BNS University
Critical Care Department
The Egyptian Journal Of Intensive Care And Emergency Medicine (JICEM)

Role of Prone Position in Acute Hypoxemic COVID-19 Patients with Spontaneous Ventilation: A Randomized Controlled Study

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Abstract:

Background: The COVID-19 pandemic has prompted the need for novel treatments for acute hypoxemic respiratory failure. Prone positioning, a method previously reserved for severe ARDS, is now being explored for its benefits in non-intubated COVID-19 patients to improve oxygenation and potentially decrease the reliance on mechanical ventilation and ICU care. **Aim:** To evaluate if prone positioning alongside standard treatment enhances outcomes in acute hypoxemic COVID-19 patients, focusing on ICU admission, mechanical ventilation rates, oxygenation, hospital stay, and 28-day mortality compared to standard treatment alone. **Material and Methods:** This prospective, randomized controlled study involved 90 COVID-19 patients, divided into Group P (proning plus standard care, n=45) and Group S (standard care alone, n=45) admitted to Tanta University Hospitals. The study assessed the impact of prone positioning on ICU admission rates, mechanical ventilation use, oxygenation improvement, hospital stay duration, and 28th-day mortality. **Results:** Improvements in PaO_2/FiO_2 and SpO_2/FiO_2 ratios were significantly better in Group P after 24 hours and at the

endpoint (p values 0.031 and 0.014; 0.028 and 0.035, respectively). Inflammatory markers and lymphocyte counts improved significantly in Group P at the endpoint. No significant difference was observed in mechanical ventilation use, cardiac arrest, or 28-day mortality between the groups. The incidence of ICU admission was significantly lower in group P than group S (P value =0.038). **Conclusions:** Prone positioning could be an effective adjunct therapy in the management of moderate COVID-19-induced respiratory failure, potentially alleviating ICU resource strain.

Keywords: Prone Position, Acute Hypoxemia, COVID-19, Spontaneous Ventilation.

1. Introduction:

Hypoxemia is prevalent among intensive care unit patients who are mechanically ventilated. Acute hypoxemic respiratory failure (AHRF) affects an estimated one million patients globally, although epidemiological data regarding its precise incidence and prognosis are highly variable [1].

Pronounced as the causative agent, the novel SARS-CoV-2 virus precipitated an extensive spectrum of clinical consequences, spanning from asymptomatic instances to critical respiratory distress necessitating intensive care and mechanical ventilation [2, 3].

Early management of hypoxemia involves supplemental oxygen, escalating to high-flow nasal cannula or non-invasive ventilation as needed, with intubation as a last resort due to the risk of ventilator-associated lung injury [4, 5].

It has been demonstrated that prone positioning, which dates back to the 1970s, improves survival and oxygenation in patients with severe ARDS by decreasing mechanical ventilation-induced lung damage [6, 7].

Recent interest has grown in applying prone positioning to awake, non-intubated patients with COVID-19 to enhance oxygenation and potentially avoid the complications associated with invasive ventilation, highlighted by the pandemic's strain on ICU resources [8, 9].

The purpose of this study was to assess the impact of utilizing the prone position in conjunction with standard treatment versus standard treatment alone on the rate of intensive care unit admission and invasive mechanical ventilation, as well as oxygenation, hospital stay, and 28th day mortality, in patients with acute hypoxemic COVID-19 who were spontaneously breathing.

2. Patients and Methods:

Study Design and patients:

This prospective randomized controlled study was carried out in Isolation Hospital for 90 patients with COVID-19 in for a period of 12 months from the beginning of December 2021 to the end of November 2022. Patients were separated into two groups from December 2021 to November 2022. Group P, consisting of 45 patients, received proning for 12 to 16 hours daily along with standard care for acute hypoxemic respiratory failure, while Group S, also with 45 patients, received standard care alone (Approval code: 34988/10/21).

