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SYSTEMATIC REVIEW

Prone ventilation in intubated COVID-19 patients: a systematic review and meta-analysis

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Abstract
Background: The efficacy and safety profiles of prone ventilation among intubated Coronavirus Disease 2019 (COVID-19) patients remain unclear. The primary objective was to examine the effect of prone ventilation on the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) in intubated COVID-19 patients.
Methods: Databases of MEDLINE, EMBASE and CENTRAL were systematically searched from inception until March 2021. Case reports and case series were excluded.
Results: Eleven studies (n = 606 patients) were eligible. Prone ventilation significantly improved PaO_2/FiO_2 ratio (studies: 8, n = 579, mean difference 46.75, 95% CI 33.35–60.15, $p < 0.00001$; evidence: very low) and peripheral oxygen saturation (SpO_2) (studies: 3, n = 432, mean difference 1.67, 95% CI 1.08–2.26, $p < 0.00001$; evidence: ow), but not the arterial partial pressure of carbon dioxide ($PaCO_2$) (studies: 5, n = 396, mean difference 2.45, 95% CI 2.39–7.30, $p = 0.32$; evidence: very low), mortality rate (studies: 1, n = 215, Odds Ratio 0.66, 95% CI 0.32–1.33, $p = 0.24$; evidence: very low), or number of patients discharged alive (studies: 1, n = 43, Odds Ratio 1.49, 95% CI 0.72–3.08, $p = 0.28$; evidence: very low).
Conclusion: Prone ventilation improved PaO_2/FiO_2 ratio and SpO_2 in intubated COVID-19 patients. Given the substantial heterogeneity and low level of evidence, more randomized- controlled trials are warranted to improve the certainty of evidence, and to examine the adverse events of prone ventilation.

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Introduction

Severe pneumonia secondary to Coronavirus Disease 2019 (COVID-19) is associated with reduced peripheral oxygen saturation (SpO_2) of < 94%, low ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of < 300 mmHg, marked tachypnea (respiratory rate of > 30 breaths per minute), and lung infiltrates of > 50%.[1] Studies have reported that 15−30% of patients hospitalized for COVID-19 will develop severe pneumonia and hypoxemia,[1] many of which will require treatment in the intensive care unit.[2] In severe COVID-19 pneumonia, patients may progress to develop Acute Respiratory Distress Syndrome (ARDS),[2] and up to 88% of patients with COVID-19 in the intensive care unit require endotracheal intubation to maintain oxygenation.[3] Several observational studies reported that severe mechanically ventilated COVID-19 pneumonia patients were associated with high mortality of 27−31% in the intensive care unit.[3,4]

The application of the prone position during mechanical ventilation has been previously studied to improve oxygenation and reduce mortality in classical ARDS prior to the emergence of COVID-19.[5,6] At present, the World Health Organization (WHO) recommends the use of the prone position in patients with severe COVID-19 who require noninvasive ventilation based on the evidence of its benefit seen in classical ARDS.[7] A recent meta-analysis demonstrated that prone positioning improved oxygenation parameters (PaO_2/FiO_2 ratio and SpO_2) in awake spontaneously breathing COVID-19 patients.[8] However, the safety and efficacy profiles of prone ventilation in patients with severe COVID-19 requiring intubation remain unclear in the literature. Thus, a systematic review and meta-analysis is timely warranted to synthesize evidence on the use of prone ventilation in intubated COVID-19 patients before any recommendation can be made with certainty.

We hypothesized that prone ventilation improved oxygenation in intubated COVID-19 patients. The primary objective of this review was to examine the effect of prone ventilation on the PaO_2/FiO_2 ratio in intubated COVID-19 patients. Secondary objectives were to investigate the effects of prone ventilation on SpO_2, arterial partial pressure of carbon dioxide ($PaCO_2$), mortality rate, and number of patients discharged alive in intubated COVID-19 patients.

Methods

This review was conducted and reported according to the Cochrane Handbook for Systematic Reviews and Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), respectively.[9,10] The protocol of this review was published on PROSPERO (CRD42021241364) before the commencement of the literature search. Review questions were formulated using the Population, Intervention, Control, and Outcomes (PICO) approach, as shown in Supplemental Table E1. The primary outcome was the PaO_2/FiO_2 ratio after prone and supine ventilation. Secondary outcomes included SpO_2, $PaCO_2$, mortality rate, and number of patients discharged alive.

