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ORIGINAL RESEARCH

Comparative analysis of standard versus prolonged prone positioning in C-ARDS: outcomes on oxygenation and respiratory mechanics

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Abstract

Background: The COVID-19 pandemic has led to increased prevalence of COVID-19-associated Acute Respiratory Distress Syndrome (C-ARDS) in intensive care units (ICUs). Prone positioning (PP) is recommended for managing ARDS to improve oxygenation and respiratory mechanics. However, the optimal duration of PP and its impact on ventilator-free days (VFD) and ICU mortality remains unclear. **Methods**: This retrospective cohort study analyzed the data of 350 C-ARDS patients intubated within 24 hours of ICU admission in the period between March 2019 and January 2023. Patients were placed in two groups based on PP duration, *i.e.*, standard PP (SPP, 16–24 hours) and prolonged PP (PPP, 25–36 hours). The primary outcome was the ICU mortality, and secondary outcomes were VFD, changes in respiratory mechanics and oxygenation indices in pre-prone, prone and post-prone periods. **Results**: SPP and PPP improved the oxygenation with significant increase in the Partial pressure of Oxygen/Fraction of inspired Oxygen (PaO_2/FiO_2) ratio and (PaO_2/FiO_2) ratio/Positive End-Expiratory Pressure (PF/PEEP) values in prone period compared to the pre-prone. Not much difference in ICU mortality or VFD was observed between the groups. Subgroup analyses showed that the survivors had lower driving pressure (DP) and mechanical power (MP) compared to those of the non-survivors. **Conclusions**: Both SPP and PPP improved the oxygenation, however no survival advantage was observed with prolonged prone sessions. PP is effective for lung-protective ventilation, and its duration should be adjusted based on the patient-specific factors. Further studies are required to optimize the PP durations for managing C-ARDS. **Clinical Trial Registration**: ClinicalTrials.gov, Registration ID: NCT06530095.

Keywords

Acute respiratory distress syndrome; COVID-19; Lung recruitment; Prone position; Respiratory mechanics; Ventilator-induced lung injury

1. Introduction

The COVID-19 pandemic has affected healthcare facilities worldwide and led to the increased prevalence of COVID-19-associated Acute Respiratory Distress Syndrome (C-ARDS) in Intensive Care Units (ICUs) [1, 2]. The mortality rates in hospitalized patients are 24–30% [3], while they are ~48% in ICU patients diagnosed with C-ARDS and received invasive mechanical ventilation [4]. Prone positioning (PP), high levels of positive end-expiratory pressure (PEEP), low tidal volume and reduced driving pressure (DP) are the recommended treatments of lung-protective ventilation in classic ARDS [5, 6]. PP improves the oxygenation and respiratory mechanics in severe ARDS patients [7]. It also homogenizes pleural pressure gradients, reduces atelectasis, allows drainage of secretions, and decreases ventilator-associated lung injury (VILI) [7]. Similarly, it improves alveolar collapse, reduces hyperinflation, and promotes homogenized lung aeration in C-ARDS [8]. There is no definite information on the PP optimal duration, however studies show that its early implementation with minimum 16–19 hours duration is more effective in ARDS patients [9–11]. Nevertheless, PP is associated with nerve damage, pressure ulcers, joint damage, retinal injury, accidental extubation and central catheter dislodgement. PP also increases the workload and burden on healthcare workers and raises exposure risks [9].

This study was aimed at investigating the impact of prolonged PP (PPP) and standard PP (SPP) on ventilator-free days (VFD) and ICU mortalities in C-ARDS patients. Moreover, the impacts of PPP and SPP on respiratory mechanics (PEEP, mean airway pressure (P_{mean}), peak inspiratory pressure (P_{peak}), respiratory rate (RR), DP, dynamic mechanical power (MP_{dyn}), *etc.*) and oxygenation indices (Oxygenation

Index (OI), Oxygenation Saturation Index (OSI)) in the pre-prone, prone, and post-prone periods were compared.

2. Materials and methods

This was an observational retrospective cohort study wherein the electronic data of C-ARDS patients intubated orotracheally within 24 hours in the ICU at Bakirkoy Dr. Sadi Konuk Training and Research Hospital for the period between 30 March 2019 and 01 January 2022 were reviewed. This dataset was retrieved by using structured query language (SQL) queries from the ImdSoft-Metavision/QlinICU Clinical Decision Support (Israel) system. The study was approved by the Bakirkoy Dr. Sadi Konuk Ethics Committee on 03 October 2022 (No: 2022-19-04) (ClinicalTrials.gov, Registration ID: NCT06530095). The moderate to severe hypoxemia patients failing to achieve PaO_2/FiO_2 ratio $>$150 despite using neuromuscular blockers were placed in prone position in 28-bed ICU. Patients were divided into group A (PP for 16–24 hours) and group B (PP for 25–36 hours). The center's pre-pandemic PP protocol for ARDS patients had sessions limited to $\leq$24 hours. This was unchanged in the initial 16 pandemic months until two factors prompted revision: (1) the evidence supporting PPP in literature [9], and (2) the need to alleviate workload on prone team. The protocol was revised by July 2021 to conduct sessions beyond 24 hours for ARDS patients. Patients having PaO_2/FiO_2 ratio $>$150 after returning to supine position following the first PP session did not undergo additional PP. Patients included in the study were of $\geq$18 years age, diagnosed with COVID-19 and confirmed by the chest computed tomography or nasopharyngeal swab PCR samples, admitted to ICU because of C-ARDS, required intubation and mechanical ventilation within 24 hours, and had at least one PP session of 16 hours. ARDS was diagnosed as per the Berlin criteria [3]. Patients were excluded from the study whose informed consent was not provided by their relatives, mean arterial pressure was $<$45 mmHg despite receiving appropriate vasoactive medications, deceased within 3 days, underwent Extracorporeal Membrane Oxygenation (ECMO), transferred to another hospital, or incomplete data entry in electronic records.