Patients aged 18 to 65 years, both sexes, patients with acute hypoxemic laboratory-confirmed moderate, able to maintain oxygen saturation above 92% with up to 4 L/min oxygen via nasal prongs up to patients with O2 saturation 92% on room air with P/F ratio ranged from 177 to 300, COVID- 19 patients and absence of decompensated respiratory acidosis [10] and laboratory-confirmed COVID-19 infection were included in the trail [10, 11].

Participations with presence of any contraindication to prone position, critically and severe ill COVID-19 patients [10, 11] and patients with organ failure were excluded.

Methods:

All patients of both groups were triaged, demographic data: weight, sex, age, height, and body mass index (BMI), vital signs, history, clinical symptoms such as dyspnea, cough, fever, chest pain, abdominal pain, and diarrhea.

Complete clinical examination and laboratory investigations were performed according to Standard protocol of management of COVID-19 patients. All patients were admitted to the Intermediate Care Unit.

Study interventions:

Group P (Proning group): Supine to Prone: The patient underwent prone positioning for 12-16 hours daily, divided into multiple sessions based on comfort, with the option to use mobile devices or watch TV. Positioning was adjusted for optimal comfort using pillows and cushions, and arms were positioned as preferred. FiO2 was initially increased by 25% above baseline before returning to normal to maintain a SpO_2 of >94%. Vitals and oxygen levels were monitored before and after each session. Enteral or oral feeding was paused 1 hour before positioning. If prone positioning was not tolerated, the patient was moved to a supine position, and reasons for discontinuation, such as specific complications or significant drops in oxygenation, were recorded. Supportive measures included

limb movement encouragement and proper mask or nasal cannula fitting to prevent complications. Supine to Prone: With the assistance of members of the healthcare team, the patient returned to the semi-recumbent supine position following the prone position period. As stated in the procedure's previous description, the FiO_2 was increased to a maximum of 25% above the baseline value and then decreased gradually to the baseline value over the next 10 minutes in an effort to achieve a SpO2 greater than 94%. SpO2, SpO2/FiO2, and vital signs were assessed both prior to and following the supine position session. If the patient did not improve after 48 hours, this is considered failure of proning.

Group S (Standard group):

The standard management of moderate COVID-19 patients was done.

Endpoint of the study:

Patients were either discharged or admitted to ICU. Patients were discharged home at O2 Saturation ≥ 95% of the room air (patients were kept under observation before discharge home for 24 or 48 hours) in ward.

Criteria for Transfer to ICU [12, 13]:

Criteria for ICU transfer include cardiovascular issues such as cardiogenic shock, cardiac arrest, the need for cardioversion or defibrillation, sustained or symptomatic arrhythmias, and high-dose inotropic agent use. Respiratory criteria encompass respiratory arrest, SpO2 ≤ 88% on ≥ 5 L facial mask, altered consciousness, significant hypercapnia or respiratory acidosis, severe dyspnea, and signs of ARDS or worsening hemoptysis. Neurological indicators include a decline to stupor or worse and acute stroke requiring monitoring. Psychiatrically, delirium necessitating respiratory care, and renal problems like acute failure requiring continuous renal replacement therapy, also prompt ICU admission.

Measurements:

At admission, patient demographics, comorbidities, symptoms, and vital signs were recorded, alongside PaO_2/FiO_2 and SpO_2/FiO_2 ratios, and initial laboratory tests. These data points were monitored upon admission, after 24 hours, and at discharge, assessing hospital stay length, oxygen support duration, ICU admissions, mechanical ventilation usage, and noting any complications like hypotension or equipment displacements.

Outcomes:

Rate of ICU admissions constituted the principal outcome of the research. The rate of invasive mechanical ventilation utilization, the duration of hospitalization, the number of days an oxygen support device was required, and mortality on the 28th day after admission constituted secondary outcomes.

Statistical Analysis:

For statistical analysis, SPSS v26 (IBM Inc., Chicago, IL, USA) was utilized. The quantitative variables were expressed as the mean and standard deviation (SD), and an unpaired Student's t-test was used to compare them between the two groups. The frequency and percentage (%) of qualitative variables were provided for analysis, and when applicable, the Chi-square or Fisher's exact test was utilized. A two-tailed P value less than 0.05 was deemed to indicate statistical significance. To compare quantitative variables between the two groups, the unpaired Student's t-test was employed. For qualitative variables, the chi-square test was utilized, and Fisher's exact test was employed when one of the cells contained fewer than five.