Databases of Ovid MEDLINE, Ovid EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched systematically from their inception until March 2021. The list of search items and strategy is presented in Supplemental Table E2. The inclusion criteria were any randomized-controlled trials or observational studies (retrospective or prospective) comparing prone and supine ventilation in adult (ages ≥ 18 years) intubated COVID-19 patients. The bibliography of the included studies was searched for any additional articles. Trial registries (clinicaltrials.gov and WHO International Clinical Trials Registry Platform Search Portal) were also searched for any ongoing studies. All case reports, case series, and editorials were excluded in this review.

The title-abstracts and full texts were screened according to the predefined inclusion and exclusion criteria by two authors (EC and ZW) independently. Any disagreement during the screening and selection of studies were resolved by consulting a third author (KN). The final list of included studies was agreed on by all the authors. Two authors (EC and ZW) extracted data independently using an online data extraction sheet. A third author (KN) cross-checked all the extracted data for any discrepancies. Any data that was presented in the form of median and interquartile range was converted to mean and standard deviation for data pooling.[11] The corresponding authors of the included studies were contacted at least twice if there was any unclear or missing data. In addition to the measured outcomes, other relevant data, namely authors, year of publication, sample size, age, duration of prone ventilation, enrollment criteria, and ventilation strategy were also extracted.

Two authors (EC and ZW) performed the risk of bias assessment for all the included studies independently, using the Newcastle-Ottawa Scale for non-randomized studies. It consists of three domains, namely selection, comparability, and outcome. Each domain was assessed using a star system with a maximum of 9 stars.[12] Studies with a total score of 7 or more were considered as low risk of bias. The certainty of evidence was assessed based on the risk of bias, inconsistency, imprecision, indirectness, and publication bias. A third author (KN) was consulted for any disagreement in the assessment of risk of bias and certainty of evidence for all the included studies.

The Review Manager software (version 5.4) was used for statistical meta-analysis. Dichotomous and continuous parameters were reported using Odds Ratio (OR) and Mean Difference (MD), respectively, with a Confidence Interval (CI) of 95%. Any p-value of < 0.05 was considered statistically significant. The I-square (I^2) test was used for assessment of statistical heterogeneity, with I^2 of < 40% categorized as low heterogeneity, I^2 of 40−60% as moderate heterogeneity, and I^2 of > 60% as substantial heterogeneity. In view of limited studies of small sample size with significant heterogeneity, a random-effect model was used for all the measured outcomes.

Results

Our search generated a total of 1722 articles and 41 articles were eligible for full text screening (Fig. 1). Twenty-eight studies were excluded after applying the inclusion and exclusion criteria, as listed in Supplemental Table E3. A total of 14 studies (a total of 658 patients) were included in this