2.1 PP-SP protocol

All the patients had arterial line catheters along with orotracheal intubation, and Pressure Controlled Ventilation (PCV) via Maquet Servo-i (Sweden) mechanic ventilator. Patients received lung protective ventilation during PP and SP. Tidal volume was set at 6–8 mL per Predicted Body Weight (PBW). PEEP was titrated to maintain DP at $<$15 mmHg [2]. Patients were considered for ECMO initiation who were diagnosed with ARDS in $<$10 days, underwent minimum 2 recruitment maneuvers, PaO_2/FiO_2 ratio was $<$80, or developed severe respiratory acidosis (pH $<$7.2) after 16 hours of PP.

The patients' conversion between PP and SP was made according to the standardized clinic protocol. A 4-person ICU team was assigned to each patient for manually rotating the head to left and right every 2 hours in PP sessions. Gel rings, pillows and foam were used on the eyes, face, knees, hands, arms and toes to prevent pressure wounds. All patients were sedated and continuously infused with neuromuscular blocker (Rocuronium) during PP. Nurses documented the pressure ulcers and complications related to PP by taking photos every 12 hours during the patient's ICU stay. They were entered into the electronic database. Enteral nutrition continued in the PP period. Non-tolerant patients received this at the rate of 15–25 kcal/kg/day. The patient's head was elevated by 30 degrees in SP, and 10 degrees in PP.

2.2 Outcomes

This study compared the ICU mortality for the two groups as primary outcome and VFD as the secondary outcome. A subgroup analysis compared the oxygenation and respiratory parameters of each group. The pre-prone, prone and post-prone phases were also compared.

2.3 Data collection

The patients' age, gender, Body Mass Index (BMI), weight, PBW, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were recorded during the ICU stay. Arterial blood gas parameters (pH, PaO_2, Partial Pressure of Carbon Dioxide (PCO_2), lactate, base excess) were collected 2 hours before PP, every 4 hours during PP, and 2 hours after PP. Hemodynamic parameters (heart rate (HR), oxygen saturation (SpO_2), systolic and diastolic blood pressure, mean arterial blood pressure (MAP), body temperature), respiratory mechanics (FiO_2, PEEP, PaO_2/FiO_2 ratio, OI, OSI, Total Mechanical Power (MP_{tot}), MP_{dyn}, RR, PEEP, expiratory tidal volume (TV_e), Expiratory Minute Volume (MV_e), P_{mean}, P_{peak}, work of breathing ventilatory (WOB_v), Inspiratory to Expiratory (I/E) ratio, compliance, DP), laboratory parameters (sodium, potassium, chloride, creatinine), Acute Kidney Injury (AKI), ICU length of stay, VFD, and Norepinephrine daily dosage were retrieved from the electronic medical records.

2.4 Statistical analysis

The statistical analysis of the study data was conducted using GraphPad Prism (v 5.01, Graphpad Software, Boston, MA, USA). Minute-by-minute time slots data were transferred from the pool to Microsoft Excel as the hourly time slots using SQL queries. The hourly mechanical ventilation parameters in the Excel dataset were calculated over 24-hour intervals (days) employing the LEFT (returns the first character or characters in a text string, based on the number of characters you specify) function. Difference was calculated between the first 10 characters each of timestamp from mechanical ventilator (Time 1) and the patient's ICU admission timestamp (Time 2). The formula was: LEFT (Time 1, 10) − LEFT (Time 2, 10). This method accurately aggregated the mechanical ventilation data regarding patient's ICU admission and in turn enabled the precise temporal analysis. The length of stay in ICU and VFD were calculated. The length of stay in ICU was calculated by the software via the difference between time when patient was intubated in ICU (T admission) and the time of death or discharge from ICU (T death or discharge), *i.e.*, The

length of stay in ICU = T death or discharge − T admission. The homogeneity of variables was determined by the Shapiro-Wilk normality test. Binary comparisons of groups for blood gas, respiratory parameters and demographic data were made using the Mann-Whitney U test. Results were presented as median with interquartile ranges (IQR 25–75). Frequency distributions and percentages of categorical variables like gender and ICU mortalities were compared by the Chi-square test. Cox proportional hazards regression analysis investigated the impact of PP durations (16–24, and 25–36 hours) on survival and VFD. Hazard Ratios (HR) and 95% confidence intervals (CI) were shown by Kaplan-Meier survival curves and analyzed with log-rank test. The blood gas and respiratory parameters of pre-prone, prone, and post-prone subgroups in both groups were compared using Multivariate Analysis of Variance (MANOVA). Bonferroni tests were conducted for the *post hoc* analyses. Statistical significance was set at $p < 0.05$. The achieved power for mortality analysis was ~79.9%.

