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Research Article

Effectiveness of prone position in acute respiratory distress syndrome and moderating factors of obesity class and treatment durations for COVID-19 patients: A meta-analysis

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A R T I C L E I N F O

Keywords:
Acute respiratory distress syndrome
COVID-19
Prone position
Coronavirus 2
Respiratory failure

A B S T R A C T

Objectives: To examine the effectiveness of prone positioning on COVID-19 patients with acute respiratory distress syndrome with moderating factors in both traditional prone positioning (invasive mechanical ventilation) and awake self-prone positioning patients (non-invasive ventilation).

Research methodology: A comprehensive search was conducted in CINAHL, Cochrane library, Embase, Medline-OVID, NCBI SARS-CoV-2 Resources, ProQuest, Scopus, and Web of Science without language restrictions. All studies with prospective and experimental designs evaluating the effect of prone position patients with COVID-19 related to acute respiratory distress syndrome were included. Pooled standardised mean differences were calculated after prone position for primary (PaO_2/FiO_2) and secondary outcomes (SpO_2 and PaO_2)

Results: A total of 15 articles were eligible and included in the final analysis. Prone position had a statistically significant effect in improving PaO_2/FiO_2 with standardised mean difference of 1.10 (95%CI 0.60–1.59), SpO_2 with standardised mean difference of 3.39 (95% CI 1.30–5.48), and PaO_2 with standardised mean difference of 0.77 (95% CI 0.19–1.35). Patients with higher body mass index and longer duration/day are associated with larger standardised mean difference effect sizes for prone positioning.

Conclusions: Our findings demonstrate that prone position significantly improved oxygen saturation in COVID-19 patients with acute respiratory distress syndrome in both traditional prone positioning and awake self-prone positioning patients. Prone position should be recommended for patients with higher body mass index and longer durations to obtain the maximum effect.

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Implications for clinical practice

- Both traditional prone positioning and awake self-prone positioning patients are effective for patients with COVID-19 ARDS.
- Implementing prone position for patients with higher BMI are supported by the study's results.
- Longer durations of prone position is recommended for more benefits in traditional prone position.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has increased the number of hospitalised patients, especially with respiratory failures (Grasselli et al., 2020). Based on previous research, patients' mortality rates were reported at 39% of 10,815 COVID-19 patients globally in all settings, while in the critical care settings, particularly in those with mechanical ventilation, the rates reached 94% (Gibson et al., 2020; Hasan et al., 2020). The SARS-CoV-2 mainly affects and causes more damage to the respiratory system than other organs (Li and Ma, 2020). The rapid onset of widespread inflammation in the lungs can result in severe hypoxemia and can develop into an acute respiratory distress syndrome (ARDS) (Bos, 2020). Examining the effectiveness of interventions and moderating factors on interventions for ARDS is essential to improve patient outcomes.

According to the World Health Organisation (WHO) guidelines, ARDS related to COVID-19 is diagnosed when someone with confirmed COVID-19 infection meets the Berlin 2012 ARDS diagnostic criteria and there are pathological changes of diffuse alveolar damage in the lungs (Gibson et al., 2020). Based on the Berlin definition with oxygenation index, arterial oxygen partial pressure to inspired oxygen fraction (PaO_2/FiO_2), ARDS can be classified into: mild (200 mmHg $<$ $PaO_2/FiO_2 \leq$ 300 mmHg), moderate (100 mmHg $<$ $PaO_2/FiO_2 \leq$ 200 mmHg), and severe ($PaO_2/FiO_2 \leq$ 100 mmHg) (Ranieri et al., 2012). However, the National Health Commission of China developed a set of classifications for ARDS related to COVID-19 where PaO_2/FiO_2 less than 150 mmHg is moderate-severe (Li and Ma, 2020).

Another definition for ARDS related to COVID-19 suggested by Brown et al. (2021) is a patient receiving high-flow nasal oxygen therapy, non-invasive ventilation, or invasive mechanical ventilation for acute hypoxemic respiratory failure owing to SARS-CoV-2 pneumonia with the Kigali modification of oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) $<$ 315 eliminating requirements for positive end-expiratory pressure and positive pressure ventilation. Brown and colleagues reasoned that this is consistent with the Berlin definition's pathophysiological rationale without meaningfully altering the specificity of the resulting diagnosis or the relevance of ARDS-specific treatments (Brown et al., 2021).

The management of ARDS-related COVID-19 interventions for oxygen therapy includes high-flow nasal oxygen therapy, non-invasive ventilation, and invasive mechanical ventilation (Brown et al., 2021). Each of those interventions could be combined with prone position as a rescue therapy (Chad and Sampson, 2020). Prone positioning refers to positioning a patient face down onto their anterior chest and abdomen to take advantage of physiologic changes that can result in improved oxygenation through decreased ventilation/perfusion mismatch and, potentially, decreased lung injury (Venus et al., 2020). In the prone position, expansion of the anterior chest wall is restricted, resulting in a more homogeneous chest wall compliance (Bamford et al., 2020).

Prone positioning is generally reserved for sedated patients who are on invasive mechanical ventilation [known as traditional ICU prone positioning], but it may be beneficial for awake patients with COVID-19 with high-flow nasal oxygen therapy and non-invasive ventilation [known as awake self-prone positioning (ASPP)] (COVID-19 Treatment Guidelines Panel, 2020; Hadaya and Benharash, 2020). Prone position has been widely adopted to treat invasive mechanical ventilation patients with ARDS related to COVID-19, the majority of patients improved their oxygenation during prone position, most likely due to a better ventilation perfusion matching (Langer et al., 2021). The WHO recommends the use of 12–16 h/day prone position to improve oxygenation and patient survival under mechanical ventilation (Guérin et al., 2013; Organization, 2020).

