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Effects of the prone position on arterial blood gas analysis and respiratory parameters of acute respiratory distress syndrome patients: An observational retrospective study

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ABSTRACT

Objective: To investigate the effect of the first prone position on arterial blood gas analysis and respiratory parameters of acute respiratory distress syndrome (ARDS) patients with and without COVID.

Methods: This study was conducted retrospectively with 22 COVID-ARDS and 22 non-COVID ARDS patients, who were placed in a prone position for at least 16 hours on the first day at the intensive care unit admission, and arterial blood gas analysis was taken in the pre-prone, prone and post-prone periods.

Results: PaO_2 were significantly increased in the pre-prone *vs*. prone comparison in both groups, but the increase in the PaO_2/FiO_2 ratio was not significant. In comparing the pre-prone *vs*. post-prone PaO_2/FiO_2 ratios, there was a significant difference only in the non-COVID ARDS group.

Conclusions: The improved oxygenation provided by prone positioning is more permanent with the "post-prone effect" in non-COVID ARDS patients. This can be attributed to the differences in the pathogenesis of the two ARDS types.

KEYWORDS: Respiratory distress syndrome; Prone position; Intensive Care Units; Respiration; Ventilation; Oxygenation

1. Introduction

Coronavirus mostly affects the respiratory system and can cause acute respiratory distress syndrome (ARDS) by damaging alveolar epithelial cells in the lung[1]. ARDS due to COVID-19 (COVID ARDS) has different features from ARDS due to other causes (non-COVID ARDS). Age and obesity are risk factors for both ARDS types, while diabetes and cardiovascular diseases (including hypertension and hyperlipidemia) are risk factors only for COVID ARDS[2]. This may be related to the difference in the pathogenesis between COVID ARDS and other ARDS types. Other pathogens cause indirect endothelial damage with their inflammatory response while coronavirus causes direct endothelial damage[2]. Autopsy studies display microvascular thrombosis, direct endothelial infection, and endothelial cell death[3,4].

Gattinnoni *et al*. divided COVID ARDS into two subtypes[5,6].

Significance

Prone positioning gained popularity with the pandemic. We investigate the effect of the first prone position on arterial blood gas analysis and respiratory parameters of acute respiratory distress syndrome (ARDS) patients with and without COVID. Our study revealed that, in comparing the pre-prone and post-prone, there was a significant difference in PaO_2/FiO_2 ratios of the non-COVID ARDS group. In other words, improvement in oxygenation with prone positioning is more lasting in non-COVID ARDS patients.

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They observed isolated viral pneumonia with preserved compliance (>50 mL/cmH_2O) in L type, and severe ARDS with impaired compliance (<40 mL/cmH_2O) in H type (20%-30% of cases). Positive end-expiratory pressure (PEEP) values of 8-10 cm H_2O will be sufficient since the recruiting ability is low in the L type and the prone position should be applied as a rescue maneuver, not routinely. In type H, higher PEEP and routine prone positioning are recommended if hemodynamics permits, since recruiting ability is high[5]. However, in a multicenter study in intensive care units (ICU) in Spain, respiratory parameters [compliance, plato pressure (Pplato), driving pressure (DP)] of COVID ARDS patients and non-COVID ARDS patients were found to be similar, and no difference was found in 28-day mortality[7].

Prone positioning has been used for years to increase oxygenation in ARDS patients[8]. Early and extended prone positioning is more effective in treating ARDS patients[9]. Considering the benefits of prone positioning in treating moderate to severe ARDS, the Surviving Sepsis Campaign 2020 and 2021 Guidelines and World Health Organization guidelines recommend 12-16 hours of prone positioning per day for adults and children with severe COVID ARDS[10-12]. Early and extended prone positioning is more effective in ARDS patients[13]. These recommendations also apply to patients with other COVID ARDS[14,15].

This study aims to investigate the effect of the first prone position on arterial blood gas analysis parameters and respiratory parameters of ARDS patients with and without COVID.

2. Patients and methods

2.1. Ethical statement

This study was approved by the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Decision Number: 2021-20-07).

2.2. Study design

ARDS patients who were admitted to Anesthesia and Reanimation General Intensive Care Unit, Bakirkoy Dr. Sadi Konuk Training, and Research Hospital between 1 January 2018 and 1 January 2021 were included retrospectively with Structured Query Language (SQL) queries. All patients were orotracheally intubated. Included patients were placed in a prone position for 16 hours on the first day of intensive care admission, and arterial blood gas analysis were taken in the pre-prone, prone and post-prone periods.