3. Results

From a total of 374 patients for inclusion in this study, 24 were excluded on following grounds: 12 patients had hemodynamic instability (arterial pressure was <45 mmHg despite administering appropriate vasoactive medications), 9 required ECMO, 2 had cardiac arrest during PP, and 1 had no available consent (Fig. 1). Consequently, 350 patients were included in this study. The patients' median age was 56 years for group A and 57.5 years for group B. group A had 174 patients and group B 176 patients. The median BMI of group A patients was 30.6 kg/m^2 and of group B as 30.4 kg/m^2. The median prone duration was 18 hours for group A and 33 for group B. The median ICU stay and median mechanical ventilation duration were 11.4 days (IQR 6.9–19) and 9.5 days 10 (IQR 5.6–14.8), respectively for group A, and 13.8 days (IQR 8.5–21.4) and 12.1 days (IQR 5.9–18.2) for group B (Table 1) (**Supplementary Table 1**). No statistically significant differences were found between groups A and B regarding ICU mortality, VFD, Norepinephrine total dose, lactate levels and respiratory mechanics (Table 2) (**Supplementary Table 1**). A significant decrease in HR, PCO_2, OI and OSI values was observed in group A during prone and post-prone periods compared to those in pre-prone. Moreover, there was a significant increase in pH, PaO_2/FiO_2 ratio, and PF/PEEP values ($p < 0.01$) (Table 3) (**Supplementary Table 2**). A significant decrease in HR, OI and OSI values was recorded in group B during prone and post-prone periods compared to those in pre-prone. There was a significant increase in pH, PaO_2/FiO_2 ratio, and PF/PEEP values ($p < 0.01$) (Table 4) (**Supplementary Table 3**).

Group A and group B comparison across the pre-prone, prone, and post-prone periods showed statistically significant difference between PCO_2, PaO_2/FiO_2 ratio, OI, OSI and PF/PEEP values in the post-prone period ($p < 0.01$) (Table 5) (**Supplementary Table 4**). A significant difference was found between the survivor and non-survivor groups in group A regarding age, daily norepinephrine dose, potassium levels, P_{peak}, DP, MP_{tot}, MP_{dyn}, ICU stay and VFD ($p < 0.01$) (Table 6) (**Supplementary Table 5**). A significant difference was observed between the survivor and non-survivor groups in group B pertaining to age, MAP, daily norepinephrine dose, PCO_2, pH, lactate, PaO_2/FiO_2 ratio, OI, OSI, PF/PEEP, P_{mean}, P_{peak}, DP, MP_{tot}, MP_{dyn}, WOB_v, compliance, prone duration and APACHE II and SOFA scores at admission, ICU stay, and VFD ($p < 0.01$) (Table 6, Fig. 2) (**Supplementary Table 5**). No significant difference was found in this study between the SPP and PPP regarding complications (4 patients with Grade 1 facial pressure ulcers in group A and 3 in group B).

4. Discussion

In this study, no superiority of PPP over SPP was found regarding mortality and VFD. Some studies in literature had demonstrated lower mortality in patients subjected to PPP [12–15]. However, no difference in mortality was observed in other studies including this one between the patients undergone PPP and SPP [16, 17]. This study, in addition to the primary outcome of mortality as in previous studies, also evaluated the effects of PPP and SPP on respiratory mechanics (PEEP, P_{mean}, P_{peak}, RR, DP, MP_{tot}, MP_{dyn}, *etc.*), oxygenation indices other than PaO_2/FiO_2 ratio (OI, OSI), and maintaining the persistent post-prone effect due to PPP. In both groups, a significant decrease in oxygenation indexes, specifically OI and OSI values, and increase in PaO_2/FiO_2 ratio and PF/PEEP values were found during the prone and post-prone periods compared to pre-prone. This improvement in oxygenation parameters after PP was described as the post-prone effect [18]. No statistically significant differences in this study were observed between the groups regarding PCO_2, PaO_2/FiO_2 ratio, OI, OSI and PF/PEEP values in the pre-prone and prone periods. However, a significant difference in these values was found in the post-prone period. Some studies have shown reduced PCO_2 in C-ARDS after PP, and this effect was improved with PPP [19]. However, this effect was not observed in this study for PPP group. PP improved oxygenation through more homogeneous lung ventilation. Moreover, the dorsal lung regions usually collapsed during the supine position in ARDS patients were recruited, which reduced the overdistension and ergotrauma in ventral lung regions [7, 18]. However, the VILI mitigation might be a conducive mechanism for clinical benefit and increased survival [7]. Large clinical trials had shown improved oxygenation by PP in ARDS, however significant reduction in mortality had been demonstrated by studies reporting a decrease in VFD [7]. Interventions to reduce high DP and MP, being the two potential causes of VILI, might be beneficial for severe ARDS patients [7, 20]. A reduction in DP and P_{peak} was observed in this study during post-prone period with PPP, however no improvement in respiratory mechanics was noted after PP. High DP (>15–17 cmH_2O) had been associated with mortality in ARDS patients as demonstrated in the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) and other studies [2, 21, 22]. The ARDS Network's lower tidal volumes (ARMA) study revealed ventilation with low tidal volumes as another factor reducing the mortality and increasing the VFD [23]. The mortality impact through reduced tidal volumes varied according to the lung compliance. Studies showed

