0.497
AIDS	1 (1.6)	1 (4.5)	0 (0.0)	0.164
Smoking, %				0.761
Smoker	9 (14.1)	4 (18.2)	5 (11.9)	
Ex-smoker	14 (21.9)	5 (22.7)	9 (21.4)	
Never Smoker	41 (64.1)	13 (59.1)	28 (66.7)	
Leukocytes, $10^3/mm^3$	8330 (6.555-11.605)	7465 (6.020-9.570)	9830 (6.610-11.660)	0.091
Lymphocytes, $10^3/mm^3$	915.4 ± 413.9	831.2 ± 381.3	959. ± 427.9	0.242
Drugs (%)				
Corticosteroids	56 (87.5)	17 (77.3)	39 (92.9)	0.111
NMB	44 (68.8)	4 (18.2)	40 (95.2)	0.010*
Vasopressor	48 (75.0)	19 (86.4)	29 (69.0)	0.129
Antimicrobial	63 (98.4)	22 (100.0)	41 (97.6)	0.466
Hydroxychloroquine	7 (10.9)	2 (9.1)	5 (11.9)	0.732
Azithromycin	39 (60.9)	14 (63.6)	25 (59.5)	0.749
Oseltamivir	21 (32.8)	9 (40.9)	12 (28.6)	0.318
C-reactive protein, mg/L	153.5 ± 64.76	141.9 ± 59.0	159.4 ± 67.4	0.393
Lactate, U/L	1.15 (1.00-2.00)	1.9 (1.0-2.0)	1.0 (1.0-1.65)	0.110
Creatine phosphokinase, U/L	130 (58-304)	135 (88-287)	124 (4-307.5)	0.341
Lactate dehydrogenase, IU/L	452.5 (361.5-675.5)	442 (367-560)	462.5 (356-774)	0.025*
Hemodialysis, n (%)	22 (34.4)	10 (45.5)	12 (28.6)	0.177
Tracheostomy, n (%)	15 (100%)	4 (27%)	11 (73%)	-
D - Dimer, ng/L	1876.5 (1131.5-5603.5)	6250 (1814-8106.4)	1590 (955.5-3747.5)	0.063
Ferritin, mcg/L	839.7 (509.7-1571.5)	866.4 (463-1373)	828.5 (529.4-1809)	0.585
Days in the ICU	17 (8-27.5)	7.5 (5-23)	18 (13-31)	0.010*
Duration in hours of the first prone	-	-	16.8 ± 1.16	-
Length of ICU stay prior to prone positioning, days	-	-	2.1 ± 1.2	-
Days of mechanical ventilation	16.7 ± 12.1	11.5 ± 9.4	19.3 ± 12.6	0.005*
Days until intubation	1.1 ± 2.0	1 ± 1.3	1.2 ± 2.2	0.862
Death in the ICU, n (%)	36 (56.3)	14 (63.6)	22 (52.4)	0.389

Values are presented as mean and standard deviation (±) or median (1st - 3rd quartiles) or percentage. SAPS 3: Simplified Acute Physiology Score 3; SOFA: Sequential Organ Failure Assessment; Charlson Index: Charlson Comorbidity Index; NMB: Neuromuscular blocker; PBW: Predicted body weight; ICU: intensive care unit. Student's t or Mann-Whitney U tests for numerical variables, and chi-square or Fisher's exact test for categorical variables. *Statistical significance - p-value < 0.05.

the exception of PaO_2/FIO_2 ratio, the ventilatory variables were not significantly different when comparing the PP and non-prone groups, as shown in Table 2.

Arterial blood gases values were compared between the patients on the first day of MV. The group who subsequently underwent PP had a lower baseline PaO_2/FIO_2 ratio; however, in both groups, the PaO_2 values exceeded 100 mmHg, characterizing hyperoxemia. The non-prone group had significantly lower values of pH and HCO_3 and higher values of $PaCO_2$, characterizing acidosis. There were no statistical differences among the investigated ventilatory variables, as shown in Table 3.

Table 2. Mean values of ventilatory variables in the studied sample over 28 days of hospitalization in the intensive care unit.