Awake self-prone positioning in non-intubated patients with acute hypoxic respiratory failure is also feasible and safe (Jayakumar et al., 2021). There's an increase in research evidence in treating COVID-19 patients on non-invasive ventilation with ASPP that have reported a significant improvement in oxygenation (Sodhi and Chanchalani, 2020). Moreover, the initiation of ASPP is associated with lower mortality and lower intubation rate (Kharat et al., 2022; Oliveira et al., 2022; Rahmani et al., 2020), and ASPP for COVID-19 patients has become a widespread intervention (Rahmani et al., 2020).

Previous meta-analyses have identified the effectiveness of prone position in patients with COVID-19 (Reddy et al., 2021). However, to our knowledge, no meta-analysis has yet examined whether the effectiveness of prone position will differ in regards to the demographic characteristics, duration, frequency, length of therapy, total time, time point measurement, underlying pathophysiology, and other respiratory supports used for COVID-19 patients with ARDS. As the prone position is currently used in up to 76% of invasive mechanical ventilation COVID-19 patients (Ferrando et al., 2020; Ziehr et al., 2020), it is essential to evaluate these moderating characteristics in detail. Therefore, we aimed to extend the previous knowledge base by conducting a comprehensive meta-analysis and meta-regression to (1) assess the effectiveness of prone position towards the oxygenation status in patients with ARDS related to COVID-19 and (2) examine moderating factors pertaining to the effectiveness of prone position in both traditional ICU prone positioning and awake self-prone positioning patients.

Methods

Reporting standards

The current review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009) (Fig. 1) and registered in PROSPERO (CRD42020225465).

Search strategy

Systematic search was conducted in the databases of CINAHL, Cochrane library, Embase, Medline-OVID, NCBI SARS-CoV-2 Resources, ProQuest, Scopus, and Web of Science. Manual searches have also been conducted on Google Scholar and reference lists of previously published studies to retrieve more relevant articles. The search was performed using combination keywords of "COVID 19" OR "Covid-19" OR "SARS-Cov 19" OR "SARS-COV 2019" OR SARS-COV-19" OR "corona virus disease" OR "corona virus 19 disease" AND "Acute respiratory syndrome" OR "ARDS" AND "Prone Positioning" OR "Proning" OR "proning position" and without date of publication and language restrictions. The last update in the search was 12th May 2021.

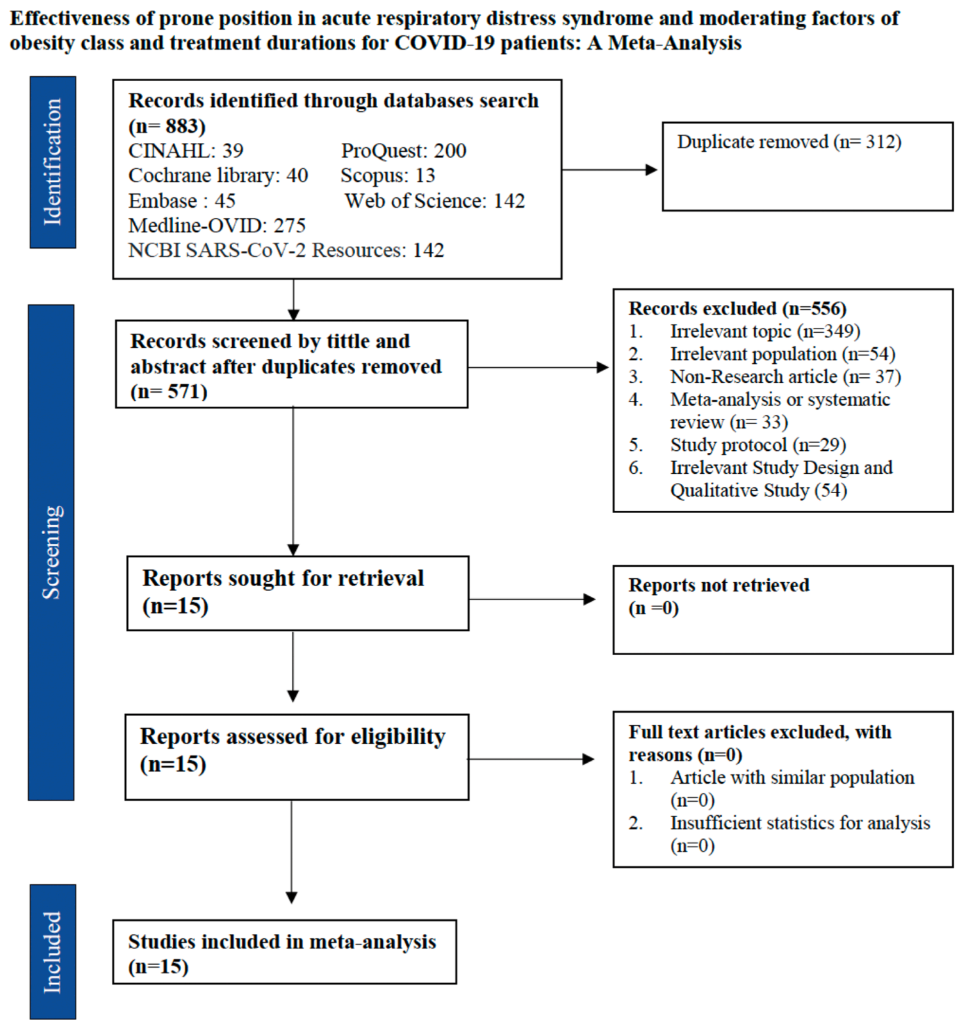

Fig. 1. Flow diagram for study selection.

Eligibility criteria and screening procedures

All articles from the databases were comprehensively screened using EndNote version 9.3 software. Systematic screening was conducted by two independent reviewers to identify eligible studies according to the PICOS criteria: This study focused on patients diagnosed with COVID-19 related to ARDS that were administered in the inpatient unit and studies that evaluate the effectiveness of prone positioning were included in the analysis.

The primary outcome of this study was PaO_2/FiO_2 after prone position. Secondary outcomes are other respiratory physiology parameters, including SpO_2 and PaO_2. This study includes all analytical studies, observational and experimental, which evaluate prone position, either with or without a control group. We included prospective studies approaches as they ranked higher in the hierarchy of evidence than retrospectives design (Euser et al., 2009).

