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ORIGINAL RESEARCH **INTENSIVE CARE**

Effect of early prone positioning among critically ill patients admitted with acute respiratory distress syndrome during the COVID-19 pandemic: A comparative retrospective observational study

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ABSTRACT

Background and objective: COVID-19 has offered an opportunity to the clinicians to try and study various oxygenation enhancing maneuvers in the patients. These included lung protective measures and prone positioning of participants admitted to the ICU with acute respiratory distress syndrome. We aimed to identify the effects of early prone positioning on the length of stay, discharge rate, and frequency of tracheostomies in the ICU patients.

Methodology: This retrospective study was conducted on critically ill patients needing mechanical ventilation with lung protective strategy, admitted to the Intensive Care Units of Al-Azhar University Hospitals between March 2020 to April 2022. All patients in the study were interpreted retrospectively by examining the patient's records. Group A (n = 39) included patients who had been early placed in prone positions within 24 h of intubation, and Group B (n = 31) included patients who had not been placed in prone positions. All patients received a lung protective strategy for ARDS. In both groups, PaO_2, $PaCO_2$, pH, SpO_2, and PaO_2/FiO_2 ratio were checked initially and later every 24 h for 6 days. Data was evaluated for the total days of both hospital and ICU length of stay, number of successful discharges to home from the hospital, and the total number of tracheostomized patients.

Results: After prone positioning, lower SOFA and APACHE II scores were noticed in the prone group. There was no significant difference in the rate of discharge between the two groups. We observed non-significant shorter hospital and ICU stays and higher frequency of tracheostomy procedures in the prone group. We noticed a significant improvement in PaO_2/FiO_2 ratios in the prone group starting from day 2 to day 6. We observed a significant improvement in PO_2 in the prone group in comparison to the non-prone group.

Conclusions: Early prone positioning of patients admitted to the ICU with acute respiratory distress syndrome during COVID-19 pandemic led to a significant improvement in both PaO_2 and PaO_2/FiO_2 ratio with a non-significant decrease in both hospital and ICU length of stay as shown by the collected data over consecutive six days.

Abbreviations: ARDS- acute respiratory distress syndrome; FiO_2: The fraction of inspired oxygen; CPAP: Continuous Positive Airway Pressure; PaO_2: Arterial oxygen partial pressure; PEEP: Positive End-Expiratory Pressure; SOFA- Sequential Organ Failure Assessment

Keywords: Prone; Lung protective measures; ARDS; APACHI II; SOFA

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1. INTRODUCTION

The effects of early lung protective measures and prone positioning on the mortality rates of critically ill people admitted to ICU with acute respiratory distress syndrome (ARDS) during the COVID-19 pandemic, need a critical analysis.[1] ARDS represents a critical medical condition associated with severe respiratory failure as explained by Kallet RH et al. in 2015.[2] It is marked by extensive pulmonary infiltrates observable on chest radiographs, diminished lung compliance, and persistent hypoxemia despite oxygen therapy.[3] Brower RG[4] explained the contemporary definition. This definition establishes and illustrates the criteria for diagnosing ARDS. The condition may emerge following aspiration pneumonia, pulmonary embolism, and inhalation of harmful gases.[4] A recent study highlighted that primary ARDS is associated with the lungs and secondary ARDS demonstrates extrapulmonary involvement with each type exhibiting different clinical outcomes and survival prospects.[5] Pulmonary ARDS is associated with alveolar epithelial damage. On the other hand, extrapulmonary ARDS comprises vascular endothelial harm. Adult cases are attributed to sepsis followed by pneumonia, trauma, and aspiration.[6]

Several studies have highlighted that despite advancements in the management including ventilatory management, permissive hypercapnia, and related supportive measures; ARDS related mortality remains high resulting from severe sepsis.[7] The mortality risk escalates in correlation with the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score; Glasgow Coma Score (GCS), Lung Injury Score (LIS), and prolonged mechanical ventilation and ICU stays.[8]

This retrospective observational study examines the outcomes of ARDS patients in ICU with prone positioning as a critical intervention regarding its effect on ICU and hospital length of stay.