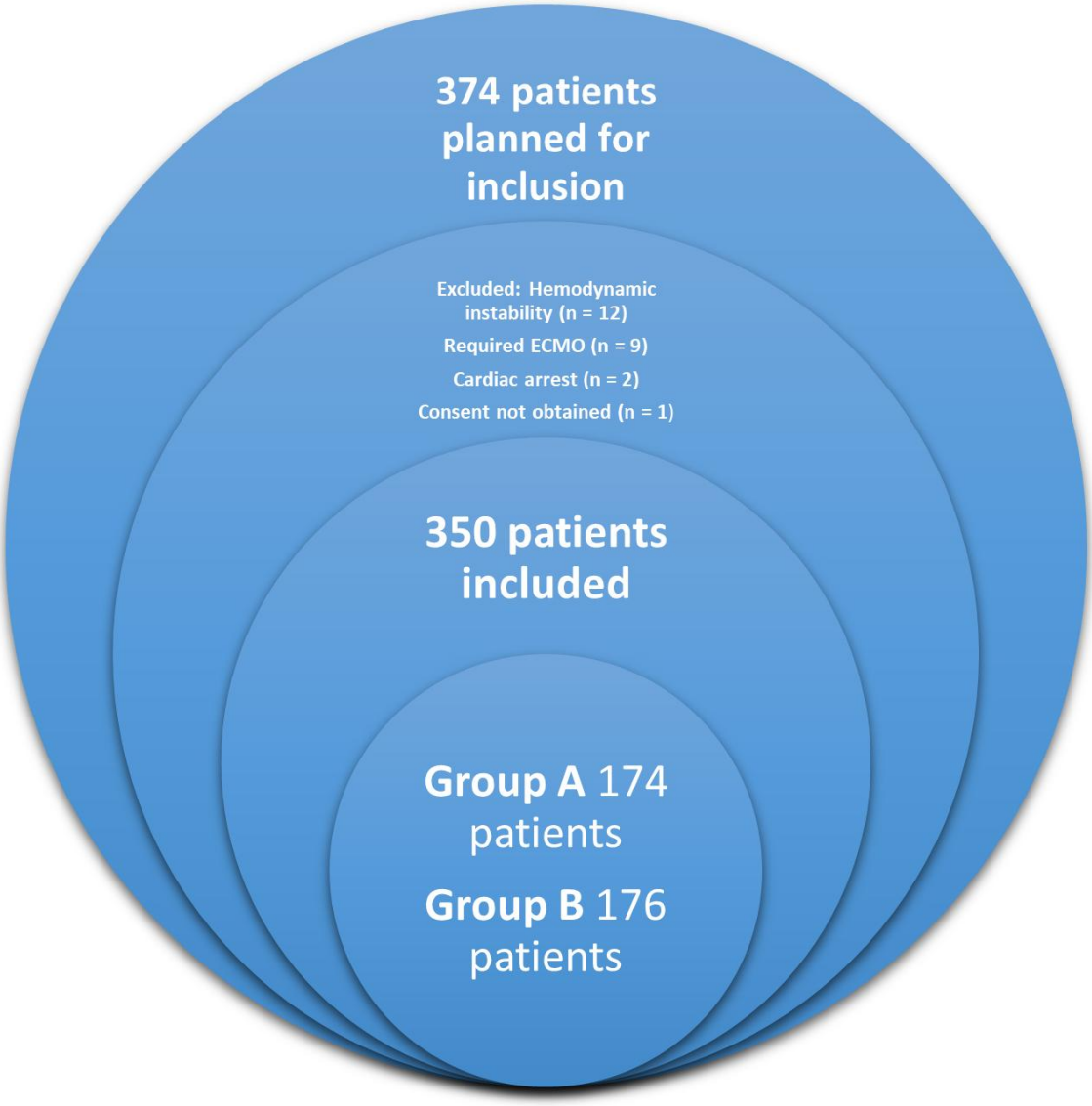

FIGURE 1. The study flowchart. ECMO: Extracorporeal membrane oxygenation.

TABLE 1. Demographic and baseline characteristics of group A (16–24 hours prone positioning) and group B (25–36 hours prone positioning) (Mann Whitney U test).

Group A (16–24 h) *vs.* Group B (25–36 h)	Group A (n = 174) Median ($Q_{25–75}$)	Group B (n = 176) Median ($Q_{25–75}$)	*p* value
Gender, Female (%)	64 (36.7%)	66 (37.5%)	0.8890
BMI (kg/m^2)	30.6 (28.4–31.1)	30.4 (28.3–30.8)	0.5622
PBW (kg)	68 (65–70)	67.5 (64–69)	0.7172
Age (yr)	56 (42–67)	57.5 (43–69)	0.9138
Prone sessions	2 (2–3)	2 (2–3)	0.5091
APACHE II score	23 (18–29)	23 (19–28)	0.6252
SOFA score (admission)	11 (8–13)	10 (8–12)	0.1771
ICU duration of stay (d)	11.4 (6.9–19.0)	13.8 (8.5–21.4)	0.1181
ICU mortality (%)	99 (57%)	95 (54%)	0.5827
MV duration of stay (d)	9.5 (5.6–14.8)	12.1 (5.9–18.2)	0.0403

BMI: Body mass index; PBW: Predictive body weight; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; MV: Mechanical ventilation.