Data extraction and study outcomes

The data extracted include: study identity, study characteristics (study design, country, and setting), participant characteristics (sample, mean age, gender, mean body mass index [BMI]), intervention characteristics (frequency, duration, and, total time of prone position, time measurement and respiratory support intervention) and outcome (PaO_2/FiO_2, SpO_2, and PaO_2).

Quality assessment

Risk of bias at the individual study level was assessed using the Methodological Index for Non-randomised Studies (MINORS) (Slim et al., 2003). The MINORS is a validated instrument used to determine the methodological quality of non-randomised surgical studies, comparative and non-comparative. It consists of eight items for non-comparative studies and an additional four items for comparative studies. The maximum score is 16 for non-comparative studies which are categorised as: 0–4, very low quality; 5–8, low quality; 9–12, moderate quality; and 13–16, high quality (Öhlin et al., 2019).

Statistical analysis

This study analysed the pooled evidence using R software version 4.0.2. The effectiveness of prone position towards oxygenation status was provided in standardised mean difference (SMD) format along with 95% confidence intervals (95% CI). Interpretation of standardised mean difference values are as follows: <0.2 are considered trivial, value of ≥ 0.2 and <0.5 are considered small, values of ≥ 0.5 and <0.8 are considered medium, and values ≥ 0.8 are considered large (Andrade, 2020).

To assess heterogeneity of treatment effects across studies, the Q-statistic and I^2 statistics were computed. The I^2 measures the extent of inconsistency among the study's results, and the outcome is interpreted as a percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins et al., 2003). Heterogeneity was quantified as low, moderate, and high, with upper limits of 25%, 50% and 75% for I^2, respectively (Melsen et al., 2014). The fixed- and random-effect models were calculated. The random-effect model was adopted in the analysis considering variations among the included studies (Serghiou and Goodman, 2019).

Sensitivity analyses were conducted to investigate the influence of individual studies on the overall effect by eliminating one study at a time.

Moderator analysis

Subgroup analysis and meta-regression were conducted for moderator analysis among the included studies (Higgins et al., 2003). We performed subgroup analysis for several potential moderator variables including, age (adult and elderly), body mass index (normal weight, pre-obesity, obesity class I, obesity class II), comorbidities (comorbidities and no-comorbidities), unit (intensive care unit [ICU] and non ICU), frequency for prone position (1 time/day, 2 times/day, 3 times/day), duration of prone position per day (less than 12 hours and equal to or greater than 12 hours), types of ARDS (mild, moderate and severe), study design (experiment and observational) and prone position (traditional ICU Prone positioning and ASPP). Meta-regression was performed for mean duration prone position/day, mean frequency prone position/day, mean total time of therapy prone position/patient, mean time measurement and mean sample size. A result with *p*-value less than 0.05 indicated a significant moderator.

Results

Descriptions of studies

From the electronic databases, 883 articles were retrieved and 312 duplicate articles were identified. After screening, 556 articles were excluded based on the title and abstract for the following reasons; irrelevant topic (349 articles), irrelevant population (54 articles), irrelevant study design and qualitative study (55 articles), non-research article (37 articles), meta-analysis or systematic review (33 articles), study protocol (29 articles). Finally, based on the full-text screening, 15 articles were eligible and included in the final analysis for this study (Abou-Arab et al., 2021; Avdeev et al., 2021; Caputo et al., 2020; Clarke et al., 2021; Elharrar et al., 2020; Fazzini et al., 2021a; Gad, 2021; Mittermaier et al., 2020; Paternoster et al., 2020; Sartini et al., 2020, Taboada et al., 2021, Taboada et al., 2020, Thompson et al., 2020, Zang et al., 2020, Ziehr et al., 2020).

Study characteristics

All of the included studies were published in 2020 and 2021 as the first case of COVID-19 was identified by the end of 2019. The settings of the studies were in the intensive care unit (8 studies) and non-intensive care unit (7 studies). From these included studies, 288 participants were identified, and the range of the sample size in each study varied from 7 to 50 participants. Most participants were male (65%) with ages ranging from 38 to 87 years and body mass index ranging from 24 to 36 kg/m^2. The intervention included: prone position with the frequency of the interventions ranged from 1 to 3 times/day with a duration of 0.5 to 12 hours/day. The primary outcome is oxygen saturation, which was measured by using PaO_2/FiO_2 (12 studies), as well as for secondary outcomes SpO_2 (5 studies) and PaO_2 (5 studies), see Table 1.

Quality assessment

Two assessors worked individually to evaluate the quality of the included studies using the MINORS. Cohen's kappa analysis showed a value at 0.218, interpreted as a fair agreement with non-significant differences between the two assessors (*p*-value 0.095) see Table 2. All included studies were evaluated using the risk of bias developed for the non-randomised study. The overall result showed 15.4% (2 studies) had high quality, and 84.6 % (11 studies) had moderate quality. Sensitivity analyses were conducted by eliminating one study each time, including studies with the lowest and highest time point measurement and the results showed the effectiveness of prone position had no significant difference with standardised mean differences ranging from 1.67 to 2.14.

Meta-analysis

Primary outcome

Prone position had a statistically significant effect in improving oxygen fraction PaO_2/FiO_2 ($p < 0.0001$), with a relatively large effect size of standardised mean difference 1.10 (95%CI 0.60–1.59) (Fig. 2.). The sensitivity analysis showed pooled standardised mean difference from 1.62 to 2.16. Heterogeneity test revealed $I^2 = 86.2\%$ and Q-value at 79.64 ($p < 0.0001$). The publication bias was analysed using Begg-Mazumdar test and found no significant result (*p*-value = 0.53).