The primary outcome was the number of patients discharged, and the secondary outcomes were; the total length of hospital stay, ICU length of stay and the number of patients needing tracheostomy.

2. METHODOLOGY

This retrospective study was conducted on critically ill patients needing mechanical ventilation with lung protective strategy and admitted to the ICUs of Al-Azhar University Hospitals, between March 2020 to April 2022. ICUs of Al-Azhar University Hospitals have 30 beds. All patients in the study were interpreted retrospectively by examining the patient's records. The study was accepted by the ethical committee of the Anaesthesia, Intensive Care, and Pain Management Department of Al-Azhar University hospitals (No. 404/2024). Informed consents from patients or patients' families were not required as the study was done retrospectively.

The ICU admitted approximately 207 patients, with 124 needing mechanical ventilation (MV) resulting from COVID-19-related respiratory failure. A total of 124 patients were recruited initially who were admitted with ARDS to the ICU; 21 patients were omitted from the study due to incomplete records, 18 patients were excluded because of hemodynamic instability, 3 pregnant patients, 5 patients older than 70 y, two patients younger than 18 y, and one patient with lung cancer were also excluded. After the inclusion of 74 patients, the other 4 patients were omitted from the study because of non-compliance to prone positioning. A total of 70 patients were finally included comprising 43 males and 27 females, with an age between 18 to 70 y.and divided into two groups. Group A (n = 39) included patients who had been early placed in prone positions within 24 h of intubation, and Group B (n = 31) included patients who had not been placed in prone position (Figure 1). Patient diagnoses were done as per the criteria of The European Society of Intensive Care Medicine (ESICM) (Box 1).[9]

Box 1: ESICM Berlin, Germany ARDS Criteria.[9]

Timing	Within one week of an obvious clinical cause or new or worsening respiratory manifestations
Chest imaging*	Opacities on both sides, not fully interpreted by effusions, Lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully interpreted by heart failure or fluid overload Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor presents
Oxygenation**	
• Mild	• 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP or CPAP ≥ 5 cmH_2O***
• Moderate	• 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O
• Severe	• PaO_2/FiO_2 ≤100 mmHg with PEEP ≥ 5 cmH_2O

** Computed Tomography scans or Chest Radiograph; **If altitude is higher than 1,000 m, then the correction factor should be calculated as follows: [PaO_2/FiO_2_(barometric pressure/760)]; ***This may be provided noninvasively in the mild cases of acute respiratory distress syndrome.*