3. Results:

In this trail, an eligibility assessment was conducted on 109 patients; eleven patients failed to meet the specified criteria, and eight patients declined to partake in the study. A total of 45 patients were randomly divided into two groups of equal size, comprising the remaining patients. All assigned patients were statistically analyzed and followed up on. **Figure 1**

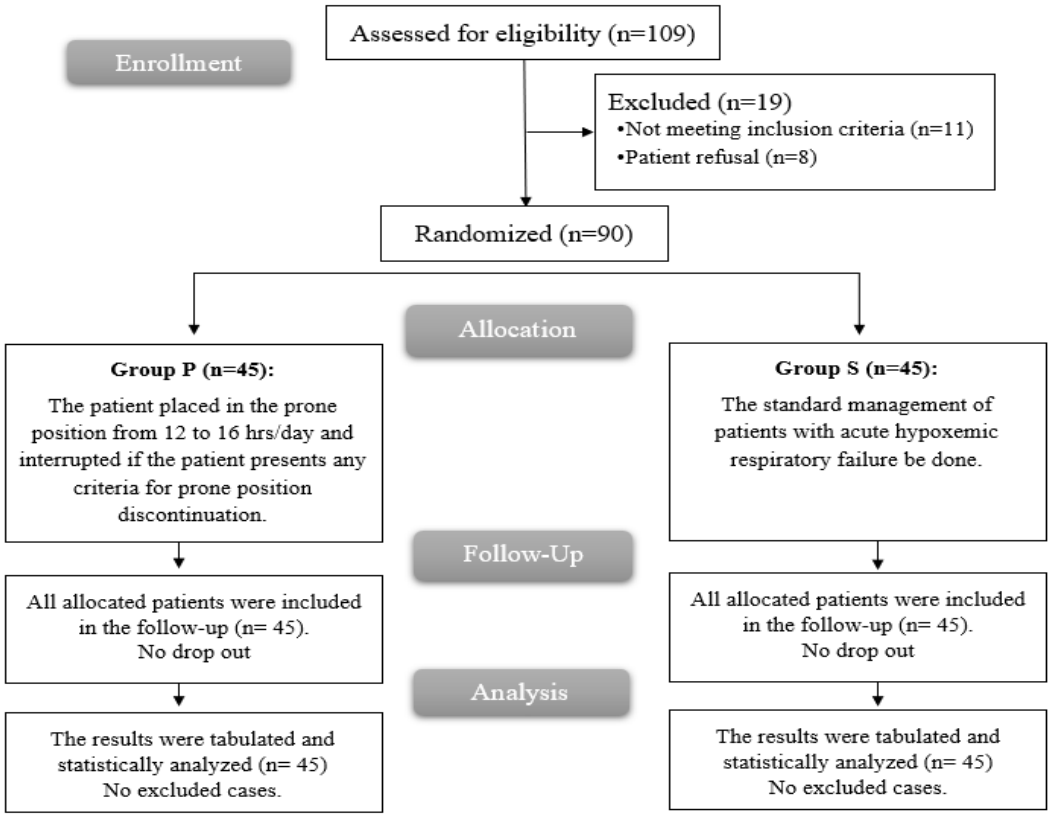

Figure 1: CONSORT flowchart of the enrolled patients.

In comparison between both groups according to age, sex, weight, height and BMI, there was not statistically significance difference among two groups. There was no statistically significant difference among two groups regarding comorbidities. **Table 1**

Table 1: Demographic data and comorbidities of the studied groups.