Secondary outcomes

Our meta-analysis also identified a significant effect of prone position in improving SpO_2 ($p = 0.001$), with a relatively large effect size of standardised mean difference 3.40 (95%CI 1.31–5.49) with I^2 97.2% and *Q*-value at 142.99 ($p < 0.0001$) (Fig. 3.). Furthermore, prone position showed a significant effect in improving PaO_2 ($p = 0.009$), with a relatively medium effect size of standardised mean difference 0.77 (95% CI 0.19–1.35) with $I^2 = 74\%$ and Q-value at 15.37 ($p = 0.004$) (Fig. 4.)

Moderator analysis

Subgroup analyses were conducted for several potential moderator variables including age, body mass index (BMI), comorbidities, unit, frequency for prone position, duration of prone position per day, types of ARDS, study design, and prone position. Of the seven studies included in the analysis, prone position showed the highest effect on obesity class II body mass index with standardised mean difference 5.53 (95%CI 4.11–6.95) followed by body mass index obesity class I standardised mean difference 2.12 (95%CI 1.66–2.58), normal weight body mass index standardised mean difference 1.79 (95%CI 0.93–2.66) and body mass index pre-obesity standardised mean difference 1.19 (95%CI 0.72–1.65). Subgroup analysis for the variables of age, comorbidities, patient unit, respiratory support intervention, frequency of prone position and type of ARDS, study design, and prone position showed no significant differences. All results are provided in Table 3.

Meta-regression was performed for mean duration prone position/day, mean frequency prone position/day, mean total time of therapy prone position/patient, mean time measurement and mean sample size. Based on the results meta-regression analysis, mean duration prone position/day (1.17, 95%CI 0.59–2.02) and mean total time prone position/patients (1.30, 95%CI 0.56–1.77) showed significant relationships to the results of the current study. The variables of mean of frequency prone position/day and sample size showed no significant differences in results (see Table 4).

Discussion

The effectiveness of prone positioning

This meta-analysis found that prone position significantly improved oxygenation for ARDS-related to COVID-19 for patients with invasive mechanical ventilation (traditional ICU prone positioning) and non-invasive ventilation or high-flow nasal oxygen therapy (ASPP). Based on the 15 included analytical studies of observational and experimental designs representing 288 patients with ARDS related to COVID-19, there

Table 1
Characteristics of the included studies (n = 15).

No	Study ID	Study characteristics		Participant characteristic				Intervention characteristics		Outcomes	
		Design	Country	Setting	n	Demographic	Comorbidities	Prone position	Respiration support intervention		Time measurements
1	Abou-arab et al., 2020	Prospective cohort study	France	ICU	25	Age: Mean = 62 Range = 57–64 Gender: M = 20 F = 5 Mean BMI: 30	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 1x/ day Duration: 16 hour session Length of therapy: 1 day Total time: 16 hours Intervention time from admission: NA	PEEP Ventilator	PaO_2/FiO_2	Baseline and 16 h after prone
2	Avdeev et al., 2021	Prospective cohort study	Russia	Non-ICU	22	Age: Mean = 48.5 Range = 39.8–62.8 Gender: M = 16 F = 6 Mean BMI: 28.7	Comorbidities: Hypertension Diabetes	Frequency: 1x/ day Duration: 3 hour/session Length of therapy: 1 day Total time: 3 hours Intervention time from admission: NA	CPAP	PaO_2/FiO_2	Baseline and 3 h after prone
3	Caputo et al., 2020	Prospective cohort study	United States	Non-ICU	50	Age: Mean = 59 Range = 50–68 Gender: M = 30 F = 20 Mean BMI: NA	Comorbidities: NA	Frequency: 1x/ day Duration: 5 minute/session Length of therapy: 1 day Total time: 5 minutes Intervention time from admission: NA	NRM, Nasal Cannula	PaO_2/FiO_2	Baseline and 5 min after prone
4	Clarke et al., 2021	Prospective cohort study	Ireland	ICU	20	Age: Mean = 54 Range = 45–59 Gender: M = 18 F = 2 Mean BMI: 36	Comorbidities: NA	Frequency: 3x/ day Duration: NA Length of therapy: NA Total time: 16.2 hours Intervention time from admission: NA	PEEP Ventilator	PaO_2/FiO_2 PaO_2	Baseline and 1 h after prone
5	Elharrar et al., 2020	Prospective cohort study	France	ICU	24	Age Mean = 66.1 Range=– Gender: M = 16 F = 8 Mean BMI: 30	Comorbidities: NA	Frequency: 1x/ day Duration: 3 hour/session Length of therapy: 1 day Total time: 3 hours Intervention time from admission: NA	HFNC Nasal Cannula	PaO_2	Baseline and 1–2 h after prone
6	Fazzini et al., 2021	Prospective cohort study	United Kingdom	ICU	46	Age: Mean = 56 Range = 30–79 Gender: M = 23 F = 11 Mean BMI: NA	Comorbidities: NA	Frequency: 1x/ day Duration: 5 hour/session Length of therapy: day Total time: 5 hours Intervention time from admission: NA	HFNO CPAP	PaO_2/FiO_2	Baseline and 1 h after prone
7	Gad, 2021	Prospective randomised trial	Egypt	ICU	15	Age: Mean = 49 Range =	Comorbidities: NA	Frequency: 5x/ day Duration: 2	HFNO CPAP HFNO	PaO_2/	Baseline and 2 h after prone

(continued on next page)

Table 1 (*continued*)