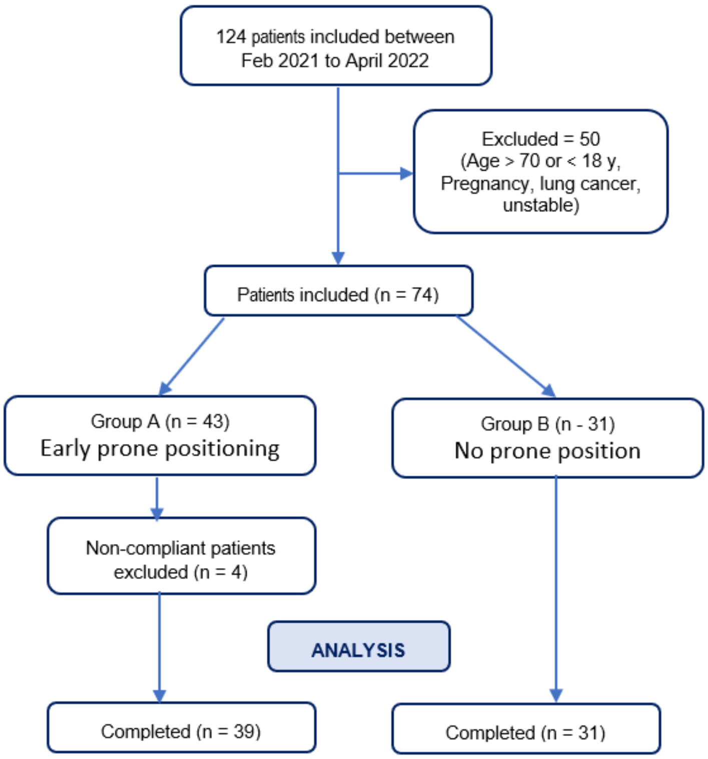

Figure 1: Study flow diagram

The diagnosis of COVID-19 infection was confirmed by PCR test (Polymerase Chain Reaction). We adopted some clinical values for the recognition of pneumonia such as cough, dyspnea, shortness of breath, and tachypnea. Other diagnostic criteria were adopted like a Computerized Tomography scan, in which, some findings can be found like multifocal opacities, consolidation, and ground-glass appearance.

We considered the patient to have moderate to severe ARDS if the PaO_2/FiO_2 ratio was less than 200, despite the traditional oxygen therapy like a non-rebreather face mask @ > 6L/min or high-flow oxygen support. In both groups, PaO_2, $PaCO_2$, and PH, oxygen saturation (SpO_2), and PaO_2/FiO_2 ratio were noted at the time of starting lung protective measures and later every 24 h for a total of 6 days.

Pulmonary ARDS is defined as a condition created by a frank lung injury, like pulmonary contusion or pneumonia, and extrapulmonary ARDS as a condition caused by other extra-pulmonary causes like multiple traumas, sepsis, massive blood transfusion, or abdominal sepsis.[10]

Patients who spent more than 24 h on mechanical ventilators before enrolment in the study; who died within the first 24 h of presentation; patients with advanced cancer, pregnant patients, and younger than 18 y or older than 70 y were excluded.

APACHE II score was utilized to document the patient's current comorbidities with age and worst vital parameters and laboratory values in the initial 24 h of ICU admission.[11]

The SOFA score was utilized to evaluate the patient's major organs like the respiratory, central nervous system, cardiovascular, renal, hepatic systems, and blood coagulation. It helps in the follow-up during sepsis, so, an increasing score is related to higher mortality.[12]

All patients were evaluated for the total days of hospital and ICU stay, number of successful discharges to home from the hospital, and the total number of tracheostomized patients.

A standard plan of care was followed for all our patients in two parts; a lung protection plan, and a pharmacological one. The lung-protection plan consisted of ventilation and fluid management, while the pharmacological plan consisted of use of corticosteroids and other therapies. A low tidal volume was started at less than 6 ml/kg to prevent barotrauma, PEEP was titrated to a target oxygen saturation of above 90% and a target FiO_2 below 60%. Plateau pressure was kept at all the time below 30 cmH_2O, and permissive hypercapnia was permitted to keep Ph more than 7.2 and to preserve the best oxygen parameters for the patient. The pharmacological plan consisted of Deep Venous Thrombosis (DVT) prophylaxis, peptic ulcer prophylaxis, steroids (dexamethasone 6 mg daily), multivitamins and zinc, antivirals, and antibiotics as and when needed.

For Group A, the prone position was applied for a total of 16 h per day. Sedation and short-time muscle relaxant infusions were used to facilitate this purpose. In the case of hemodynamic instability, prone position was aborted immediately.

Statistical analysis

The evaluation of the data collected was implemented through the SPSS. The analysis incorporated the explanation of numerical data through frequency analysis; the computation of means and standard deviations and the identification of minimum and maximum values. The Mann-Whitney U test was utilized for continuous numerical data lacking normal distribution, while the chi-square test was employed for the assessment of categorical and nominal data to