TABLE 2. Hemodynamic and respiratory parameters of group A (16–24 hours prone positioning) and group B (25–36 hours prone positioning) (Mann Whitney U test).

Group A (16–24 h) *vs.* Group B (25–36 h)	Group A (n = 174) Median ($Q_{25–75}$)	Group B (n = 176) Median ($Q_{25–75}$)	*p* value
MAP (mmHg)	82.0 (75.2–87.8)	82.7 (77.8–88.6)	0.1814
Norepinephrine (mg/d)	20 (9.4–40)	20 (8.9–48)	0.8754
Creatinine (mg/dL)	0.93 (0.56–1.63)	0.80 (0.60–1.23)	0.1838
AKI (n) (%)	35 (20%)	40 (23%)	0.5515
Lactate (mmol/L)	1.7 (1.3–2.0)	1.5 (1.3–1.9)	0.1000
PaO_2/FiO_2 ratio	170.9 (125.1–477.8)	149.0 (118.1–433.7)	0.0150
OI	10.6 (7.7–15.8)	12.5 (9.0–16.2)	0.0301
OSI	9.4 (6.8–12.4)	10.2 (8.6–12.7)	0.0218
PF/PEEP	18.6 (13.3–26.8)	16.4 (11.9–20.9)	0.0050*
MP_{tot} (J/min)	16.4 (13.5–18.8)	17.2 (14.8–20.4)	0.0097*
MP_{dyn} (J/min)	10.2 (8.2–12.4)	10.8 (9.0–12.5)	0.0638
WOB_v (j/L)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	0.9807
Compliance (mL/cmH_2O)	28.8 (23.2–35.9)	30.7 (23.6–35.7)	0.3091
DP	15.6 (13.7–18.0)	15.4 (13.9–17.9)	0.7405
VFD (d)	1.0 (0.2–3.6)	0.8 (0.2–3.4)	0.8841

**Significant at 0.05 level.*
MAP: Mean arterial blood pressure; AKI: Acute kidney injury; PaO_2: Partial pressure of oxygen in arterial blood; FiO_2: Fraction of inspired oxygen; OI: Oxygen index; OSI: Oxygen saturation index; PF: Ratio of PaO_2 to FiO_2; PEEP: Positive end expiratory pressure; MP_{tot}: Total mechanical power; MP_{dyn}: Dynamic mechanical power; WOB_v: Work of breath (ventilatory); DP: Driving pressure; VFD: Ventilatory free days.

TABLE 3. Respiratory parameters, oxygenation indices, and mechanical ventilation metrics during pre-prone, prone, and post-prone periods in group A (one-way ANOVA and Bonferroni tests).

Group A (n = 122)	Pre-prone Mean (95% CI)	Prone Mean (95% CI)	Post-prone Mean (95% CI)	*p* value
PCO_2 (mmHg)	59.3 (55.4–63.2)	55.8 (52.2–59.4)	52.7 (49.6–55.8)	<0.0001*
PaO_2/FiO_2	136.9 (123.8–150.1)	204.7 (188.5–220.8)	215.4 (197.8–233.0)	<0.0001*
OI	15.1 (13.7–16.6)	9.7 (8.7–10.8)	9.3 (8.2–10.3)	<0.0001*
OSI	12.2 (11.3–13.1)	9.2 (8.5–9.9)	8.6 (7.9–9.3)	<0.0001*
PF/PEEP	16.3 (14.3–18.2)	24.6 (22.2–27.0)	26.5 (23.6–29.4)	<0.0001*
MP_{tot} (J/min)	16.2 (15.2–17.1)	16.5 (15.6–17.4)	16.0 (15.0–17.0)	0.5385
MP_{dyn} (J/min)	10.2 (9.5–10.9)	10.5 (9.8–11.2)	10.2 (9.5–11.0)	0.5565
Compliance (mL/cmH_2O)	30.2 (28.1–32.3)	30.3 (28.4–32.1)	30.7 (28.6–32.8)	0.7041
DP	16.1 (15.4–16.8)	15.9 (15.2–16.6)	15.8 (15.1–16.6)	0.4379

**Significant at 0.05 level.*
PCO_2: Partial pressure of carbon dioxide in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; FiO_2: Fraction of inspired oxygen; OI: Oxygen index; OSI: Oxygen saturation index; PF: Ratio of PaO_2 to FiO_2; PEEP: Positive end expiratory pressure; MP_{tot}: Total mechanical power; MP_{dyn}: Dynamic mechanical power; DP: Driving pressure; CI: confidence intervals.

TABLE 4. Respiratory parameters, oxygenation indices, and mechanical ventilation metrics during pre-prone, prone, and post-prone periods in group B (one way ANOVA and Bonferroni tests).