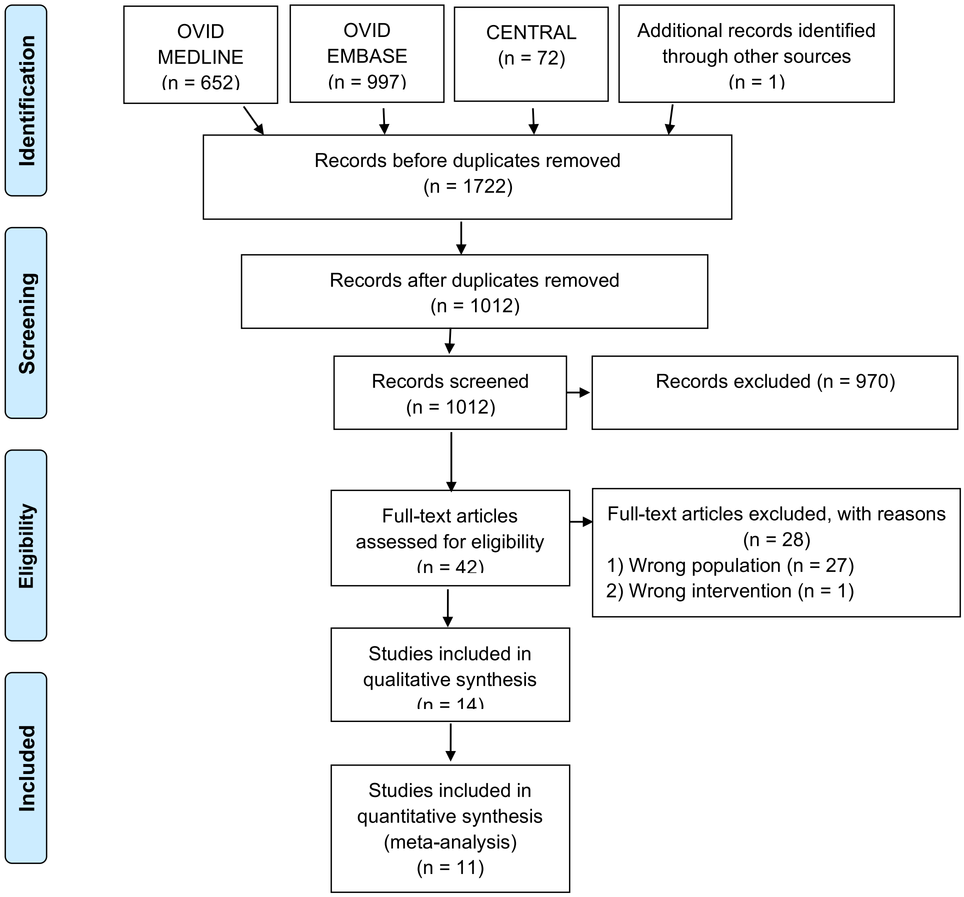

Figure 1 PRISMA flow diagram.

review. However, only eleven studies (a total of 606 patients) were included in quantitative meta-analysis, as three of the included studies did not report any of the outcomes of interest.[13-15] Search on trial registries did not identify any ongoing studies comparing prone and supine ventilation in intubated COVID-19 patients.

The clinical characteristics of our included studies are listed in Table 1. All 14 studies were single center cohort studies (6 prospective,[14,16-20] 8 retrospective[13,15,21-26]) Of all, only one study compared two separate cohorts of supine and prone ventilation in intubated COVID-19 patients.[25] The rest were crossover cohort studies, in which patients underwent both supine and prone ventilation regimens. The sample size varied from 9 to 261 patients in the included studies. The mean age and Body Mass Index (BMI) of patients ranged from 52.8 to 69.5 years and from 27.9 to 36.5 kg.m^{-2}, respectively. In terms of the settings of mechanical ventilation, the tidal volume varied across the included studies, ranging from 4 to 8 mL.kg^{-1} predicted body weight. The extrinsic Positive End-Expiratory Pressure (PEEP) used during mechanical ventilation also differed across the included studies. Most of our included studies used prolonged duration of prone ventilation per session, with the mean duration of prone ventilation ranging from 14.3 to 24 hours per session. The mean number of days of prone positioning ranged from 3.2 to 4.7 days across all the included studies.

The risk of bias assessment for all the included studies and PRISMA checklist are summarized in Supplemental Tables E4 and E5. Out of all included studies, eleven studies were considered as low risk of bias as they scored at least 7 out of 9 stars based on the domains of selection, comparability, and outcome in the Newcastle-Ottawa Scale.[13-15,17-19,21-23,25,26] Three studies were of high risk of bias as they had a total score < 7 due to potential bias in the comparability domain.[16,20,24] The summary of findings for all measured outcomes and certainty of evidence are outlined in Table 2 and Table 3.

Eight studies (n = 579 patients) examined the PaO_2/FiO_2 ratio after supine and prone ventilation.[16,17,19,21-24,26] Intubated COVID-19 patients who received prone ventilation had significantly higher mean PaO_2/FiO_2 ratio compared to the supine ventilation group (MD = 46.75, 95% CI 33.35 to 60.15, $p < 0.00001$; Fig. 2). However, the observed statistical heterogeneity was substantial ($I^2 = 78\%$). The certainty of evidence was graded as very low due to the observational studies in nature, inconsistency, and publication bias.

Pooling of data from three studies (n = 432 patients) demonstrated that those with prone ventilation were associated with higher SpO_2 (MD = 1.67, 95% CI 1.08 to 2.26, $p < 0.00001$; $I^2 = 0\%$; certainty of evidence: low, Suppementary Fig. E1).[18,20,26] Among all included studies, five of them (n = 396 patients) recorded the $PaCO_2$ after mechanical ventilation in the prone and supine position.[16,17,22,23,26] Our

Table 1 Clinical characteristics of included studies.