Variable	Total sample (n = 64, 100%)	Non-Prone (n = 22, 34%)	Prone (n = 42, 66%)	*p*
ΔP, cmH_2O	13.4 ± 2.8	12.8 ± 3.0	13.7 ± 2.6	0.218
C_{rs}, mL/cmH_2O	34.2 ± 10.3	36.9 ± 12.5	32.7 ± 8.8	0.126
VT/kg, mL/kg PBW	7.4 ± 1.2	7.2 ± 1.2	7.5 ± 1.2	0.423
PaO_2/FIO_2, mmHg	227.5 ± 73.6	269.7 ± 92.0	205.4 ± 50.4	0.005*

Values are presented as mean and standard deviation (±). ΔP (cmH_2O), Driving Pressure; Crs (mL/cmH_2O), respiratory system compliance; VT/kg, (mL/kg PBW) tidal volume by predicted body weight (PBW); PaO_2/FIO_2 (mmHg), ratio of partial oxygen pressure to inspired oxygen fraction; ICU, intensive care unit; Mann-Whitney U tests for numerical variables.*Statistical significance - p-value < 0.05.

Table 3. Arterial blood gases and ventilatory variables of studied subjects on the first day of mechanical ventilation.

Variable	Total sample (n = 64, 100%)	Non-Prone (n = 22, 34%)	Prone (n = 42, 66%)
Ventilatory variables			
PCV, n (%)	51 (79.7)	21 (95.5)	30 (71.4)
RRa, breaths/min	20.0 (18.0-22.0)	20.0 (18.0-20.0)	20.0 (18.0-22.0)
RRt, breaths/min	20.0 (18.0-24.0)	20.0 (20.0-24.0)	20.0 (18.0-24.0)
PEEP, cmH_2O	10.0 (8.0-12.0)	10.0 (8.0-10.0)	10.0 (8.0-12.0)
Peak, cmH_2O	26.0 ± 5.3	24.4 ± 5.1	26.9 ± 5.2 *
Pplateau, cmH_2O	23.9 ± 4.7	24.3 ± 4.9	23.7 ± 4.7
ΔP, cmH_2O	14.2 ± 3.9	14.8 ± 3.3	14.00 ± 4.1
C_{rs}, mL/cmH_2O	30.0 (24.6-35.3)	30.15 (23.3-35.7)	29.3 (25.3-35.0)
VT, mL	409.0 ± 79.0	416.3 ± 86.0	405.1 ± 75.9
Ti, s	0.90 (0.90-1.00)	0.98 (0.90-1.00)	0.90 (0.85-1.00)
FIO_2, %	1.00 (0.80-1.00)	1.00 (0.70-1.00)	1.00 (0.80-1.00)
Arterial blood gases variables			
pH	7.33 ± 0.1	7.29 ± 0.1	7.35 ± 0.1*
PaO_2, mmHg	110.5 (88.0-160.0)	161.9 ± 65.3	111.4 ± 45.8 *
$PaCO_2$, mmHg	43.0 (36.0-48.0)	42.0 (35.0-47.0)	43.0 (38.0-48.0) *
HCO_3, mEq/L	22.5 (19.0-26.0)	20.1 ± 6.7	24.2 ± 4.4 *
SaO_2, %	98.0 (96.0-99.0)	99.0 (98.0-100.0)	97.0 (95.0-99.0) *
PaO_2/FIO_2	142 (100-192)	187.5 ± 59.1	130.5 ± 58.1 *

Values are presented as mean and standard deviation (±) or median (1st - 3rd quartiles) or percentage. PCV: pressure-controlled ventilation; RRa: adjusted respiratory rate; RRt: total respiratory rate; PEEP: positive end-expiratory pressure; Peak: peak pressure; Pplateau: plateau pressure; ΔP: driving pressure; Crs: pulmonary static compliance; VT: tidal volume; Ti: inspiratory time; FIO_2: fraction of inspired oxygen. PaO_2: partial pressure of arterial oxygen; PaCO2, partial pressure of arterial carbon dioxide; HCO3, sodium bicarbonate; SaO2, arterial oxygen saturation; PaO2/FIO2, ratio of arterial oxygen partial pressure to inspired oxygen fraction; Mann-Whitney U tests for numerical variables. *Statistical significance p-value < 0.05 vs. no prone.