No	Study ID	Study characteristics		Participant characteristic				Intervention characteristics		Outcomes	
		Design	Country	Setting	n	Demographic	Comorbidities	Prone position	Respiration support intervention		Time measurements
						38–62 Gender: M = 9 F = 6 Mean BMI: NA		hour/session Length of therapy: 4 day Total time: 40 hours Intervention time from admission: NA			
8	Mittermaier et al., 2020	Prospective observational study	Germany	ICU	9	Age: Mean = 62 Range = NA Gender: M = 6 F = 3 Mean BMI: 30.4	Comorbidities: Diabetes Respiratory disease Obesity	Frequency: 1x/ day Duration: 2–3 hour/session Length of therapy: 6 days Total time: 12 hours Intervention time from admission: NA	PEEP	PaO_2/ FiO_2	Baseline and 12 h after prone
9	Paternoster et al., 2020	Prospective cohort study	Italy	ICU	11	Age: Mean = 62 Range = NA Gender: M = 4 F = 7 Mean BMI: NA	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 1x/ day Duration: 12 hour/session Length of therapy: 3 days Total time: 36 hours Intervention time from admission: NA	CPAP	PaO_2/ FiO_2	Baseline and 24 h after prone
10	Sartini et al., 2020	Quasi-experiment	Italy	Non-ICU	15	Age: Mean = 59 Range = NA Gender: M = 13 F = 2 Mean BMI: 24	Comorbidities: NA	Frequency: 2x/ day Duration: 3 hour/session Length of therapy: 1 day Total time: 6 hours Intervention time from admission: 5 hours	Face Mask High-Oxygen	PaO_2/ FiO_2 SpO_2	Baseline and 1 h after prone
11	Taboada et al., 2020 (a)	Prospective cohort study	Spain	ICU	7	Age: Mean = 65 Range = 49–77 Gender: M = 3 F = 4 Mean BMI: NA	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 2x/ day Duration: 2 hour/session Length of therapy: 3 days Total time: 12 hours Intervention time from admission: NA	Ventilator	PaO_2/ FiO_2 PaO_2	Baseline and 12 h after prone
12	Taboada et al., 2020 (b)	Prospective cohort study	Spain	Non-ICU	29	Age: Mean = 64 Range = NA Gender: M = 21 F = 8 Mean BMI: 29.2	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 1x/ day Duration: 1 hour/session Length of therapy: 1 days Total time: 1 hour Intervention time from admission: NA	HFNC	PaO_2/ FiO_2 SpO_2	Baseline and 1 h after prone
13	Thompson et al., 2020	Prospective cohort study	United States	Non-ICU	25	Age: Mean = 66.5 Range = 45–87 Gender: M = 18 F = 7 Mean BMI: 29	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 1x/ day Duration: 5 hour/session Length of therapy: 2 days Total time: 10 hours	NRM Nasal Cannula	SpO_2	Baseline and 1 h after prone

(*continued on next page*)

Table 1 (*continued*)

No	Study ID	Study characteristics		Participant characteristic				Intervention characteristics		Outcomes	
		Design	Country	Setting	n	Demographic	Comorbidities	Prone position	Respiration support intervention		Time measurements
								Intervention time from admission: 3.25 hours			
14	Zang, et al., 2020	Prospective cohort study	China	ICU	23	Age: Mean = 59,78 Range = 48–79 Gender: M = 14 F = 9 Mean BMI: NA	Comorbidities: NA	Frequency: 1x/ day Duration: 0.5 hour/session Length of therapy: 1 days Total time: 0.5 hours Intervention time from admission: NA	HFNC	SpO_2	Baseline and 10 min after prone
15	Zeihr et al., 2020	Prospective cohort study	Israel	ICU	31	Age: Mean = 58 Range = 23–87 Gender: M = 20 F = 11 Mean BMI: 30	Comorbidities: Hypertension Diabetes Respiratory disease	Frequency: 1x/ day Duration: 18 hour/session Length of therapy: 1 days Total time: 18 hours Intervention time from admission: NA	Ventilator	PaO_2/FiO_2	Baseline and 18 h after prone

Abbreviation: ICU: intensive care unit; Non-ICU: non-intensive care unit; BMI: body mass index; Freq: frequency; Dur: duration; CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannula; HFNO: high-flow nasal oxygen; PEEP: positive end-expiratory pressure; NRM: nonrebreathing mask; PaO_2/FiO_2: ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO2); RR: respiratory rate; SpO_2: oxygen saturation in blood; FiO2: fraction inspired oxygen; PaO_2: partial pressure of oxygen.

Table 2
Quality assessment using the methodological index for non-randomized studies (MINORS).

No.	Study	Score								
		1	2	3	4	5	6	7	8	Total
Non-comparative studies										
1.	Abou-Arab et al., 2021	2	2	2	2	0	2	1	2	13
2.	Avdeev et al., 2021	2	2	2	2	0	2	2	2	14
3.	Caputo et al., 2020	2	2	2	1	0	2	1	2	12
4.	Clarke et al., 2021	2	2	2	2	0	2	1	1	10
5.	Elharr et al., 2020	2	2	2	2	0	2	1	1	12
6.	Fazzini et al., 2021	2	2	2	1	0	2	0	2	11
7.	Gad, 2021	2	2	2	1	0	2	1	2	12
8	Mittermaier et al., 2020	2	1	2	2	0	2	0	2	11
9.	Paternoster et al., 2020	2	1	2	2	0	2	2	2	13
10.	Sartini et al., 2020	2	2	2	1	0	2	1	1	11
11	Taboada et al., 2020	2	2	2	2	0	0	2	2	12
12.	Taboada et al., 2020	2	2	2	2	0	0	2	1	11
13.	Thompson et al., 2020	2	2	2	1	0	0	1	1	9
14	Zang, et al., 2020	2	1	2	1	0	0	2	1	9
15.	Ziehr et al., 2020	2	2	2	2	0	2	1	1	12

Note: The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). For non-comparative studies, the scores are as follows: 0–4 very low quality, 5–8: low quality, 9–12: moderate quality, and 13–16: high quality.

was an increase of 50% PaO_2/FiO_2 before and after prone positioning. The effectiveness of prone position can also be found in the outcomes of SpO_2 (pooled SMD was at 3.39) and in PaO_2 (pooled SMD was at 0.77). The differences between traditional prone positioning and ASPP were not statistically significant in terms of the above-mentioned outcomes (Fig. 5).

Classic ARDS is commonly related to the reduction of lung compliance and severe hypoxemia. Reduction of lung compliance increases the carbon dioxide dead space calculation, meanwhile, hypoxemia occurs as a result of ventilation-to-perfusion mismatching. COVID-19-related lung injury can be managed using the same principles of lung protective ventilation strategies as those in classic ARDS (Swenson and Swenson, 2021). As a rescue therapy, the prone position significantly relieves lung compression which is squeezed by the gravity of the heart and abdominal organs in a supine position. The prone position increases the capability of the body to transfer blood and airflow more equally and improves the gas exchanges. Therefore, the dependency of the patients on supporting medical devices (i.e., ventilators) can be reduced (Hadaya and Benharash, 2020).