2.3. Inclusion and exclusion criteria

The definite COVID-19 diagnosis was confirmed by both radiological images (chest computed tomography) and PCR test (Bio-Speedy Covid-19 RT-Qpcr detection Kit-Bioeksen, Turkey) obtained from the nasal swab sample. Patients aged 18 years or older, diagnosed with ARDS, hospitalized in the ICU for more than 24 hours and prone positioned for more than 16 hours were included in the study. Patients stayed in the ICU for less than 24 hours, or were not placed in the prone position on the first day of the ICU admission, or were placed in the prone position for less than 16 hours, patients whose arterial blood gas sample was not taken 8 hours before and after the prone position or 16 hours during the prone positioning, COVID ARDS patients with negative PCR during the first 24 hours of ICU admission, and patients with missing data were excluded.

2.4. Demographic and arterial blood gas analysis parameters

Demographic parameters of the patients (age, height, weight, SOFA, APACHE-II scores, *etc.*) and arterial blood gas analysis parameters [pH, partial arterial carbon dioxide pressure ($PaCO_2$), partial arterial oxygen pressure (PaO_2), arterial bicarbonate (HCO_3), lactate] were obtained from the data pool with SQL queries and transferred to Excel.

2.5. Respiratory parameters

All patients were ventilated in pressure control mode (PCV) with a Maquet Servo-i (Sweden) ventilator. The respiratory parameters of the patients [end-inspiratory pressure (P_{peak}), airway inspiratory pressure (driving pressure, ΔP_{insp}), positive end-expiratory pressure (PEEP), mean airway pressure (P_{mean}), respiratory rate (frequency, RR), expiratory tidal volume (TVe), inspiratory time (T_{insp}), compliance (C), work of breathing (WOBv), and inspiratory-expiratory ratio (I:E ratio)] were obtained from mechanical ventilators when they were ventilated with PCV. All patients were ventilated with 5% inspiratory slope time. The ventilatory parameters of the patients were obtained by writing the patient data generated at zero value per minute to the database *via* the customized driver for integration (Metavision back server). Since all patients were deeply sedated and paralyzed, ventilated with PCV, these values representing the ventilatory parameters per minute recorded by the software and mechanical power (MP) values were calculated with the pre-defined pressure control practical mechanical power equation ($MP_{pcv(simpl)}$)[16]:

$$MP_{pcv(simpl)} = 0.098 \times RR \times \Delta V \times (PEEP + \Delta P_{insp})$$

2.6. Statistical analysis

GraphPad Prism (v5.01) program was used for statistical analysis. The homogeneity of the variables was determined by the Shapiro-

Wilk normality test. Measurement data were expressed as median (Q1, Q3) and compared by the Mann-Whitney *U* test. Categorical variables were expressed as frequency distribution and percentage and compared by the chi-square test. Pre-prone, prone, and post-prone arterial blood gas analysis and respiratory parameters were compared with repeated multivariate ANOVA. Benforini tests were used for *post hoc* analysis. *P* value <0.05 was considered statistically significant.

3. Results

A total of 355 patients diagnosed with COVID ARDS (confirmed by chest computed tomography at admission) and 96 patients diagnosed with non-COVID ARDS were included retrospectively with SQL queries. Among all ARDS patients, 185 COVID ARDS and 44 non-COVID ARDS patients were placed in a prone position for 16 hours on the first day of intensive care admission, out of