Group B (n = 154)	Pre-prone Mean (95% CI)	Prone Mean (95% CI)	Post-prone Mean (95% CI)	*p* value
PCO_2 (mmHg)	59.2 (56.6–61.9)	57.2 (54.3–60.1)	58.0 (55.6–60.4)	0.2648
PaO_2/FiO_2	122.6 (112.6–132.6)	186.4 (175.2–197.6)	188.0 (175.4–200.6)	<0.0001*
OI	17.3 (15.8–18.8)	10.6 (9.6–11.5)	10.3 (9.5–11.1)	<0.0001*
OSI	13.6 (12.8–14.4)	9.9 (9.3–10.5)	9.8 (9.2–10.3)	<0.0001*
PF/PEEP	13.2 (12.1–14.4)	20.6 (19.1–22.1)	20.5 (18.9–22.1)	<0.0001*
MP_{tot} (J/min)	17.4 (16.6–18.2)	17.9 (17.2–18.7)	16.9 (16.1–17.7)	0.0321
MP_{dyn} (J/min)	10.9 (10.4–11.5)	11.2 (10.6–11.7)	10.4 (9.8–11.0)	0.0303
Compliance (mL/cmH_2O)	29.6 (28.0–31.1)	30.7 (29.3–32.1)	30.4 (29.0–31.9)	0.0508
DP	16.5 (15.9–17.1)	16.0 (15.4–16.5)	15.5 (15.0–16.1)	0.0002*

**Significant at 0.05 level.*
PCO_2: Partial pressure of carbon dioxide in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; FiO_2: Fraction of inspired oxygen; OI: Oxygen index; OSI: Oxygen saturation index; PF: Ratio of PaO_2 to FiO_2; PEEP: Positive end expiratory pressure; MP_{tot}: Total mechanical power; MP_{dyn}: Dynamic mechanical power; DP: Driving pressure; CI: confidence intervals.

TABLE 5. Respiratory parameters, oxygenation indices, and mechanical ventilation metrics of groups A and B during pre-prone, prone, and post-prone periods (Mann Whitney U test).

Group A *vs.* Group B (n = 276)	Pre-prone Median ($Q_{25–75}$)	*p* value	Prone Median ($Q_{25–75}$)	*p* value	Post-prone Median ($Q_{25–75}$)	*p* value
PCO_2 (mmHg)	55.2 (45.3–66.7) *vs.* 56.6 (47.3–68.4)	0.4915	50.5 (43.9–61.6) *vs.* 52.0 (45.8–62.8)	0.1800	49.0 (42.2–59.0) *vs.* 54.6 (47.3–66.0)	0.0006*
PaO_2/FiO_2	123.0 (79.5–175.0) *vs.* 108.5 (77.2–147.0)	0.1691	196.0 (137.0–259.0) *vs.* 176.0 (142.0–222.5)	0.1404	204.5 (140.3–271.3) *vs.* 170.0 (137.8–229.5)	0.0143*
OI	13.9 (9.2–19.6) *vs.* 15.3 (10.2–22.0)	0.0814	8.2 (5.4–8.2) *vs.* 9.1 (7.0–12.4)	0.0615	8.2 (5.2–11.0) *vs.* 9.3 (6.9–12.5)	0.0084*
OSI	11.5 (8.8–15.9) *vs.* 13.3 (10.0–16.0)	0.0482	8.8 (6.4–11.5) *vs.* 9.2 (7.4–12.0)	0.1677	7.9 (5.8–10.4) *vs.* 8.9 (7.2–12.2)	0.0034*
PF/PEEP	12.7 (8.9–20.2) *vs.* 11.3 (8.0–17.5)	0.0473	22.4 (14.0–34.4) *vs.* 18.5 (13.5–25.8)	0.0368	21.6 (15.2–34.2) *vs.* 18.1 (12.9–25.3)	0.0015*
MP_{tot} (J/min)	16.2 (12.8–19.4) *vs.* 16.7 (14.0–20.7)	0.0902	16.5 (13.3–19.8) *vs.* 17.9 (15.1–21.3)	0.0307	15.6 (12.7–18.9) *vs.* 16.9 (13.9–19.2)	0.1330
MP_{dyn} (J/min)	10.2 (7.8–12.0) *vs.* 10.1 (8.3–12.9)	0.2526	10.1 (8.3–12.9) *vs.* 10.8 (9.0–12.8)	0.1810	9.9 (7.6–12.5) *vs.* 10.3 (8.5–11.8)	0.6536
Compliance (mL/cmH_2O)	28.4 (23.2–35.2) *vs.* 29.5 (23.7–35.3)	0.9425	30.1 (24.3–36.2) *vs.* 31.2 (24.0–36.7)	0.5867	30.0 (23.2–39.3) *vs.* 30.9 (23.5–36.9)	0.9691
DP	15.8 (13.8–18.1) *vs.* 15.9 (14.0–19.1)	0.4698	15.5 (13.3–18.2) *vs.* 15.6 (13.9–17.7)	0.9933	15.3 (13.0–18.0) *vs.* 15.1 (13.3–16.9)	0.7343

**Significant at 0.05 level.*
PCO_2: Partial pressure of carbon dioxide in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; FiO_2: Fraction of inspired oxygen; OI: Oxygen index; OSI: Oxygen saturation index; PF: Ratio of PaO_2 to FiO_2; PEEP: Positive end expiratory pressure; MP_{tot}: Total mechanical power; MP_{dyn}: Dynamic mechanical power; DP: Driving pressure.