Table 1: Demographic data, basal scores, and comorbidities at admission

Parameter	Group A (n = 39)	Group B (n = 31)	P-value
Age (y)	48.7 ± 15	68.8 ± 2	0.0002*
Body Mass Index (kg/m^2)	31.4 ± 2.2 (22.8-4.2)	28.2 ± 2.9 (20.9-34.4)	0.081**
Gender (male/female)	24 M/15 F	19 M/12 F	0.37
APACHE II score	35 ± 5	41 ± 5	0.24
Lung Injury Score (LIS)	2.2 ± 0.1	2.4 ± 0.1	0.13
SOFA score	13.6 ± 4.1	17.8 ± 2.8	0.250
GCS	8.1 ± 0.5	6.9 ± 1.4	0.231
Patients comorbidities			
Hypertension	21 (53.8)	29 (93.5)	0.211
Diabetes Mellitus	9 (23)	13 (41.9)	0.347
Bronchial Asthma	4 (10.4)	7 (22.6)	0.221
Chronic kidney disease (No Hemodialysis)	0 (0)	2 (6.5)	0.314
Liver cirrhosis	0 ()0	0 (0)	0.143
Hematological diseases	1 (2)	2 (6.5)	0.116
Dyslipidaemia	17 (2.6)	25 (80.6)	0.244

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II score; SOFA: Sequential Organ Failure Assessment score; GCS: Glasgow Coma Score; ICU: intensive care unit.

**Student t and ** Mann Whitney U Test. Values are mean ± SD, median (IQR) or n (%)*

Table 2: Lung protection measures and oxygenation parameters

Parameter	Group A (n = 39)	Group B (n = 31)	P-Value
PEEP (cmH_2O)	12.9 ± 2.2	13.1 ± 1.1	0.02
Frequency (breaths/min)	18 ± 6	21 ± 1	0.02
pH	7.26 ± 0.5	7.24 ± 0.8	0.17
PaO_2 (mmHg)	88 ± 11	81 ± 13	0.14
PCO_2 (mmHg)	44 ± 12	46 ± 13	0.22
PaO_2/FiO_2 (mmHg)	122 ± 15	119 ± 18	0.31

PEEP: positive end-expiratory pressure; PaO_2: partial pressure of arterial oxygen; FiO2: fraction of inspired oxygen; CO_2: carbon dioxide. Data presented as mean ± SD.

differentiate between groups. The study established a statistical significance threshold at a $P < 0.05$.

3. RESULTS

Patient demographic data like age, gender, BMI, initial APACHE score, Lung Injury Score (LIS), SOFA score, and Glasgow coma scale are shown in Table 1.

In the study, Group A had a lower mean age than Group B highlighting age disparity with implications for mortality risk (P = 0.0001). The evaluation of clinical scoring systems initially was comparable between both groups.

Before prone positioning, the study illustrated a non-significant difference in LIS scores between Group A and Group B (P = 0.13). The APACHE II scores appeared lower in Group A compared to Group B indicating a decrease in mortality risk (P = 0.24). The GCS scores differed between the groups with Group A scoring higher than Group B (P = 0.002). On the other hand, the SOFA scores corroborated this trend, highlighting a higher severity of organ failure in the Group B (P = 0.002).

Patient comorbidities have been documented in both groups in Table 1. The differences in between the groups were insignificant (P > 0.05).

The ICU management was standardized between both groups, PEEP was titrated to a target oxygen saturation of above 90% and a target FiO_2 below 60%. Before starting prone positioning, initial Ph, PaO_2, PCO_2, and PaO_2/FiO_2 ratios were comparable between both groups as shown in (Table 2).

After prone positioning, lower values of SOFA (P < 0.219) and APACHE II (P < 0.221) scores were noticed in patients who underwent prone positioning than those who were not in the prone position. Regarding management, steroid therapy, Remdesivir, and Tocilizumab were administered (Table 3). The current medical treatments were based on the hospital protocols of the COVID-19 pandemic and updated management at the time of the study. The ventilatory management was guided by serial arterial blood gases and the decision to adjust ventilator settings was taken by both the intensivist and respiratory therapist.

As regards study outcomes shown in Table 4, there was no significant difference in the rate of discharge among the two groups (P = 0.759). However, we observed a shorter hospital and ICU lengths of stay in Group A than in Group B (P = 0.035 and 0.256) respectively but it was not significant. Higher frequency of tracheostomy procedures were performed in Group A than in Group B (P < 0.001), this statistically significant difference may show a better outcome for patients in Group A.