		Group P (n=45)	Group S (n=45)	P value
Age (years)	**Mean ± SD**	42.18 ± 9.76	45.91 ± 12.36	0.115
	Range	23 - 65	22 - 65	
Sex	**Male**	28 (62.22%)	35 (77.78%)	0.107
	Female	17 (37.78%)	10 (22.22%)	
Weight (kg)	**Mean ± SD**	78.53 ± 15.13	82.73 ± 11.07	0.136
	Range	47 - 111	58.5 - 103.5	
Height (cm)	**Mean ± SD**	171.87 ± 7.54	170.91 ± 6.3	0.516
	Range	157 - 183	158 - 183	
BMI (kg/m^2)	**Mean ± SD**	26.64 ± 4.95	28.25 ± 2.87	0.064
	Range	14.8 - 33.5	23.4 - 32.7	
Hypertension	**Yes**	15 (33.33%)	20 (44.44%)	0.280
	No	30 (66.67%)	25 (55.56%)	
DM	**Yes**	13 (28.89%)	22 (48.89%)	0.052
	No	32 (71.11%)	23 (51.11%)	

BMI: Body mass index, DM: Diabetes mellitus

There was non statistically significant difference between both groups regarding (dyspnea, cough, fever, chest pain, abdominal pain and diarrhea). **Figure 2**

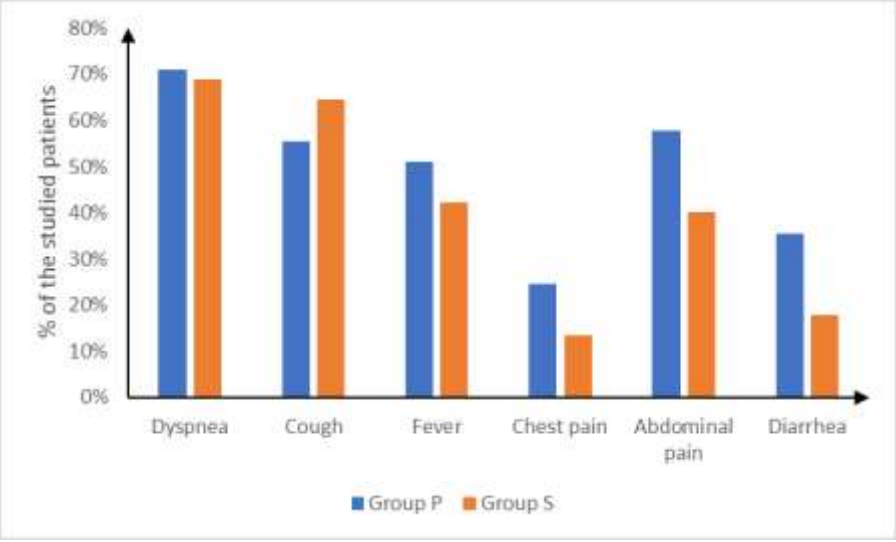

Figure 2: Symptoms of the studied groups.

There was no statistically significant difference among the two groups regarding heart rate at admission while there was significantly decrease in group P compared to group S after 24h and at endpoint (P value <0.05). There is no statistically significant difference among both groups regarding mean arterial blood pressure at admission, after 24h and at endpoint. Respiratory rate was insignificantly different at admission between both groups, while was significantly lower in group P than group S after 24h and endpoint (P value <0.05). Temperature was insignificantly different between both groups at admission, after 24h and endpoint. **Table 2**

Table 2: Vitals signs of the studied groups

	Group P (n=45)		**Group S (n=45)**		**P value**
	Mean ± SD	**Range**	**Mean ± SD**	**Range**	
Heart rate (beats/min)					
At admission	102.33 ± 9.67	89 – 123	99.62 ± 10.91	88 – 122	0.216
After 24h	89.58 ± 9.54	80 – 117	95.22 ± 11.79	84 – 123	**0.014***
Endpoint	81.02 ± 13.05	66 – 121	89.58 ± 19.58	70 – 136	**0.017***
Mean arterial blood pressure (mmHg)					
At admission	91.9 ± 5.77	78 - 104.2	93.41 ± 5.84	81.7 - 103.3	0.221
After 24h	89.92 ± 5.6	78.2 - 101.8	91.5 ± 5.74	80.3 - 100.8	0.189
Endpoint	87.21 ± 7.2	63 - 99.6	85.8 ± 10.98	62 - 99.6	0.472
Respiratory rate (breaths/min)					
At admission	25.67 ± 1.8	22 – 29	25.44 ± 1.65	23 – 29	0.542
After 24h	21.4 ± 2.34	19 – 30	24.76 ± 3.81	19 - 33	**<0.001***
Endpoint	16.64 ± 3.35	15 – 31	21.36 ± 6.11	16 - 35	**<0.001***
Temperature (°C)					
At admission	38.45 ± 1.32	36.5 - 41.1	38.57 ± 1.52	36.9 - 41.6	0.696
After 24h	37.61 ± 1.03	36.1 - 40.6	37.75 ± 1.1	36.5 - 40.2	0.528
Endpoint	37.08 ± 0.62	36.4 - 39.5	37.32 ± 0.84	36.4 - 39.5	0.138