Author	Year	Design	Sample size	Country	Setting	Age (mean ± SD)	BMI (mean ± SD)	Criteria for enrolment	Criteria for stopping	Ventilation strategy		Mean duration of prone positioning per session (hours)	Mean number of days of prone positioning (days)
										Tidal volume (mL kg^{-1} predicted body weight)	Extrinsic PEEP (cmH_2O)		
Abou-Arab et al.	2020	Single center cohort study (prospective)	25	France	ICU	61.0 ± 5.5	30.0 ± 3.1	PaO_2/FiO_2 ratio < 150 mmHg for 12 hours despite LPV	–	< 6	–	16	–
Astua et al.	2020	Single center cohort study (prospective)	31	USA††	–	58.3 ± 1.7	27.9 ± 3.8	Moderate to severe ARDS (PaO_2/FiO_2 ratio ≤ 150 mmHg on $FiO_2 \geq 0.6$ and PEEP ≥ 5 cm H_2O)	PaO_2/FiO_2 ratio > 200 for 8 hours supine	6 – 8	≥ 5	16	–
Berrill et al.	2020	Single center cohort study (retrospective)	34	UK	ICU	58.5 ± 11.1	31.0 ± 5.1	-	–	6 – 8	≥ 5 or 10	16.5	4.2
Clarke et al.	2021	Single center cohort study (prospective)	20	Ireland	ICU	52.8 ± 11.6	36.5 ± 10.7	Met the Berlin criteria for diagnosis of ARDS	–	< 8	–	16.4	–
Douglas et al.	2021	Single center cohort study (retrospective)	61	USA	ICU	56.7 ± 13.5	33.4 ± 8.9	Persistent severe hypoxemia (PaO_2/FiO_2 ratio < 150 mmHg, $FiO_2 > 60\%$ and PEEP > 10 cm H_2O) despite 2–6 hours stabilization with LPV in the assist-control mode applying PEEP according to the ARDS Network	$FiO_2 < 0.6$ with PEEP < 10 cm H_2O for ≥ 4 hours	< 8	> 10	24	–
Doussot et al.	2020	Single center cohort study (prospective)	67	France	ICU	67.5 ± 8.3	30.0 ± 6.1	Persistent PaO_2/FiO_2 ratio < 150 mmHg despite mechanical ventilation, sedation, and curarisation	–	–	–	16	4.7
Gleissman et al.	2021	Single center cohort study (retrospective)	44	Sweden	ICU	61.0 ± 13.0	-	-	-	6 – 8	-	14.3	3.2

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Table 1 (*Continued*)

Author	Year	Design	Sample size	Country	Setting	Age (mean ± SD)	BMI (mean ± SD)	Criteria for enrolment	Criteria for stopping	Ventilation strategy		Mean duration of prone positioning per session (hours)	Mean number of days of prone positioning (days)
										Tidal volume ($mL\ kg^{-1}$ predicted body weight)	Extrinsic PEEP (cmH_2O)		
Khullar et al.	2020	Single center cohort study (retrospective)	23	USA	-	53.5 ± 13.0	32.3 ± 6.0	Met the Berlin definition for moderate-to-severe ARDS: PaO_2/FiO_2 ratio < 200 mmHg with PEEP $\geq$ 5 cm H_2O	–	4 – 6	≥ 5	16	–
Mittermaier et al.	2020	Single center cohort study (prospective)	9	Germany	ICU	62.0 ± 14.2	30.4 ± 6.5	PaO_2/FiO_2 ratio < 150 mmHg	–	–	–	15.4	–
Perier et al.	2020	Single center cohort study (prospective)	9	France	–	54.3 ± 8.7	32.8 ± 5.1	ARDS based on Berlin definition, within 72 hours of intubation	–	–	–	–	–
Sang et al.	2021	Single center cohort study (retrospective)	20	China	ICU	69.5 ± 9.5	-	Severe ARDS based on Berlin definition	–	6	5 – 15	–	–
Sharp et al.	2020	Single center cohort study (retrospective)	12	UK	ICU	56.5 ± 14.0	–	–	–	–	–	–	–
Shelhamer et al.	2020	Single center cohort study (retrospective)	261	USA	Wards; ICU	64.0 ± 13.4	31.6 ± 7.2	PaO_2/FiO_2 ratio < 150 mmHg, PEEP > 10 cm H_2O and $FiO_2 > 0.6$	–	–	>10	16	3.2
Weiss et al.	2020	Single center cohort study (retrospective)	42	USA	ICU	59.9 ± 13.4	34.2 ± 7.5	PaO_2/FiO_2 ratio of < 20 kPa with PEEP set $\geq$ 10 cm H_2O and $FiO_2 \geq 0.6$.	PaO_2/FiO_2 ratio > 20 kPa in the supine position or if ECMO or palliative care was needed	6	≥10	16.3	3.7

SD, Standard Deviation; BMI, Body Mass Index; PEEP, Positive End-Expiratory Pressure; ICU, Intensive Care Unit; PaO_2/FiO_2 ratio, Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; LPV, Lung Protective Ventilation; USA, United States of America; ARDS, Acute Respiratory Distress Syndrome; FiO_2, Fraction of inspired Oxygen; UK, United Kingdom; ECMO, Extracorporeal Membrane Oxygenation.