Most patients (79.7%) were ventilated in the pressure-controlled ventilation (PCV) mode, with a respiratory rate of 20 (18.0-22.0) breaths per minute, and PEEP of 10.0 (8.0-12.0) cmH_2O, C_{rs} of 30.0 (24.6-35.3) cmH_2O; no significant differences between groups were observed. The mean values of ΔP (14.2 ± 3.9 cmH_2O) and Pplateau (23.9 ± 4.8 cmH_2O) demonstrated that patients required the lung-protective ventilatory strategy (Table 3). A binary logistic regression was performed to verify whether C_{rs} was a predictor of PP in the sample. The model containing C_{rs} was not significant (x^2 (1) 1.043; p = 0.292; R^2 Nagelkerke = 0.518). Thus, C_{rs} was not a significant predictor of PP (OR 1.702; CI 95% 0.962 – 1.131).

Discussion

The main findings of the present study were: (1) the values of ventilatory variables in patients who required PP did not differ significantly in relation to patients who remained in supine position while receiving MV. Variables of ventilatory mechanics, such as ΔP, C_{rs}, Pplateau, and Vt, showed no significant differences between the groups of patients. (2) The PaO_2/FiO_2 ratio was the only ventilatory variable that characterized the group that required PP, and (3) patients who underwent PP required longer periods of MV, leading to a prolonged stay in ICU. (4) The clinical and demographical characteristics such as age, PBW, SAPS 3, SOFA score, comorbidities, days until intubation, and death in ICU were similar for PP and supine position groups.

The mortality of patients in this study was lower than that presented by Ranzani et al.[13], in an investigation with data collection from the first 250,000 hospital admissions for COVID-19 in Brazil. The global mortality rate in the ICU was 55%, while among those patients who underwent MV it was 86%[13]. The median length of ICU stay was 7 (3-15) days, similar to the present study which was 7.5 (5-23) days for patients in the non-prone group. In contrast, patients in the PP group had longer ICU stay of 17 (8-27) days. Several factors can contribute to differences in mortality rates between different regions of Brazil, such as heterogeneity of the health system and resources, the temporal spread of the epidemic, and disparities in adherence to best practices for the clinical management of critically ill patients[13]. Some of these factors may explain the difference in mortality rates found in our study.

In the present study, the mortality rate between the PP and non-prone groups did not show any significant differences, unlike the findings of Langer et al.[10] and Guérin et al.[14]. In the latter study, prone patients had a more severe form of the disease and significantly higher mortality rate (45% vs. 33%, p < 0.001)[14]. If there were a comparison between the two groups with indications for PP, and one group was not provided the PP treatment, there would likely be a difference in mortality, as demonstrated in other studies[15]. Our results are interesting as patients who theoretically were more severe from a ventilatory point of view, had a mortality rate similar to those who did not meet the criteria for PP.

According to Gu et al.[16], the PaO_2/FiO_2 ratio was an independent predictor of COVID-19-related mortality, with an area under the ROC curve of 0.865 (95% CI: 0.748-0.941, p <0.0001). Therefore, PP, in theory, is in line with the mortality rate of a group more susceptible to worse outcomes (lower PaO_2/FiO_2 ratio) relative to that of a lower risk group (higher PaO_2/FiO_2 ratio). PP increased baseline PaO_2/FiO_2 ratio from a value indicative of moderate ARDS to a value indicative of mild ARDS (D0, 130.5 ± 58.1 versus 28-day mean, 205.39 ± 50.43). Pronation improves the perfusion-ventilation coupling, as shown by Lamm et al.[17], which results in an improvement in the PaO_2/FiO_2 ratio[18]. Interestingly, our results pointed to an important oxygenation deficit, even after almost a month of hospitalization in the ICU.

In the PROSEVA study, the average length of ICU stay was longer for patients who survived, in both PP and supine groups[14]. We believe that the improvement in oxygenation in PP allowed for patient support with less harmful MV parameters, thereby preventing early negative outcomes, justifying the longer duration of ICU stay. According to Galiatsou et al.[19], PP, compared to the supine position, markedly reduces hyperinflated lung areas while promoting alveolar recruitment, thereby acting as an extension of the lung-protective strategy.

A survey composed of several reports on the transmission of COVID-19 infection in Brazil showed that a high proportion (65.5%) of infections occurred in individuals aged > 50 years[20]. Patients older than 65 years with comorbidities, who were infected with SARS-CoV-2, showed increased ICU admission and mortality rates[21]. This was following the present findings, wherein the sample was composed of patients with severe COVID-19-related ARDS who underwent invasive MV. The mean age of the sample was 64.5 ± 12.8 years, with no significant age difference between PP and non-prone groups (63.4 ± 12.4 vs 66.7 ± 13.5, p > 0.05). The most prevalent comorbidity was systemic arterial hypertension (67.2%).