TABLE 6. Survivors and non-survivors in groups A (16–24 hours) and B (25–36 hours) (Mann Whitney U test).

Parameters	Group A (16–24 h) Survivor *vs.* Non-survivor Median ($Q_{25–75}$)	*p* value	Group B (25–36 h) Survivor *vs.* Non-survivor Median ($Q_{25–75}$)	*p* value
Lactate (mmol/L)	1.6 (1.3–2.1) *vs.* 1.7 (1.3–2.0)	0.9863	1.4 (1.1–1.5) *vs.* 1.6 (1.3–2.2)	<0.0001
PaO_2/FiO_2	178.0 (126.9–228.1) *vs.* 167.3 (125.0–210.0)	0.4013	159.4 (140.7–211.9) *vs.* 137.9 (105.4–170.7)	0.0002
PF/PEEP	19.2 (12.7–31.4) *vs.* 17.6 (13.3–25.2)	0.2659	17.3 (12.7–22.6) *vs.* 15.0 (11.7–19.2)	0.0096
OI	9.7 (7.3–14.5) *vs.* 10.9 (8.4–15.8)	0.2916	10.6 (7.8–14.2) *vs.* 13.1 (10.4–18.7)	0.0003
OSI	8.6 (6.0–11.9) *vs.* 10.0 (7.5–12.7)	0.0180	9.2 (7.5–11.3) *vs.* 11.2 (9.7–14.6)	<0.0001
MP_{tot} (J/min)	14.9 (11.4–17.3) *vs.* 17.2 (14.7–19.7)	0.0006	16.1 (14.4–19.1) *vs.* 18.7 (15.8–21.7)	0.0001
MP_{dyn} (J/min)	9.1 (6.6–10.7) *vs.* 11.2 (9.1–12.0)	0.0001	9.8 (8.1–11.2) *vs.* 11.9 (9.9–13.3)	<0.0001
WOB_v (j/L)	1.2 (1.1–1.4) *vs.* 1.3 (1.1–1.5)	0.0170	1.2 (1.0–1.3) *vs.* 1.3 (1.2–1.5)	<0.0001
Compliance (mL/cmH_2O)	30.3 (24.0–39.9) *vs.* 28.0 (21.6–33.7)	0.1008	32.5 (27.3–39.4) *vs.* 27.6 (21.3–33.5)	0.0003
DP	14.7 (12.8–17.4) *vs.* 16.3 (14.7–18.3)	0.0051	14.8 (13.0–16.1) *vs.* 16.9 (14.4–19.2)	<0.0001
Prone sessions	2 (2–3) *vs.* 2 (2–3)	0.7146	2 (2–3) *vs.* 2 (2–3)	0.9197
APACHE II score	23 (17–29) *vs.* 24 (18.7–29.2)	0.4634	21 (17–25) *vs.* 25 (20.0–29.0)	<0.0001
SOFA score (admission)	10 (7.0–12.0) *vs.* 11 (9.0–13.5)	0.0268	8 (7–11) *vs.* 11 (9–14.0)	<0.0001
ICU duration of stay (d)	14.9 (7.7–22.9) *vs.* 10.4 (5.7–15.1)	0.0044	17.0 (11.0–24.8) *vs.* 12.0 (5.9–18.5)	0.0015
MV duration of stay (d)	9.2 (6.0–14.7) *vs.* 10.1 (5.1–14.9)	0.8861	13.2 (6.7–18.9) *vs.* 11.3 (5.6–16.4)	0.2220
VFD (d)	3.6 (1.4–6.0) *vs.* 0.3 (0.2–1.0)	<0.0001	3.0 (1.2–5.1) *vs.* 0.2 (0.1–0.8)	<0.0001

PaO_2: Partial pressure of oxygen in arterial blood; FiO_2: Fraction of inspired oxygen; PF: Ratio of PaO_2 to FiO_2; PEEP: Positive end expiratory pressure; OI: Oxygen index; OSI: Oxygen saturation index; MP_{tot}: Total mechanical power; MP_{dyn}: Dynamic mechanical power; WOB_v: Work of breath (ventilatory); DP: Driving pressure; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; MV: Mechanical ventilation; VFD: Ventilatory free days.