Table 2 Summary of findings for primary and secondary outcomes.

N°	Outcomes	Trials	n	I^2(%)	Effect model	MD/OR (95% CI)	*p*-value
1	PaO_2/FiO_2 ratio	8	579	78	REM	46.75 (33.35, 60.15)	< 0.00001
2	$PaCO_2$	5	396	90	REM	2.45 (-2.39, 7.30)	0.32
3	SpO_2	3	432	0	REM	1.67 (1.08, 2.26)	< 0.00001
4	Mortality rate	1	261	-	REM	0.66 (0.32, 1.33)	0.24
5	Number of patients discharged alive	1	261	-	REM	1.49 (0.72, 3.08)	0.28

I^2, Heterogeneity; MD, Mean difference; OR, Odds Ratio; PaO_2/FiO_2 ratio, Ratio of Arterial Partial pressure of oxygen to fraction of inspired oxygen; REM, Random Effect Model; $PaCO_2$, Arterial Partial pressure of Carbon Dioxide; SpO_2, Peripheral Oxygen Saturation.

pooled data showed no significant difference in $PaCO_2$ between the prone and supine groups (MD = 2.45, 95% CI -2.39 to 7.30, $p = 0.32$; $I^2 = 90\%$; certainty of evidence = very low, Supplementary Fig. E1). Of all included studies, only one study examined the mortality rate and number of patients discharged alive between the prone and supine groups.[25] No significant differences were reported in the outcomes of mortality (n = 261 patients, OR = 0.66, 95% CI 0.32 to 1.33, $p = 0.24$; certainty of evidence = very low, Supplementary Fig. E1) and number of patients discharged alive (n = 261 patients, OR = 1.49, 95% CI 0.72 to 3.08, $p = 0.28$; certainty of evidence: very low, Supplementary Fig. E1).

Discussion

To the best of our knowledge, this is the first systematic review that has summarized the evidence of prone ventilation in intubated COVID-19 patients during mechanical ventilation. Our systematic review and meta-analysis demonstrated that prone ventilation was associated with higher PaO_2/FiO_2 ratio and SpO_2 than supine ventilation in intubated COVID-19 patients. However, the level of evidence was graded as very low due to the nature of observational studies, inconsistency of substantial heterogeneity, and publication bias. Our findings were consistent with the systematic review and meta-analysis conducted by Munshi and colleagues,[5] which showed that prone positioning during mechanical ventilation in classical ARDS was associated with a significantly higher PaO_2/FiO_2 ratio on day 4 of intervention. Although most of our included studies reported the PaO_2/FiO_2 ratio on day 1 of intervention (during the first prone session),[16,17,22,23,26] it was suggested that the improvement in oxygenation parameters from prone ventilation was reproducible with repeated prone positioning.[27]

Prone ventilation has been widely used during the outbreak of COVID-19 pandemic. Several observational studies reported high frequency use of prone ventilation in intubated COVID-19 patients with ARDS, which ranged from 60% to 79%.[28-31] This phenomenon may be explained by a greater predominance of moderate-to-severe hypoxemia among patients with COVID-19 pneumonia, resulting in a drastic rise in the occupancy of intensive care units.[32] Moreover, the adaptation of prone ventilation in COVID-19-related ARDS may have derived from the intervention that had been proven to be beneficial in ARDS of other causes in previous studies.[29] The seminal PROSEVA trial, which showed significant reduction in mortality with prone positioning being applied early in the course of disease (< 24 h) for prolonged periods (> 16 h per session), was likely a fundamental contributing factor.[33,34]