From day 1 to day 6, serial daily arterial blood gases were done to make a correlation between pH, PO_2, and PO_2/FiO_2 ratios over a total of 6 days. For Ph values, we did not notice any significant variance between both groups as shown in Figure 2. For PO_2 values, we noticed a significant variance between both groups starting from day 2 to day 6 as shown in Figure 3 (P < 0.001). Also, in Figure 3, we can observe a significant variance between both groups as regards PO_2/FiO_2 ratios which were significantly higher in Group A in comparison with Group B from day 2 and onwards (P < 0.001).

We observed a significant improvement in both PO_2 and PO_2/FiO_2 ratios in Group A in comparison to Group B during prone positioning from day 2 which extended up to 6 days in all patients.

Table 3: Scores, and medical treatments after the prone position

Patient Characters	Group A (n = 39)	Group B (n = 31)	P-Value
APACHE II score	32 ± 5	39 ± 5	0.221
Lung Injury Score (LIS)	2.0 ± 0.1	2.1 ± 0.1	0.341
SOFA score	11.4 ± 3.7	13.2 ± 2.9	0.219
Treatment			
• Steroid therapy	36 (92.3)	29 (93.5)	0.842
• Antivirals (Remdesivir)	3 (7.6)	2 (6.4)	0.695
• IL-6 inhibitor (Tocilizumab)	12 (30.7)	9 (29.0)	0.512

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II score; LIS: Lung Injury Score;
SOFA: Sequential Organ Failure Assessment score; GCS: Glasgow Coma Score; ICU: intensive care unit.
**Student t and Test. ** Mann Whitney U Test. Values are mean ± SD, or n (%)*

Table 4: Study outcomes among both groups

Study outcomes	Group A (n = 39)	Group B (n = 31)	P-value
Primary outcome			
Discharged	21 (53.8)	15 (48.3)	0.759
Secondary outcomes			
• LOS, median (days)	15 (13–35)	20 (11–25)	0.035
• ICU LOS, median (days)	9 (4–20)	12 (6–19)	0.257
• Tracheostomy	10 (32.2)	2 (6.4)	< 0.001

LOS: Length of Stay; ICU: Intensive Care Unit.
Data presented as n (%) or median (range)