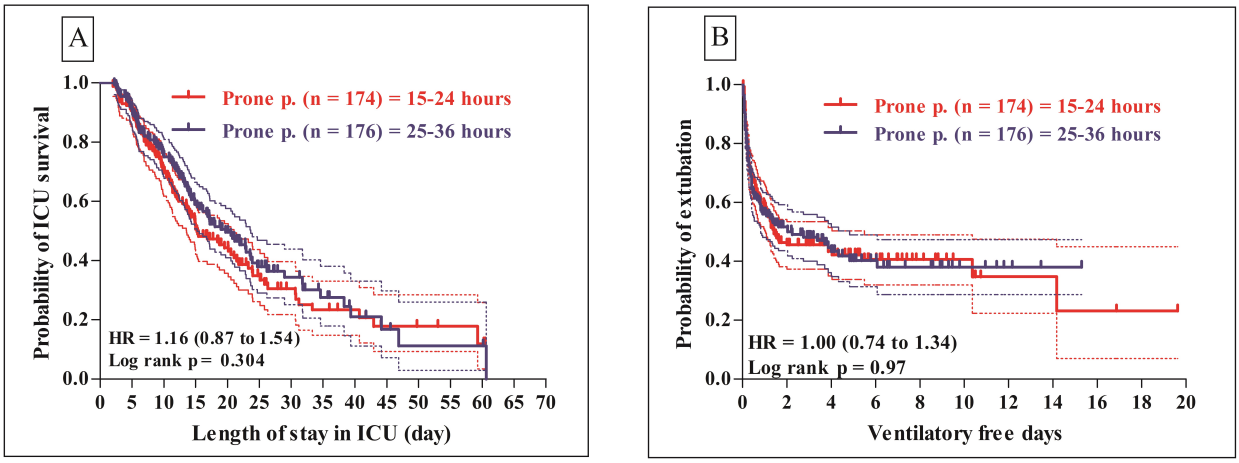

FIGURE 2. Kaplan-Meier curves comparing ICU survival. (A) survival probability between group A and group B (Log-rank $p = 0.304$). (B) probability of extubation (ventilator-free days) between group A and group B (Log-rank $p = 0.97$). ICU: Intensive care unit; HR: Hazard ratio.

greater benefits in patients with higher lung elastance and lower lung compliance [21, 22]. High MP (>17.0 J/min) had been associated with higher ICU frequency, hospitalization, and 30-day mortality rates even in patients ventilated with low tidal volumes [24, 25]. Costa *et al.* [25] demonstrated DP and RR being equivalent to MP and associated with mortality. No significant differences were observed in this study regarding respiratory mechanics values (MP_{tot}, MP_{dyn}, TV_e, P_{peak}, P_{mean}, compliance and DP) when comparing SPP and PPP across pre-prone, prone, and post-prone periods. However, statistically significant differences were found in P_{peak}, DP, MP_{tot}, MP_{dyn}, ICU length of stay, and VFD in the subgroup analyses of survival and non-survival groups. High PEEP prevented the alveolar collapse; however it might lead to overdistension of well-ventilated alveoli [26, 27]. High PEEP in conjunction with PP increased the lung aeration, reduced regional hyperinflation, and decreased the incidence of small airway opening/closing events [26, 27]. Therefore, PP might protect against VILI by reducing barotrauma and atelectrauma [7, 26, 27]. Studies have shown that the positive effects of PPP on oxygenation increased with the PP duration and it also reduced the need for recruitment [7, 27]. Schmidt M *et al.* [28] demonstrated that the recruitment of posterior zones depended on PP duration. The PEEP values for both groups in this study were similar in the pre-prone, prone, and post-prone periods. A recent study by Thais Walter *et al.* [29] reported a median duration of 39 hours PP wherein it was observed that PPP was safe with 26% incidence of grade 2 pressure ulcers and 2.5% grade 3–4.

The study herein had several limitations. The results might not be generalized to entire population because of being a retrospective study, sample size and single-center study. Long-term complications and mortality were not recorded, and thus prolonged extrapolations on outcomes were not possible. Early mortality (≤48–72 hours) had often been influenced by factors not related to prone positioning, such as irreversible baseline severity (*e.g.*, multiorgan failure at admission). The study herein aimed to assess the PP effect on mortality in patients surviving long enough to benefit from the intervention. The patients died in first 3 days of admission were thus excluded from the study. This exclusion introduced a survivorship bias as the cohort with inherently lower baseline mortality risk was selected. This might overestimate the effect of treatment in this analysis. Furthermore, the results pertained only to C-ARDS patients, while the patients with non-COVID ARDS and extrapulmonary ARDS were excluded.

5. Conclusions

In this study, no significant difference in ICU mortality or VFD was found between the SPP and PPP groups. Improvement in oxygenation indices was observed in both standard and prolonged groups. Prolonged PP might increase the risk of unwanted complications, however extending the PP duration could be better compared to continuously alternating between the SP and PP in recruitable patients as it would reduce the need for recruitment. Preventing VILI and achieving persistent post-prone effect through several PP sessions in C-ARDS patients had positive impact on respiratory mechanics and oxygenation. It is thus recommended to incorporate both SPP and PPP as part of lung protective ventilation rather than life-saving treatments.

6. What is known

- Prone positioning (PP) is a well-established strategy to improve oxygenation and respiratory mechanics in Acute Respiratory Distress Syndrome (ARDS) patients.
- Standard prone positioning (SPP) lasts 16–24 hours, while prolonged prone positioning (PPP) up to 36 hours.

7. What is new

- The study specifically compares the effects of SPP (16–24 hours) and PPP (25–36 hours), and evaluates the outcomes regarding oxygenation, respiratory mechanics, ventilator-free days (VFD), and ICU mortality.
- PPP does not show significant survival advantage over SPP.
- Findings suggest that the PP duration should be tailored to patient-specific factors rather than a one-size-fits-all approach.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

PR—methodology; project administration; supervision; validation; writing–original draft. TYY—resources; validation; visualization. DB—conceptualization; data curation; writing–original draft. SA—data curation; formal analysis; software. ZC—project administration; writing-review & editing. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Bakirkoy Dr. Sadi Konuk Ethics Committee on 03 October 2022 (Decision no: 2022-19-04). Informed consent was obtained from all participants or their legal guardians where applicable.

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CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1928365167808004096/attachment/Supplementary%20material.docx.

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