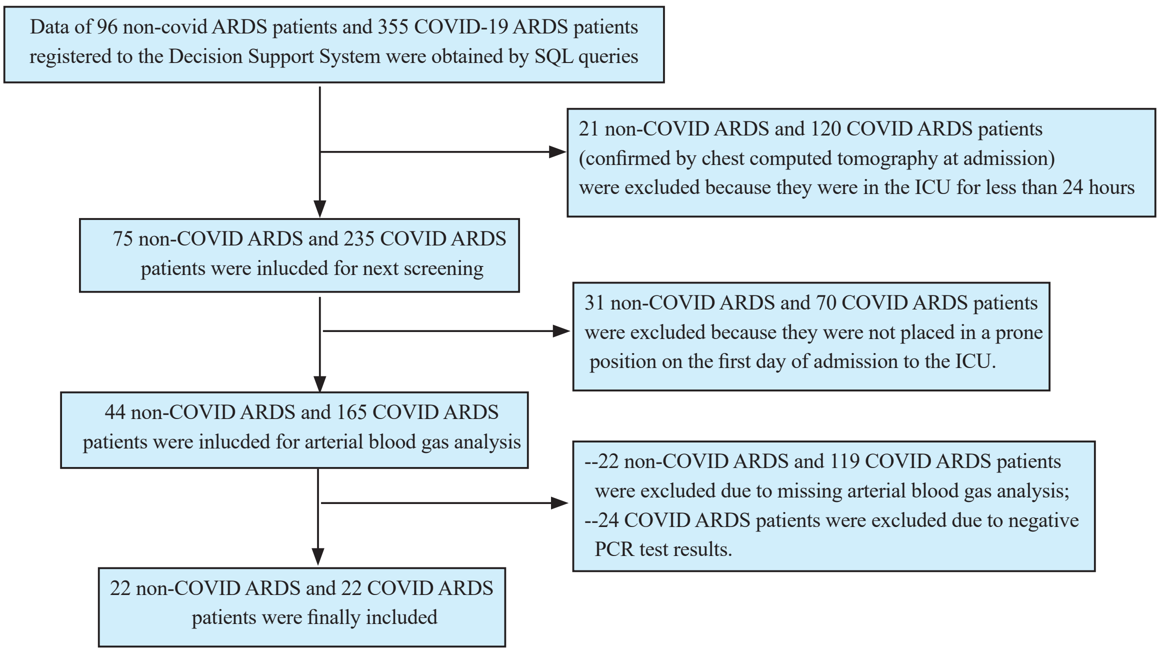

Figure 1. The study flow diagram. ARDS: acute respiratory distress syndrome.

Table 1. Demographic characteristics, respiratory parameters, and arterial blood gas analysis result at admission.

Characteristics	**COVID ARDS (*n*=22)**	**non–COVID ARDS (*n*=22)**	**χ^2/*U***	***P***
Sex				
Female, %	18	27	1.8	0.2
Intensive care mortality, %	50	27	10.2	0.001
Age, year, median, Q1, Q3	51 (45, 61)	59 (46, 67)	196.5	0.3
Height, cm, median, Q1, Q3	171 (170, 180)	175 (160, 178)	222.5	0.7
Predicted body weight, kg, median, Q1, Q3	66 (62, 75)	68 (54, 72)	228.0	0.8
Length of stay in ICU, hours, median, Q1, Q3	455 (252, 586)	367 (228, 590)	225.5	0.7
Mechanical ventilation time, hours, median, Q1, Q3	348 (222, 469)	302 (182, 513)	224.0	0.7
APACHE II score, median, Q1, Q3	20 (17, 23)	21 (16, 24)	230.5	0.8
SOFA score, median, Q1, Q3	8 (6, 11)	9 (5, 11)	231.5	0.8
MP, J/minute, median, Q1, Q3	15.5 (13.5, 18.3)	14.4 (12.7, 18.2)	197.0	0.3
WOBv, J, median, Q1, Q3	1.3 (1.2, 1.5)	1.3 (1.2, 1.5)	220.0	0.6
Respiratory rate, /min, median, Q1, Q3	14 (13, 15)	13 (12, 14)	119.5	0.01
PEEP, cmH_2O, median, Q1, Q3	9.3 (8, 10)	8.5 (7.8, 9.5)	168.5	0.08
TVe, mL, median, Q1, Q3	499 (452, 540)	472 (438, 532)	214.0	0.5
P_{peak}, cmH_2O, median, Q1, Q3	24 (22, 27)	25 (23, 27)	232.0	0.8
T_{insp}, second, median, Q1, Q3	–0.03 (–0.3, 0.3)	–0.2 (–0.5, 0.05)	231.5	0.8
Compliance, mL/cmH_2O, median, Q1, Q3	33 (29, 42)	30 (27, 37)	223.0	0.8
I:E ratio, median, Q1, Q3	0.8 (0.6, 1.0)	0.7 (0.5, 0.9)	185.0	0.2
pH, median, Q1, Q3	7.35 (7.30, 7.42)	7.35 (7.21, 7.44)	228.0	0.7
$PaCO_2$, mmHg, median, Q1, Q3	60 (45, 67)	57 (42, 66)	209.0	0.4
PaO_2, mmHg, median, Q1, Q3	71 (63, 95)	88 (62, 120)	197.0	0.3
Horowitz ratio, median, Q1, Q3	135 (117, 240)	180 (134, 250)	204.0	0.3
FiO_2, median, Q1, Q3	49 (41, 60)	45 (50, 53)	234.0	0.8
Lactate, meq/L, median, Q1, Q3	1.0 (1.5, 1.6)	1.2 (1.9, 1.9)	192.5	0.2