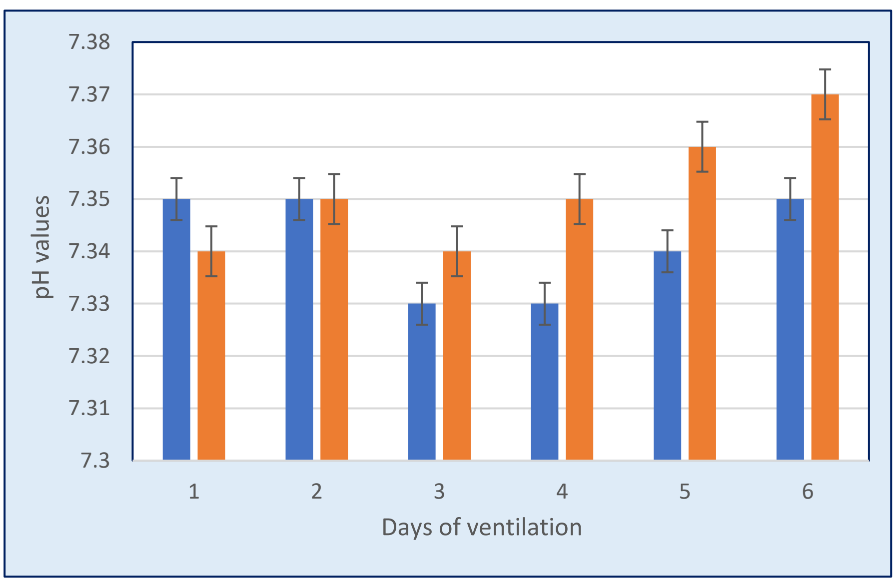

Figure 2: Correlation between both groups regarding pH readings

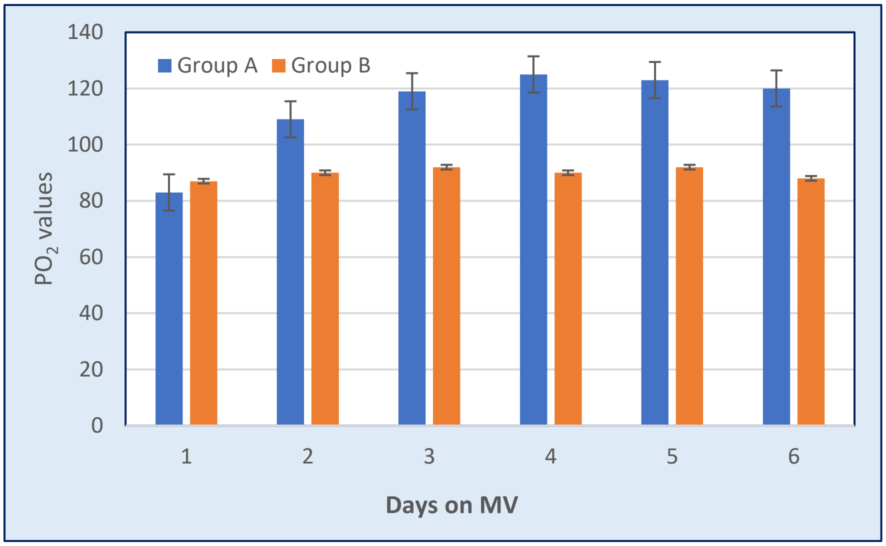

Figure 3: Correlation between both groups regarding PO_2 readings

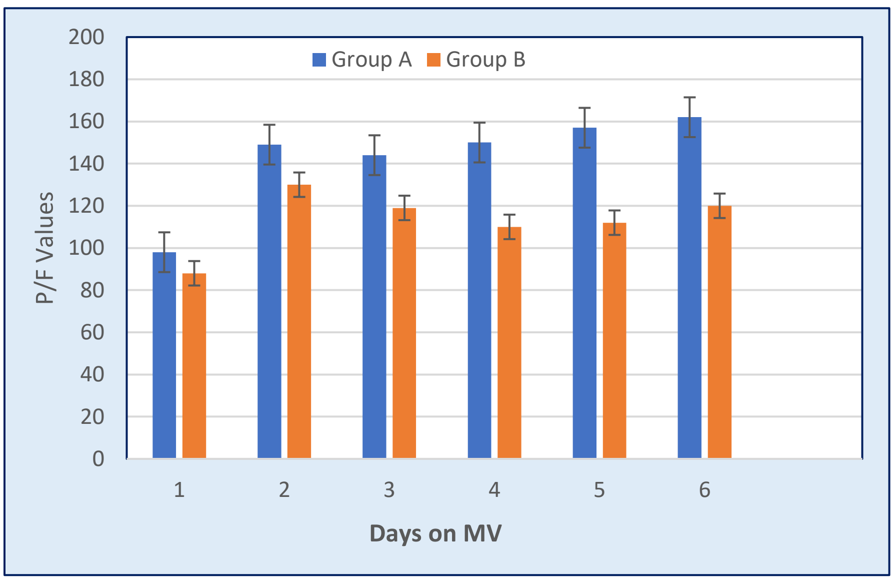

Figure 4: Correlation between both groups regarding P/F ratio readings; P: PO2; F: FiO2.

4. DISCUSSION

COVID-19 infection presents in a variety of manifestations, from mild rhinorrhoea to severe ARDS that needs tracheal intubation and mechanical ventilation.[13] Early prone position during mechanical ventilation is a well-established protocol among patients with ARDS which helps in enhanced ventilation-perfusion matching and survival rate. However, the use of prone positioning remains limited in moderate to severe ARDS patients. Late research during the SARS-COV-2 era indicates a compelling rise in the use of prone positioning and escalated knowledge among ICU staff.[14]

An analysis of comorbid conditions highlighted a statistically significant increase in mortality rates among patients with concurrent respiratory failure and cardiac disease or renal failure and diabetes, underlining the critical influence of existing health conditions on ARDS outcomes.[15] Mechanical ventilation modalities, including airway pressure release ventilation (APRV) and adaptive support ventilation (ASV), have been employed variably, with APRV being the most common.[16]

This study highlighted the impact of early application of prone positioning after intubation and initiation of lung protective strategy on discharge rate, hospital and ICU length of stay.