In classical ARDS, the development of alveolar flooding with exudates and atelectasis due to inflammatory alveolar injury causes intrapulmonary shunting of blood and hypoxemia.[35] Prone ventilation is believed to reduce the compression on dorsal regions of alveoli by internal organs and ventral regions of the lungs, which occurs in the supine position due to gravity, and helps to even out the transpulmonary pressures across the different regions in the lungs.[27] The improved alveolar recruitment and ventilation-perfusion matching with more homogenous ventilation would benefit patients with severe COVID-19 pneumonia,[36] and impaired hypoxia-induced pulmonary vasoconstriction and higher incidence of intravascular thrombosis.[37] A diverse nature of severe COVID-19 pneumonia can contribute to a substantial degree of heterogeneity. Two recent large, multicenter prospective studies revealed that the form of lung injury in patients with COVID-19-related ARDS was similar to that of classical ARDS, which is characterized by reduced lung compliance and increased lung weight.[37,38] However, the nature of ARDS itself is a heterogenous syndrome,[39] thus severe COVID-19 induced ARDS patients may respond differently to the effect of prone ventilation.

In this review, most of our included studies recruited COVID-19 patients with PaO_2/FiO_2 ratio of < 100–150 mmHg,[16-19,21,22,26] which corresponded to moderate-to-severe ARDS as defined by the Berlin criteria.[40] The Berlin criteria, however, did not take lung compliance into consideration. In a study conducted by Puah and colleagues, COVID-19-related ARDS patients with high lung compliance (> 40 $mL.cm^{-1}$ H_2O) on the day of intubation showed significantly higher mortality rates.[41] Therefore, the great degree of heterogeneity in COVID-19-related ARDS among our included studies could have introduced bias to our findings. Future studies are warranted to examine the use of prone ventilation in a particular subgroup (severe, moderate, or mild) of COVID-19 ARDS patients.

Our included studies, with the exception of the study by Clarke and colleagues, did not report the duration of patients' illness from the onset of symptoms prior to intubation.[17] Moreover, it is unknown whether the patients in our included studies were subjected to early or late intervention. The variation in lung compliances in COVID-19 at different timings of intubation may have affected the efficacy of prone ventilation. Pandya and colleagues reported that COVID-19 patients with late intubation (> 1.26 days from time of presentation) had lower lung compliance as

Table 3 GRADE assessment of primary and secondary outcomes.

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	supine	Relative (95% CI)	Absolute (95% CI)		
PaO_2/FiO_2 ratio												
8	Observational studies	Not serious	Serious [a]	Not serious	Not serious	Publication bias strongly suspected [b]	324	255	–	MD **46.75 higher** (33.35 higher to 60.15 higher)	⊕◯◯◯ VERY LOW	
$PaCO_2$												
5	Observational studies	Not serious	Very serious [a]	Not serious	Not serious	Publication bias strongly suspected [b]	198	198	–	MD **2.45 higher** (2.39 lower to 7.3 higher)	⊕◯◯◯ VERY LOW	
SpO_2												
3	Observational studies	Not serious	Not serious	Not serious	Not serious	None	216	216	–	MD **1.67 higher** (1.08 higher to 2.26 higher)	⊕⊕◯◯ LOW	
Mortality rate												
1	Observational studies	Not serious	Not serious	Not serious	Serious [c]	None	48/62 (77.4%)	167/199 (83.9%)	**OR 0.66** (0.32 to 1.33)	**64 fewer per 1,000** (from 214 fewer to 35 more)	⊕◯◯◯ VERY LOW	
Number of patients discharged alive												
1	Observational studies	Not serious	Not serious	Not serious	Serious [c]	None	13/62 (21.0%)	30/199 (15.1%)	**OR 1.49** (0.72 to 3.08)	**58 more per 1,000** (from 37 fewer to 203 more)	⊕◯◯◯ VERY LOW	

CI, Confidence Interval; PaO_2/FiO_2 ratio, Ratio of Arterial Partial Pressure of Oxygen to Fraction of Inspired Oxygen; MD, Mean Difference; OR, Odds Ratio; $PaCO_2$, Arterial Partial Pressure of Carbon Dioxide; SpO_2, Peripheral Oxygen Saturation.

[a] Substantial heterogeneity $I^2 > 60\%$.

[b] Funnel plot is suggestive of publication bias.

[c] Total number of events less than 300.