Moderator variables of prone positioning

Variables that moderated the pooled effect size of this meta-analysis were body mass index, duration and total time prone position. Whereas the variables of age, gender, comorbidities, patient unit, respiratory support intervention, frequency of prone position and type of ARDS showed no statistically significant differences.

There are challenges for prone position that should be considered on an individual basis, such as tolerance and lung compliance for ASPP and dislodgement of medical devices, breathing tubes, and drains for traditional ICU prone positioning (Hadaya and Benharash, 2020). Prone positioning in COVID-19 pandemic has been adopted by healthcare professionals even for patients prior to intubation and ASPP has been included as a part of ARDS management (Guérin et al., 2020). From the subgroup analysis in this study, prone position in the group of patients with ASPP type showed a higher effect size than in the group of patients with traditional prone positioning, although the differences were not statistically significant.

The traditional prone position in the ICU showed that the main mechanisms for prone position are oxygenation improvement, drainage of respiratory secretions, stabilisation/improvement of hemodynamic

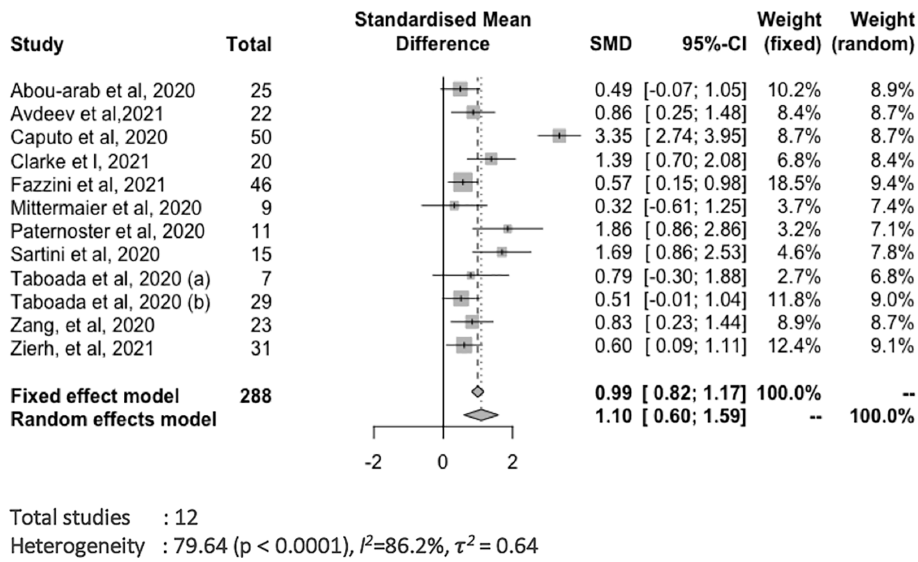

Fig. 2. Forest plot the effects of prone position towards PaO_2/FiO_2.

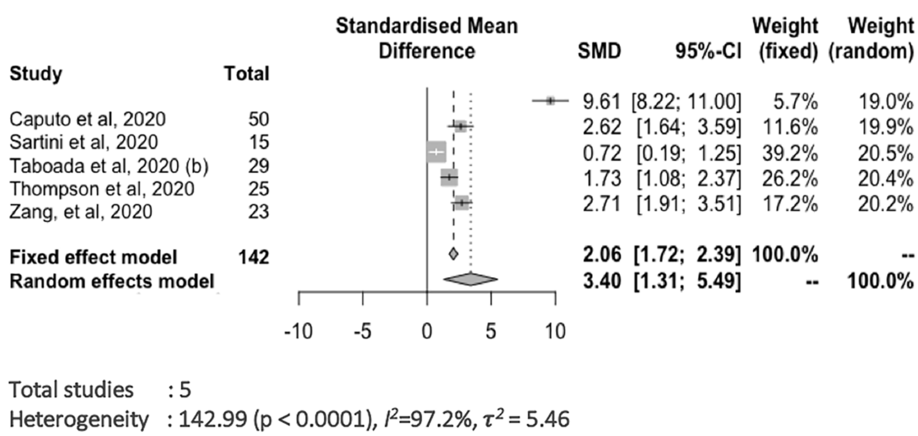

Fig. 3. Forest plot the effects of prone position towards SpO_2.

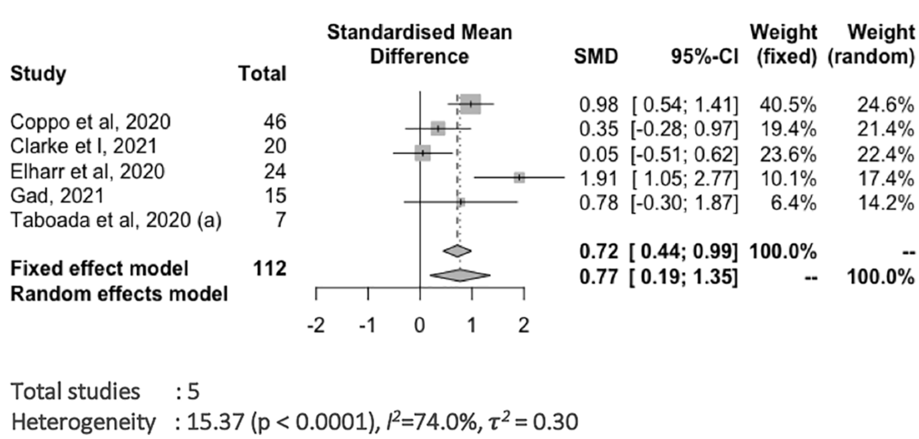

Fig. 4. Forest plot the effects of prone position towards PaO_2.

and prevention of ventilator-induced lung injury (Kharat et al., 2022). Several studies showed that the traditional ICU prone position of the patients with COVID-19 ARDS had significant improvements (Abou-Arab et al., 2021; Clarke et al., 2021; Mittermaier et al., 2020; Paternoster et al., 2020; Ziehr et al., 2020). However, traditional prone position in the ICU in patients with critical illness is not without risk because of patient condition (e.g., the need for heavier sedation, hemodynamic instability, device displacement, pressure ulcers) (Binda et al., 2021).