MP: Mechanical power; I:E ratio: inspiratory-expiratory ratio; PEEP: positive end-expiratory pressure; Tve: expiratory tidal volume; P_{peak}: end-inspiratory pressure; T_{insp}: inspiratory time; WOBv: work of breathing ventilatory.

which, only 22 non-COVID ARDS patients and 46 COVID ARDS patients had the result of arterial blood gas analysis. Since the PCR test results of 24 of the COVID ARDS patients turned negative during the first 24 hours of ICU stay, the remaining 22 patients were included in the study (Figure 1).

3.1. Demographic characteristics, respiratory parameters, and arterial blood gas analysis result at admission

The demographic data, respiratory parameters, and arterial blood gas analysis parameters at admission to the ICU are shown in Table 1. No statistically significant difference was found between the gender, age, height, predicted body weight (PBW), intensive care mortality, length of stay in the ICU, mechanical ventilation time, and scores (SOFA, APACHE-II) between the COVID ARDS and non-COVID ARDS groups (Table 1). The ICU mortality rate is statistically significantly higher in COVID ARDS patients (P=0.001) (Table 1).

There was a statistically significant difference in respiratory rate between the COVID ARDS and non-COVID ARDS groups (P=0.01). However, no difference was found in other respiratory parameters (Table 1). No significant difference was found in pH, lactate, PaO_2, FiO_2, or Horowitz ratio values (Table 1).

3.2. Respiratory parameters and arterial blood gas analysis result in pre–prone, prone, and post–prone periods

A statistically significant difference was found in PaO_2 of both COVID ARDS and non-COVID ARDS patients (P=0.01 and P=0.03), and a statistically significant difference was found in the Horowitz ratio and I:E ratio of non-COVID ARDS patients with prone position (P=0.02 and P=0.002). In post hoc analysis (Benforini tests), a statistically significant difference was found in PaO_2 of both COVID ARDS and non-COVID ARDS patients when pre-prone *vs*. prone (P=0.006 and P=0.03), and a statistically significant difference was found in the Horowitz ratio and I:E ratio of non-COVID ARDS

Table 2. Respiratory parameters and arterial blood gas analysis result of COVID ARDS patients in pre-prone, prone and post-prone periods (n=22, mean±SD).

Parameters	Pre–prone	Prone	Post–prone	*F*	*P*
MP, J/min	16.30 ± 4.00	17.4 ± 4.7	16.5 ± 5.4	1.534	0.23
WOBv, J	1.34 ± 0.26	1.39 ± 0.27	1.35 ± 0.29	0.944	0.40
RR, 1/min	14.10 ± 1.16	4.30 ± 1.12	14.00 ± 1.63	0.840	0.44
PEEP, cmH_2O	9.34 ± 1.35	9.32 ± 1.38	9.10 ± 1.62	1.019	0.40
TVe, mL	492 ± 72	505 ± 69	502 ± 91	0.611	0.45
P_{peak}, cmH_2O	24.92 ± 3.52	25.43 ± 4.10	24.82 ± 4.56	0.609	0.55
T_{insp}, s	1.83 ± 0.28	1.74 ± 0.27	1.85 ± 0.29	1.456	0.25
C, mL/cmH_2O	34.10 ± 8.81	33.77 ± 7.88	34.94 ± 10.63	0.452	0.64
I:E ratio	0.78 ± 0.20	0.73 ± 0.21	0.78 ± 0.17	0.705	0.50
pH	7.35 ± 0.09	7.36 ± 0.12	7.40 ± 0.08	2.227	0.12
$PaCO_2$, mmHg	58 ± 14	57 ± 19	53 ± 13	0.858	0.43
PaO_2, mmHg	81 ± 27	101 ± 24	93 ± 27	4.989	0.01
Horowitz ratio	188 ± 87	210 ± 72	213 ± 87	2.770	0.07
FiO_2 (%)	50 ± 13	50 ± 9	48 ± 13	0.750	0.48
Lactate, meq/L	1.40 ± 0.46	1.35 ± 0.51	1.12 ± 1.55	0.241	0.79

RR: respiratory rate; C: compliance.