	Prone			Supine				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Weiss 2020	211.5	91.5	42	134.3	54	42	9.1%	77.20 [45.07, 109.33]	2020
Astua 2020	152.8	11.2	31	108	5.4	31	18.7%	44.80 [40.42, 49.18]	2020
Berrill 2020	151.9	58.9	89	87.8	38.2	20	13.1%	64.10 [43.36, 84.84]	2020
Clarke 2021	276.3	122	20	125.7	43.1	20	4.3%	150.60 [93.89, 207.31]	2020
Douglas 2021	134.7	45	61	100	41.8	61	15.3%	34.70 [19.29, 50.11]	2020
Gleissman 2020	144.7	56	44	104	27.6	44	14.0%	40.70 [22.25, 59.15]	2020
Sharp 2020	110.18	28.11	12	88.95	19.34	12	13.7%	21.23 [1.92, 40.54]	2020
Abou-Arab 2020	123.3	40.9	25	102	46.4	25	11.8%	21.30 [-2.95, 45.55]	2020
Total (95% CI)			**324**			**255**	**100.0%**	**46.75 [33.35, 60.15]**	

Heterogeneity: Tau² = 244.54; Chi² = 31.65, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 6.84 (P < 0.00001)

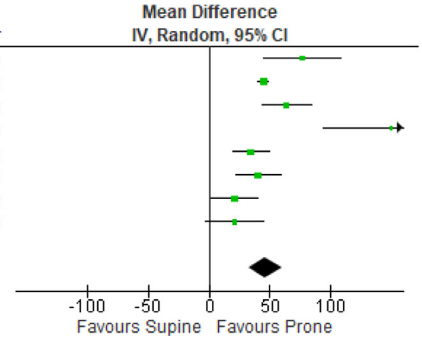

Figure 2 Forest plot of ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio).

compared to those who were intubated earlier.[42] Therefore, patients may have responded differently towards prone ventilation at different timepoints during the course of severe COVID-19-related ARDS, and this may have been another source of heterogeneity.

Scholten and colleagues suggested that the clinical benefit of prone positioning ventilation on mortality in ARDS may be related to the attenuation of ventilator-associated lung injury, which stems from the reduction of alveolar hyperinflation in the ventral regions of the lungs during prone ventilation.[43] In our review, however, there was no significant difference in mortality rate and number of patients discharged alive between the prone and supine groups, despite the similarities in ventilation strategy across our included studies. A significant number of patients in our included studies were obese with a mean BMI ranging from 27.9 to 36.5 $kg.m^{-2}$. A recent review revealed that obesity is associated with increased disease severity in COVID-19 pneumonia.[44] Ni and colleagues showed that obesity was significantly associated with reduced mortality in patients with classical ARDS.[45] Thus, our findings cannot be generalized to COVID-19 ARDS patients who are not obese, as obesity contributes to a significant disease burden for patients with multiple comorbidities. In addition, the majority of our included population were elderly patients (> 60 years old). Zhou and colleagues reported that the mortality rate of severe COVID-19 patients was significantly higher with an increased age group.[46] Nevertheless, our current findings are highly premature in view of the limited number of studies with small sample size.

The fall in $PaCO_2$ indicated an increased removal of carbon dioxide as a result of lung recruitment and reduced fraction of dead-space in patients with ARDS.[47] However, our review showed no significant improvement in $PaCO_2$ following the use of prone ventilation in COVID-19 patients. The $PaCO_2$ may decrease, remain unchanged or even increase, depending on the resultant effect of prone position on alveolar ventilation and minute ventilation (the ventilator setting of respiratory rate and tidal volume). Although prone position improves ventilation-perfusion matching in the lungs, it may also reduce chest wall compliance by restricting the movement of the anterior chest wall, and thus limiting carbon dioxide excretion.[48] Thus, the effect of prone ventilation on $PaCO_2$ in ARDS has been reported to be inconsistent.

There were several limitations in this review. One of the limitations was the lack of data from randomized controlled trials. Our included studies comprised only retrospective or prospective cohort studies, which contributed to methodological heterogeneity as well as to the low level of evidence. None of the studies reported the complications of both prone and supine ventilation (e.g., pressure ulcers and endotracheal tube obstruction) in COVID-19 patients. Thus, we were unable to assess the safety profile of prone and supine position in the mechanical ventilated COVID-19 patients in this review.

Conclusions

In this meta-analysis, prone ventilation improved PaO_2/FiO_2 ratio and SpO_2 in intubated COVID-19 patients. However, given the substantial heterogeneity and low level of evidence, more randomized controlled trials are warranted to improve the certainty of evidence, and to examine the adverse events of prone ventilation.

Conflicts of interest

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.06.007.

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