The physiological basis behind traditional prone position patients with COVID-19 infection also applies to patients breathing spontaneously or in ASPP (Ng et al., 2020). Previous studies found that the

Table 3
Subgroup analysis.

Variable	Subgroup analysis			
	n	SMD (95% CI)	*p*-value	I^2
Age				
Adult (18–65 years old)	10	1.00 (0.63–1.37)	0.13	69.4
Elderly (>65 years old)	2	0.55 (0.07–1.02)		
BMI				
Normal weight	1	1.79 (0.93–2.66)	**<0.0001**	93.9
Pre-obesity	2	1.19 (0.72–1.65)		
Obesity class I	3	2.12 (1.66–2.58)		
Obesity class II	1	5.53 (4.11–6.95)		
Comorbidities				
Comorbidities	7	0.65 (0.39–0.91)	0.10	86.2
No-comorbidities	5	1.53 (0.50–2.55)		
Unit				
ICU	6	0.97 (0.45–1.49)	0.78	69.4
Non-ICU	6	0.88 (0.49–1.27)		
Respiration Support Intervention				
Ventilator	3	0.83 (0.83–1.58)	0.53	74.9
Non-ventilator	5	1.13 (0.55–1.71)		
Frequency Prone Position/day				
1 time/day	8	0.97 (1.15–1.04)	0.85	86.2
2 times/day	2	1.82 (1.10–2.55)		
3 times/day	2	5.53 (4.11–6.95)		
Duration Prone Position/day				
<12 hours	8	0.93 (0.49–1.36)	0.95	69.4
Equal to or great 12 hours	4	0.94 (0.41–1.48)		
Type of ARDS				
Mild	2	1.06 (−0.17 to 2.31)	0.10	69.4
Moderate	7	0.67 (0.44–0.89)		
Severe	3	3.30 (−0.17 to 2.31).		
Study design				
Experimental	2	0.96 (0.58–1.34)	0.66	69.4
Observational	10	0.82 (0.28–1.36)		
Prone Position				
Traditional	5	0.84 (0.37–1.31)	0.64	69.4
ASPP	7	0.99 (0.54–1.45)		

Abbreviation: Study size (n); Confident interval (CI); Reference (ref), Significance level <0.05.

Table 4
Meta-regression.

Variable	Meta-regression analysis				
	n	SE	Z-value	SMD (95% CI)	*p*-value
Mean duration prone position/day	**12**	**0.36**	**3.59**	**1.17 (0.59–2.02)**	**<0.0001**
Mean frequency frone position/day	12	0.75	0.35	0.21 (−1.26 to 1.68)	0.09
Mean total time prone position/patient	**12**	**0.30**	**3.77**	**1.30 (0.56–1.77)**	**<0.0001**
Mean time point measurement	12	0.03	−0.55	−0.01 (−0.08 to 0.04)	0.58
Sample size	12	0.02	−0.09	−0.002 (−0.05 to 0.05)	0.92

Abbreviation: Study size (n); Confident interval (CI); Reference (ref), Significance level <0.05.

addition of prone positioning might have contributed to the avoidance of intubation in 11 of 20 patients and that the PaO_2/FiO_2 ratio was significantly higher in patients who avoided intubation (Ding et al., 2020). During the COVID-19 pandemic, the use of ASPP increased in cases of hypoxemia, and evidence on the benefit of ASPP in COVID-19 was reported (Sodhi and Chanchalani, 2020). Various studies that applied ASPP to patients with COVID-19 ARDS showed a significant improvement (Caputo et al., 2020; Ding et al., 2020; Elharrar et al., 2020; Fazzini et al., 2021a; Gad, 2021; Paternoster et al., 2020; Sartini et al., 2020; Taboada et al., 2021; Taboada et al., 2020; Thompson et al., 2020; Zang et al., 2020). Evidence show that prone positioning should be applied to all patients regardless of whether they are on invasive mechanical ventilation, high-flow nasal oxygen therapy or non-invasive ventilation, as it is a simple intervention that can be done in most circumstances, and it is compatible with all forms of basic respiratory support, and requires little or no equipment in the conscious patient (Bamford et al., 2020).

However, in ASPP, besides the risk of pressure ulcer, being unable to tolerate prone position due to discomfort may lead to anxiety in these patients, and they may require light sedation (Gürün Kaya et al., 2020). Thus, in patients with ARDS related to COVID-19, specific protocols to support decisions and limit the occurrence of complications should be applied when using prone positioning in both ICU and non-ICU settings.

In terms of patient characteristics, our analysis showed a statistically significant difference in the effect of prone positioning among body mass index, as patients in the obese class II had the highest benefits compared to other levels. Anatomic and physiological alterations are observed in obese patients, affecting the face, neck, pharynx, chest wall, and lungs. In obese patients, the reduced functional residual capacity can trigger the closure of peripheral dependent airways during tidal ventilation and decreased lung compliance and these changes result in atelectasis and ventilation-perfusion mismatch and hypoxemia (De Jong et al., 2019). These effects are being decreased in the prone position which increases the relief of pressure on the diaphragm, thereby opening small airways and the dependent parts of the lungs. Generally, prone position should not be a contraindication in patients in higher obese classes, however, turning these patients may pose more procedural challenges and require an experience team to work together (Guérin et al., 2013).