The mode of MV employed in this study encompassed P-SIMV mode, with no discernible impact on mortality rates across these different methodologies. In the current study, APACHE II, LIS, and SOFA scores were found to be a little lower in Group A in comparison with Group B at the time of admission ($P = 0.24$), ($P = 0.13$) and ($P = 0.250$) respectively.

After prone positioning, there was no significant variation in all these scores. These findings can explain that the impact of prone positioning is mainly on the improvement of oxygenation and ventilation-perfusion matching with no special impact on the inflammatory process.

Al-Hashim et al. (2023) monitored both APACHE II and SOFA scores only at the time of admission and the median results were 20 (13–22) and 5 (3–5), respectively. Even higher SOFA scores ($P < 0.001$), and APACHE II scores ($P < 0.001$) were noticed in patients who underwent prone positioning than those who were not in the prone position, no follow-up up done for these scores.[17]

Our study observed a mean pH of 7.26 ± 0.05 with limited significant hospital or ICU length of stay difference between groups, indicating that early prone position does not inherently decrease mortality or length of stay in ARDS-related COVID-19 patients. Our results coincide with the results of a meta-analysis by Tan W et al., who included more than 243 patients through 16 studies and focused on early prone position in awake patients. They found that early prone positioning decreased the breathing rate and increased the PaO_2/FiO_2 ratio significantly.[18]

We found a significant increase in the number of cases needing tracheostomy procedures in the early prone positioning group more than non-prone group (32.2 % vs 6.4% respectively; P-value < 0.001). This number may represent as a part of successful weaning from the mechanical ventilator and it shares to decrease the percent of mortality. The findings also coincide with the results of Mostafa Altinay et al., who found a significant increase in the number of tracheostomized patients in the prone group in comparison to the supine group (30% vs. 9.6%; P < 0.001).[19]

In the current study, we did not find any significant variation in PH, PaO_2, or PaO_2/FiO_2 ratios initially or within 24 h after prone positioning. However, there was a significant variation in both PaO_2 and PaO_2/FiO_2 ratios in Group A than in Group B from the second day onwards (P < 0.001).

Our results match with the results of Mostafa Altinay et al.[19] with some differences, they found a significant variation in PaO_2/FiO_2 ratios among the two groups (prone and non-prone groups) and an interaction between the position and the duration of mechanical ventilation from the first day of prone position up to the 4th day (P < 0.001). The median value of PaO_2/FiO_2 was 190 in the prone group vs 164 in the non-prone group after 24 h from the prone position (P < 0.001).

In the current study, PaO_2 increased significantly in prone position patients than in the non-prone patients from the second day up to the 6th day; these findings agree with the results of Sud S, et al.[20] with some differences. They found that PaO_2 values were significantly lower in the prone group from day 2 after prone up to day 4 in comparison to the non-prone group. We applied prone position for a total of 6 days as per our hospital protocol.

5. LIMITATIONS

The study has some limitations, as it involved only a limited sample size due to the high number of exclusion criteria; also it was a single-centre study.

6. CONCLUSION

Early prone positioning led to a significant improvement in both PaO_2 and PaO_2/FiO_2 ratio with a non-significant decrease in both hospital and ICU length of stay. We collected data over consecutive six days. More researches are needed to check the effect of early prone positioning on patients' mortality.

7. Data availability

All study numerical data are available with the authors.

8. Funding

Our study used only institutional resources, and no external or industry funding was involved.

9. Conflict of interests

The authors declare no conflict of interests.

10. Authors contribution

SHS; Concept, Design, Funding, Literature Review, Manuscript Writing, Critical Review
IMA; Supervision, Materials, Data Collection and/or Processing, Analysis and/or Interpretation

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