*: Significant as P value ≤0.05

There is non statistically significant difference among both groups regarding PaO_2/FiO_2 at admission, while was a significantly increase in group P than group S after 24h and endpoint (P value =0.031 and 0.014 respectively). There was non statistically significant difference among both groups regarding SpO_2/FiO_2 at admission while was significantly higher in group P than group S after 24h and endpoint (P value =0.028 and 0.035 respectively). **Table 3**

Table 3: PaO_2/FiO_2 and SpO_2/FiO_2 ratio of the studied groups

	Group P (n=45)		Group S (n=45)		P value
	Mean ± SD	Range	Mean ± SD	Range	
At admission	257.71 ± 39.67	177 – 300	256.09 ± 31.34	200 - 300	0.830
After 24h	320.4 ± 47.51	151 – 385	294.02 ± 65.48	170 - 380	**0.031***
Endpoint	357.33 ± 62.24	106 – 423	312.6 ± 102.47	98 - 409	**0.014***
At admission	357.62 ± 37.93	260 – 410	356.69 ± 36.7	255 - 442	0.906
After 24h	419.16 ± 45.81	251 - 476	392.47 ± 66.01	270 - 476	**0.028***
Endpoint	443.73 ± 70.04	183 - 476	406.16 ± 94.39	200 - 500	**0.035***

**: Significant as P value ≤0.05. PaO_2: Partial pressure of oxygen, FiO2: Fraction of inspired oxygen, SpO_2: Saturation of Peripheral Oxygen.*

CRP was insignificantly different at admission and after 24h between the two groups while was significantly lower at endpoint in group P than group S (P value =0.029). There was non statistically significant difference among the two groups regarding interleukin 6 at admission and after 24h while was significantly lower in group P than group S at endpoint (P value =0.038). There was non statistically significant difference among both groups regarding LDH at admission and after 24h while was significantly lower at endpoint in group P than group S (P value <0.001). There was no statistically significant difference between both groups regarding serum ferritin at admission and after 24h while was a significantly decrease in group P than group S at endpoint (P value =0.041). Lymphocytes were insignificantly different at admission and after 24h between both groups while were significantly increase in group P than group S at endpoint (P value =0.011). **Table 4**