In our study, there were no significant differences between the PP and non-prone groups in demographic, clinical, and baseline therapeutical variables, except for the Charlson comorbidity index. This was comparable to the results of the PROSEVA study, wherein PP and non-prone group characteristics were similar on admission, except for the use of vasopressors, the SOFA score, and the use of neuromuscular blockers, the last of which, in our study, was also used more often in the PP group[14].

There were no differences in the values of Vt, C_{rs}, and ΔP when comparing the PP and non-prone groups. The mean values of these ventilatory variables suggested that the patients underwent protective lung ventilation (ΔP). Vt/kg values were above 6 mL/kg because at the beginning of hospitalization, patients received lower Vt; however, with the improvement in clinical parameters, there was a progressive increase in Vt with the transition to assisted and spontaneous

ventilation modes. Thus, the average values exceeded 6 mL/kg.

Ferrando et al.[22] reported no differences in C_{rs} and ΔP values when comparing mild, moderate, and severe COVID-19-related ARDS cases. The ventilatory variables C_{rs}, Pplateau, and ΔP in our study were comparable to previously published ARDS patient cohorts, in which there were no differences at baseline for COVID-19-related ARDS and non-COVID-19-related ARDS[23]. We evaluated the mean 28-day C_{rs}; however, Laverdure et al.[24] evaluated the daily evolution of this variable and found that high baseline C_{rs} values did not decrease during the 28 days, suggesting a lack of transition from a high to low C_{rs} phenotype.

Gu et al.[16] found PaO_2/FiO_2 as an independent predictor of COVID-19 mortality. In our study, the baseline PaO_2/FiO_2 ratio in samples was indicative of moderate ARDS, with 44% (28) of them having this diagnosis. Hyperoxia was observed in both the PP and non-prone groups, however, low values of the PaO_2/FiO_2 ratio indicated alterations in gases exchanges. According to the LUNG-SAFE study, hyperoxia is frequent at the beginning of ARDS, but in most cases, it is not sustained, which concurred with our findings, showing a significant reduction in FiO_2 over the days of evaluation[25].

Our analyses were based on arterial blood gases analysis and FiO_2, which were daily obtained at a specific time; therefore, they may not reflect the spectrum of values that occurred throughout that day. However, we believe that this fact did not interfere with the mortality outcome since there was no significant difference in the PaO_2/FiO_2 ratio on discharge and at death (Table 1S, supplementary material.).

Our study has some limitations related to its observational nature. It restricts the possibility of attesting chance between different outcomes and between-group differences. It is impossible to ensure the equal distribution of confounding factors. They interfere with the sample size of the groups, which can result in loss of statistical efficiency. However, this study in COVID-19-related ARDS provides an important contribution to the scientific community by demonstrating the clinical, demographical and ventilatory aspects of patients who progress to the PP stage, a MV strategy still underexplored and evolving with new findings.

In conclusion, most patients with ARDS due to COVID-19 required PP, especially women over 60 years old, with the first prone cycle within the first three days of hospitalization. These patients used more neuromuscular blockers and had a longer hospital stay. Regarding their ventilatory characteristics, upon admission to the ICU, these patients had mechanical respiratory values (C_{rs}, Pplateau, and ΔP) similar to those of patients who did not require PP. Only the PaO_2/FiO_2 ratio indicated previous patients who progressed to the prone position.

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Conflict of interest

The authors declare no conflict of interest

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GBC, HAM, EVC, EPG: data acquisition; GBC, HAM, EPG, MMR, BVP: analysis and interpretation; EVC, EPG, BVP: study conception and design; GBC, HAM, EVC: providing intellectual content of critical importance; EPG, MMR, BVP: drafting of preliminary versions; GBC, HAM, EVC, EPG, MMR, BVP: revision of preliminary versions; GBC, HAM, EVC, EPG, MMR, BVP: approval of the final version.

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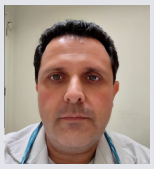

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Supplementary Material

Supplementary material accompanies this paper.

Table 1S. Demographic, oxygenation, and baseline severity scores among patients with death outcome and discharge from the intensive care unit

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