Table 3. Respiratory parameters and arterial blood gas analysis result of non-COVID ARDS patients in pre-prone, prone and post-prone periods (n=22, mean±SD).

Parameters	Pre–prone	Prone	Post–prone	*F*	*P*
MP, J/min	14.94 ± 3.15	15.89 ± 2.82	15.96 ± 3.12	1.161	0.32
WOBv, J	1.35 ± 0.27	1.43 ± 0.19	1.38 ± 0.20	1.641	0.21
RR, 1/min	13.04 ± 0.98	13.60 ± 1.66	13.54 ± 1.63	1.226	0.30
PEEP, cmH_2O	8.51 ± 1.37	8.95 ± 1.13	8.58 ± 0.83	2.351	0.11
TVe, mL	486 ± 56	469 ± 71	497 ± 76	1.823	0.17
P_{peak}, cmH_2O	25.24 ± 4.03	26.69 ± 2.81	25.41 ± 2.38	2.302	0.11
T_{insp}, s	1.81 ± 0.38	1.84 ± 0.57	2.06 ± 0.50	2.567	0.09
C, mL/cmH_2O	34.40 ± 10.70	31.34 ± 9.40	33.11 ± 8.25	1.570	0.22
I:E ratio	0.74 ± 0.28	0.81 ± 0.28	0.93 ± 0.30	6.988	0.002
pH	7.33 ± 0.13	7.32 ± 0.16	7.34 ± 0.17	0.100	0.91
$PaCO_2$, mmHg	55 ± 20	59 ± 21	56 ± 19	0.293	0.75
PaO_2, mmHg	92 ± 32	112 ± 38	110 ± 33	3.804	0.03
Horowitz ratio	187 ± 64	228 ± 68	237 ± 79	4.463	0.02
FiO_2 (%)	50 ± 7	50 ± 8	47 ± 8	0.922	0.41
Lactate, meq/L	1.55 ± 0.50	1.57 ± 1.28	1.78 ± 1.32	0.370	0.69

patients when pre-prone *vs*. post-prone (P=0.02 and P=0.03). A significant difference in Horowitz ratios was found only in the non-COVID ARDS group. No statistically significant difference was found in other parameters (Tables 2 & 3).

4. Discussion

Prone positioning is known to be effective in the treatment of both COVID ARDS and non-COVID ARDS and its use has increased gradually during the pandemic period[17,18]. While the use rate of prone positioning was 61% in a multicenter study of COVID ARDS patients, this rate was only 6% in a LUNG SAFE study of non-COVID ARDS patients[19,20].

Oxygenation increases in ARDS patients in prone positioning[17]. Moreover, this improvement in oxygenation continues for hours after returning to the supine position in some patients[21-23]. However, it is not yet clear in which ARDS type this "post-prone effect" will be more permanent. In our study, a statistically significant increase in PaO_2 (pre-prone *vs*. prone) was observed in both COVID and non-COVID ARDS patients in prone positioning. Whilst, when we compared the pre-prone with post-prone to evaluate the post-prone effect, a significant difference in Horowitz ratios was found only in the non-COVID ARDS group. The improvement in oxygenation continues in the non-COVID ARDS group with a prone position when the patient is turned to the supine position. This can be explained by recent studies, which compared two types of ARDS patients with invasive hemodynamic monitoring in the prone and supine positions[24,25]. In these studies, Extra Vascular Lung Water (EVLW) and Pulmonary Vascular Permeability Index (PVPI) values were found to be higher in the COVID ARDS group than in the non-COVID ARDS group. As it is known, EVLW and PVPI values are associated with ARDS severity[26-28] and are determinants of prognosis in ARDS patients[29,30]. Prone position contributes to permanent recovery by reducing EVLW and PVPI in non-COVID ARDS patients[31]. These data reveal the reasons why the improvement in oxygenation of non-COVID ARDS patients in prone positions becomes more permanent with the "post-prone effect". It also strengthens the idea that COVID ARDS is a variant of classical ARDS with different pathogenesis[24].