Table 4: Inflammatory markers of the studied groups

	Group P (n=45)		Group S (n=45)		P value
	Mean ± SD	Range	Mean ± SD	Range	
CRP (mg/L)					
At admission	81.67 ± 24.56	32 - 180	71.56 ± 31.28	30 - 200	0.092
After 24h	55.93 ± 27.26	26 - 151	59.27 ± 40.06	26 - 220	0.646
Endpoint	20.78 ± 36.34	3 - 171	45.13 ± 64.1	3 - 250	**0.029***
Interleukin 6 (pg/ml)					
At admission	66.27 ± 25.28	26 - 112	64.71 ± 27.92	22 - 117	0.782
After 24h	55.36 ± 22.98	19 - 107	61.18 ± 27.93	19 - 113	0.283
Endpoint	39.22 ± 20.08	10 - 100	50.33 ± 29.19	12 - 110	**0.038***
LDH (U/L)					
At admission	359.93 ± 108.76	121 - 544	388.89 ± 91.63	267 - 543	0.175
After 24h	289.42 ± 127.36	111 - 524	335.67 ± 123.81	128 - 514	0.084
Endpoint	191.84 ± 71.98	100 - 473	271.53 ± 102.67	114 - 550	**<0.001***
Serum ferritin (µg/L)					
At admission	373.67 ± 99.21	133 - 550	335.16 ± 138.23	158 - 624	0.133
After 24h	275.42 ± 130.96	45 - 570	315.18 ± 143.82	45 - 570	0.174
Endpoint	141.09 ± 118.86	48 - 573	202.76 ± 159.98	48 - 600	**0.041***
Lymphocytes (µL)					
At admission	808.22 ± 291.22	340 - 1500	785.67 ± 235.19	300 - 1250	0.687
After 24h	1052.89 ± 299.68	555 - 1785	947.56 ± 326.42	450 - 1700	0.114
Endpoint	1387.78 ± 333.94	560 - 2000	1184.69 ± 400.28	500 - 1866	**0.011***

**: Significant as P value ≤0.05. CRP: C-reactive protein, LDH: Lactate dehydrogenase.*

Hospital stays and days on oxygen supply were significantly lower in group P than group S (P value <0.001). Group P had a significantly lower incidence of ICU admissions than group S (P value = 0.038). No statistically significant distinction was observed between the two groups with respect to the outcome variables of mechanical ventilation, cardiac arrest, and 28-day mortality. **Table 5**

Table 5: Hospital stays, days on oxygen supply, ICU admission, mechanical ventilator, cardiac arrest and 28-day mortality of the studied groups

		Group P (n=45)	Group S (n=45)	P value
Hospital stays (days)	**Mean ± SD**	9.91 ± 3.68	17.49 ± 6.27	**<0.001***
	Range	5 - 27	7 - 30	
Days on oxygen supply (days)	**Mean ± SD**	8.91 ± 3.73	16.62 ± 6.49	**<0.001***
	Range	4 - 27	6 - 30	
Incidence of ICU admission	**Yes**	3 (6.67%)	11 (24.44%)	**0.038***
	No	42 (93.33%)	34 (75.56%)	
Invasive mechanical ventilator	**Yes**	3 (6.67%)	9 (20%)	0.063
	No	42 (93.33%)	36 (80%)	
Cardiac arrest	**Yes**	1 (2.22%)	7 (15.56%)	0.058
	No	44 (97.78%)	38 (84.44%)	
28-day mortality	**Yes**	1 (2.22%)	7 (15.56%)	0.058
	No	44 (97.78%)	38 (84.44%)	

**: Significant as P value ≤0.05. ICU: Intensive care unit*

4. Discussion:

Regarding symptoms, our results were in accordance with the present findings, Bahloul et al. [14] conducted a study to determine whether COVID-19 patients with spontaneous respiration could benefit from early application of the prone position in order to mitigate severe hypoxemia and respiratory failure. An absence of statistically significant difference was noted in present symptoms at admission between the two groups (groups in the prone position and those not in the prone position), with the exception of dyspnea, which was significantly more prevalent in the prone position group.

Also, Nay et al. [15] found that the primary outcome was not significantly impacted by the intervention; however, the prone position group had a reduced risk of intubation, as well as death, compared to the usual care group.

Regarding vital signs, our results were similar to Chiumello et al. [16] conducted a research investigation with the purpose of assessing the impacts of maintaining an awake prone position during helmet continuous positive airway pressure (CPAP) ventilation on hypoxemic COVID-19 patients' comfort of breathing, gas exchange, and inspiratory effort. This study found that a prone position was associated with decreased respiratory rate and improved heart rate compared to a supine position.

Regarding PaO_2/FiO_2 at admission, our study was in line with early case series studies by Sartinin et al. [17] and Elharrar et al., [18] demonstrated that the prone position

decreased respiratory rate and increased SpO2, PaO2, and PaO2/FIO2.

Moreover, the improvement in respiratory parameters was confirmed in subsequent cohort studies conducted by Jouffroy et al. [19] ,Barker et al., [20] and Perez-Nieto et al., [21].