Based on our analysis, significant moderators related to intervention characteristics that need to be considered are duration of prone position/day and total time prone position/patient. Our study found that duration was a statistically significant factor in prone position's effect on outcomes, an increase in hours correlated with a larger standardised mean difference effect. Previous studies recommended that patients with severe ARDS receive prone positioning for more than 12 hours per day (Fan et al., 2017; Rahmani et al., 2020). Our study confirmed that the application of the prone position that yielded the greatest benefit were those that were done for more than 12 hours per day. Thus, prone position appears to be more advantageous in ARDS patients, and especially when applied for a longer daily duration (Munshi et al., 2017).

As the beneficial effect is linked to the length spent in prone position, it might be more beneficial to extend the sessions rather than increase the frequency of sessions for patients with invasive mechanical ventilation, as changes in body position might dislodge medical devices, breathing tubes, and drains. Also, complications during turning manoeuvres, which are rare in experienced teams, could occur more in the smaller medical centres (Hadaya and Benharash, 2020; Jochmans et al.,

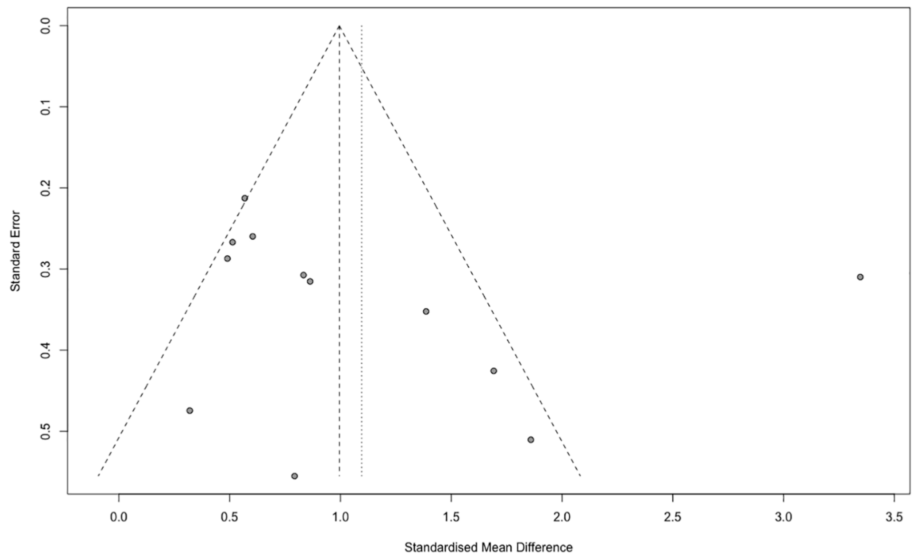

Fig. 5. Funnel plot.

2020). Most of the studies done on traditional ICU prone ventilation lasted six to eight hours per day, but some used prolonged prone position lasting 12–24 hours per day (Carsetti et al., 2020; Malhotra and Kacmarek, 2020; Parker et al., 2021; Petrone et al., 2021) and showed improvement in oxygenation. Previous study showed that patients with ARDS and severe hypoxemia (PaO_2/FiO_2 ratio of <150 mm Hg, with an FiO_2 of ≥0.6 and a positive end-expiratory pressure of ≥5 cm of water) can benefit from prone position when it is used early and in relatively long sessions (White, 2020).

However, application for ASPP should consider the tolerance of the patient and more frequent changes in position might be better than one prolonged session (Golestani-Eraghi and Mahmoodpoor, 2020). A previous meta-analysis related to the application of ASPP showed improvement in oxygenation when applied for at least four hours of repeated sessions (Fazzini et al., 2021b). Although our study found frequency/day not to be a statistically significant factor in prone position's effect on outcomes, there was a marked increase for greater than three times/day for prone positioning. Thus, guidelines such as those from WHO for doing prone position should be followed as the previous study has also shown that patients remaining in longer prone position sessions are associated with a decrease in mortality rates (Henderson et al., 2014).

Strengths and Limitations

The main strength of this study is its applications for the practice of critical care, as this is the first meta-analysis study to show the effectiveness of traditional ICU prone positioning and ASPP on respiratory status in all patients with ARDS related to COVID-19 with subgroup analysis and meta-regression conducted for various moderating factors. In addition, a rigorous approach was taken with systematic search to include the highest available level of evidence which was prospective and experimental designs. Typically, prospective and experimental designs are ranked higher in the hierarchy of evidence than retrospective designs. However, this study has some limitations. This review was based on data from single-arm observational case series and some cohort studies that had no comparator groups. Consequently, heterogeneity was present. However, sensitivity analyses were performed to account for the heterogeneity.

Conclusions

This meta-analysis supports the effectiveness of prone position to improve oxygenation in patients with high-flow nasal oxygen therapy or non-invasive ventilation (ASPP) and those with invasive mechanical ventilation (traditional ICU prone positioning) with ARDS related to COVID-19. In additional, knowing the differences of both of these prone positioning will help nurses to optimise oxygenation and ventilation for patients. However, according to our results, patient-centred considerations such as the BMI profile, duration, and total time prone position should be taken into account when applying prone position. Nurses play important roles in implementing and monitoring the application of prone position for COVID-19 patient with ARDS as they are the ones spending the most time with patients (Butler et al., 2018). Our study results show that knowing the moderating factors such as the body mass index, duration for prone position, and total time for prone position could benefit more patients and improve outcomes. Nurses have to be responsible for applying the prone position and monitoring patients; thus, education and training are essential for nurses in the ICU and outside the ICU.

Data Statement

As this study is a meta-analysis of previous data, no new data were generated in support of this research.

Ethical statement

Not required.

CRediT authorship contribution statement

Fauzi Ashra: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft. **Ruey Chen:** Validation. **Xiao Linda Kang:** Validation, Writing – review & editing. **Kai-Jo Chiang:** Validation, Writing – review & editing. **Li-Chung Pien:** Validation, Writing – review & editing. **Hsiu-Ju Jen:** Validation, Writing – review & editing. **Doresses Liu:** Validation, Writing – review & editing. **Shu-Tai Shen Hsiao:** Validation, Writing – review & editing. **Kuei-Ru Chou:** Conceptualization, Validation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Registration Number

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