There was no significant difference in the mean MPrs, WOB, PEEP, P_{peak}, Tve, and compliance values between COVID and non-COVID ARDS patients at ICU admission. While a statistically significant difference was found in RR between the two groups, this difference is not considered clinically significant (mean RR was 14 in the COVID ARDS group and 13 in the non-COVID ARDS group). A multicenter prospective study comparing the respiratory mechanics of COVID ARDS and non-COVID ARDS patients shows no difference in TVe, PEEP, plateau pressure, compliance, and driving pressure[7]. However, in a study conducted on 301 COVID ARDS patients in Italy, median lung compliance values were found to be 28% higher in COVID ARDS than in non-COVID ARDS[32]. Similarly, in another study, lung compliance was found to be higher in COVID ARDS patients than in non-COVID ARDS patients[5]. In another study, no significant difference was found in the median MP, PEEP, P_{peak}, TVe, dynamic compliance, RR, and I:E ratio values between the COVID and non-COVID ARDS groups[24].

In our study, PaO_2 values increased significantly after patients were in prone positioning in both the COVID and non-COVID ARDS groups, but the increase in the PaO_2/FiO_2 ratio was not significant (pre-prone *vs* prone). In previous studies, patients whose PaO_2/FiO_2 ratio increased by more than 20 mmHg during prone positioning were defined as "O_2 responders" and others as "O_2 non-responders"[33,34]. It was found that "O_2 non-responders" patients had more severe respiratory failure and a significantly higher mortality rate[19]. In another study, improvement in oxygenation after initial prone positioning was found to be an important predictor of mortality in moderate-to-severe ARDS patients[35]. Although we did not determine a cut-off for the increase in the PaO_2/FiO_2 ratio in our study, the lack of a significant increase in the Horowitz ratio may be due to this study population consisting of patients with more severe respiratory failure and higher mortality.

In addition, there was no significant difference in median MPrs, WOBv, PEEP, P_{peak}, TVe, compliance, RR, T_{insp}, and median pH, $PaCO_2$, lactate values after prone positioning in both COVID ARDS and non-COVID ARDS groups. Only in non-COVID ARDS patients, the I:E ratio in the post-prone position is significantly higher than in the pre-prone position, however, this has not been evaluated as clinically significant. In a meta-analysis of 28 studies of COVID ARDS patients, the prone position significantly increased PaO_2 and significantly decreased $PaCO_2$, but did not affect RR[36]. Again, a multicenter study on COVID ARDS patients revealed that the prone position did not affect compliance. A reduction in chest wall compliance is expected with the prone position in ARDS patients. This will cause a decrease in TVe if the patient is ventilated in PCV, and an increase in plato pressure if the patient is ventilated in volume control mode; if these are not observed, chest wall rigidity is tolerated by an increase in lung compliance[8]. In addition, the positive effects of the prone position on right ventricular function and hemodynamics lead to a decrease in hypoxia, hypercarbia, driving pressure, and Pplato[8]. ARDS patients with a greater decrease in $PaCO_2$ in the prone position have a more recruitable lung[37].

In our study, the ICU mortality rate is statistically significantly higher in COVID ARDS patients (P=0.001), but no significant difference was found in the length of stay in the ICU, and the mechanical ventilation time of all patients. A study showed that the duration of mechanical ventilation was longer in COVID ARDS patients, but no difference was found in 60-day mortality[38]. Another study found no difference in 28-day mortality between the two types of ARDS[19]. The limited number of patients in the groups (n=22) may have affected the difference in mortality rate in our study.

No significant difference was found between COVID ARDS and non-COVID ARDS in terms of sex, age, height, and predicted body weight. In a study conducted in the USA, it was determined that COVID ARDS is observed more frequently in people with high body mass index and black people[38]. In our study, these demographic parameters (race, body mass index) were not considered.

Since prone positioning in intensive care is given by the clinician's decision, different clinicians can apply this treatment to patients with ARDS of different severity. In addition, prone positioning requires an experienced team and equipment, so the treatment can be applied with a delay due to the problems in the supply of healthcare professionals or types of equipment[15].

Although there is still an ongoing debate about the similarities and differences between the two ARDS types, COVID ARDS is an ARDS variant. Prone positioning is a proven, inexpensive treatment that has been used for years in the treatment of ARDS. Its popularity has gradually increased during the pandemic period and has been frequently used. However, the improvement in oxygenation provided by prone positioning is more permanent with the "post-prone effect" in non-COVID ARDS patients. This may be attributed to the differences in the pathogenesis of the two ARDS types.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

FT, BY, SA, GOH, and ZC gave substantial contributions to the conception or the design of the manuscript; FT, SA, ZC, GOH contributed to acquisition, analysis, and interpretation of the data. All authors have participated to drafting the manuscript. FT and SA revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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