Similarly, Bahloul et al. [14] demonstrated that one hour after adopting the prone position, SpO2 increased significantly from 82%±12% to 96%±3% (P0.001). Furthermore, there was a significant reduction in respiratory rate from 31±10 to 21±4 breaths per minute (P<0.001) when in the prone position. Moreover, following prone positioning, the proportion of patients demonstrating indications of respiratory distress decreased from ten (47%) to three (14%) (P=0.04).

Regarding inflammatory markers, our results were in agreement with the present findings, Wang et al. [22] who showed that prone position was statistically significant associated with decreased CRP and interleukin on third day of prone position application.

Regarding hospital stay, our results were similar to the present study, Wormser et al. [23] who comprised patients with confirmed hypoxemia to COVID-19 who were treated with at least one prone position session. An association between the application of the prone position and a reduced length of hospital stay was found to be statistically significant in COVID-19 patients, according to this study.

In disagreement with the present findings, Rosén et al., [24] conducted a study to determine whether a protocol for awake prone positioning among patients with moderate to severe hypoxemic respiratory failure caused by COVID-19 reduces the rate of endotracheal intubation compared to standard care. This research demonstrated that there was no discernible distinction between prone and standard care in terms of the duration of hospitalization or oxygen therapy.

Also, Fralick et al. [25] undertook a research investigation to evaluate the efficacy of prone positioning in mitigating the mortality or respiratory failure risk among non-critically ill patients who were admitted to the hospital with COVID-19. Patients were assigned to standard of care or prone positioning in a 1:1 randomization. This study revealed that there was no statistically significant difference in the length of hospital stay until discharge between the two groups included.

In disagreement with our study, different from the present results, Nay et al. [15] showed no difference among prone position and usual care regarding duration of hospital stay and duration of oxygen therapy.

Furthermore, Peng et al. [26] performed a meta-analysis and systematic review which

evaluated the effects of the awake prone position on acute hypoxic respiratory failure in patients with COVID-19 with all randomized controlled trials. This showed no effect for prone position on length of hospital stay.

Regarding ICU admission and other outcomes, our study was in agreement with the present findings, Perez-Nieteo et al., [21] reported that maintaining an awake prone position was correlated with a decreased likelihood of intubation and mortality. Additionally, there was a significant correlation between the prone position and a reduced number of ICU admissions, which is consistent with the current findings.

Also, Rosén et al., [24] indicated non statistically significant difference among prone and supine positions regarding 30-day mortality and ventilation. However, they differed from our study as they showed non statistically significant difference was observed among prone and supine positions regarding ICU admission.

Moreover, Bahloul et al. [14] demonstrated that the utilization of invasive mechanical ventilation or early application of the prone position did not significantly reduce the mortality rate when compared to the control group (the group that did not use the prone position). Nevertheless, it was observed that the initiation of invasive mechanical ventilation was postponed in the prone position group of patients in comparison to the control group.

In agreement with the present findings, Fralick et al. [25] reported that there was non significant difference among prone position and control regarding mortality, and ventilation of the included patients.

In agreement with the present findings, Nay et al. [15] reported non statistically significant difference among the prone position group and the usual care group regarding mortality, while ventilation was statistically significantly lower in prone position patients. However, they differed from our study as they showed non statistically significant difference between the prone position group and the usual care group regarding ICU admission.

In disagreement with our results, two meta-analyses by Fazzini et al. [25] and Beran et al. [27] pooling randomized controlled studies and non-randomized controlled studies together have also established that prone position was significantly associated with lower mortality compared with supine positioning [28].

Moreover, the RCT by Alhazzanni et al. [29] has also shown non difference in mortality among prone position and control groups.

5. Conclusions:

Prone positioning significantly improves oxygenation, reduces inflammatory markers, and shortens hospital stay and

oxygen dependency, with a notable reduction in ICU admissions. It could be an effective adjunct therapy in the management of moderate COVID-19-induced respiratory failure, potentially alleviating ICU resource strain.

Acknowledgement: Nil.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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