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Effect of prone position on respiratory parameters, intubation and death rate in COVID-19 patients: systematic review and meta-analysis

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Prone position (PP) is known to improve oxygenation and reduce mortality in COVID-19 patients. This systematic review and meta-analysis aimed to determine the effects of PP on respiratory parameters and outcomes. PubMed, EMBASE, ProQuest, SCOPUS, Web of Sciences, Cochrane library, and Google Scholar were searched up to 1st January 2021. Twenty-eight studies were included. The Cochran's Q-test and I² statistic were assessed heterogeneity, the random-effects model was estimated the pooled mean difference (PMD), and a meta-regression method has utilized the factors affecting heterogeneity between studies. PMD with 95% confidence interval (CI) of PaO₂/FIO₂ Ratio in before–after design, quasi-experimental design and in overall was 55.74, 56.38, and 56.20 mmHg. These values for SpO₂ (Sao₂) were 3.38, 17.03, and 7.58. PP in COVID-19 patients lead to significantly decrease of the Paco₂ (PMD: -8.69; 95% CI -14.69 to -2.69 mmHg) but significantly increase the PaO₂ (PMD: 37.74; 95% CI 7.16–68.33 mmHg). PP has no significant effect on the respiratory rate. Based on meta-regression, the study design has a significant effect on the heterogeneity of SpO₂ (Sao₂) (Coefficient: 12.80; p < 0.001). No significant associations were observed for other respiratory parameters with sample size and study design. The pooled estimate for death rate and intubation rates were 19.03 (8.19–32.61) and 30.68 (21.39–40.75). The prone positioning was associated with improved oxygenation parameters and reduced mortality and intubation rate in COVID-19 related respiratory failure.

Abbreviations

PMD	Pooled mean difference
CI	Confidence interval
ARDS	Acute Respiratory Distress Syndrome
VILI	Ventilator-induced lung injury
PaO ₂	Pressure of arterial oxygen
FIO ₂	Fraction of inspired oxygen
WHO	World Health Organization
PP	Prone position
NIV	Non invasive ventilation
IMV	Intermittent mandatory ventilation
HFNO	High flow nasal oxygen
PEEP	Positive end expiratory pressure

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CPAP	Continuous positive airway pressure
SD	Standard deviation
IQR	Interquartile range

Recently a new virus called coronavirus 2019 (COVID-19) is spreading all around the world^{1,2} and caused a global pandemic with increasing incidence, mortality, and medical resource consumption which impose enormous socio-economic burdens^{3,4}. COVID-19 disease ranges from mild respiratory tract illness to severe progressive pneumonia, primarily manifesting as acute respiratory distress syndrome (ARDS) requiring admission to the intensive care unit (ICU)⁴. ARDS occurs in 20–41% of patients⁵. The mortality rate among ARDS patients is high and has been reported to be between 30 and 40%^{6,7}. Higher mortality of COVID-19 patients may be related to higher incidences of barotrauma and ventilator-induced lung injury (VILI)⁸. The COVID-19 pandemic presented a unique challenge for the health care systems. The shortage of resources is one of these problems that pandemic imposed, include human resources, ICU beds, and mechanical ventilators⁹. In the absence of effective therapies for COVID-19, the implementation of supportive care is essential¹⁰. Prone positioning is one of these interventions for patients with severe ARDS, which could improve oxygenation and has a survival benefit¹¹ and also could improve outcomes in COVID-19 patients. It has been suggested as the standard of care in international guidelines¹². Prone positioning can reduce ventral-dorsal trans-pulmonary pressure differences and lung compression by the heart and diaphragm, resulting in lung perfusion improvement. Prone positioning has been demonstrated to improve lung compliance and lung recruitability and reduce VILI incidence⁸. Studies of prone ventilation in COVID-19 ARDS patients have shown improvement in the ratio of the partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) (PaO₂/FiO₂)⁸ by 35 mmHg¹³. Prone positioning may play a role in reducing systemic inflammation by increasing alveolar fluid drainage. Inflammatory responses related to ARDS or secondary to VILI may be attributed with pulmonary and extra-pulmonary organ dysfunction and strategies to reduce inflammation may lead to increased survival¹⁸. Prone positioning also increases chest wall elastance and amplifies active expiration during coughing¹⁴. Studies report that prone positioning reduced 28-day and 90-day mortality rates^{15,16} and accelerated the time for extubation¹⁵. The World Health Organization (WHO) recommends its use for periods of 12–16 h/day^{17–19}.

Correct selection of patients and applying the accurate treatment protocol for prone positioning are crucial to its efficacy⁶. Special precautions are required for placing and monitoring a patient in the prone position²⁰. Intubated patients in prone positioning are at risk, such as accidental removal of the tracheal tube, pressure ulcer, facial edema, gastroesophageal reflux, and other problems. Overall, it seems that correct patient selection, timely initiation, and duration of patient's placement in this position can all affect the effectiveness of this intervention⁶. Considering that COVID-19 is a novel disease that caused many difficulties and due to lack of sufficient evidence, the need to assess the effects of prone positioning as a supportive care in hypoxemic patients is necessary, so we conducted this systematic review and meta-analysis to determine the effects of prone position on respiratory parameters and outcomes of COVID-19 patients.

Materials and methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for designing and implementing systematic review studies, the following steps were taken: a systematic literature search, organization of documents for the review, abstracting and quality assessment of each study, synthesizing data, and writing the report²¹. The protocol of the study was registered in the International Prospective Register Of Systematic Reviews (PROSPERO) at the National Institute For Health Research. Registration number in PROSPERO is CRD42021257619.

Search strategy. According to the PICO framework, the systematic literature search was conducted on PubMed, EMBASE, ProQuest, SCOPUS, Web of Sciences, Cochrane library, and Google Scholar databases. MeSH Keywords were connected with AND, OR and NOT prone position and respiratory parameters, and their suggested entry terms were the main keywords in the search strategy.

1. 'Coronavirus Disease 2019 [Title/Abstract], OR 'COVID-19' [Title/Abstract], OR 'Coronavirus' [Title/Abstract], OR 'SARS-cov-2' [Title/Abstract], OR 'Sever acute respiratory syndrome coronavirus-2' [Title/Abstract], '2019-nCov' [Title/Abstract], OR 'SARS-Cov' [Title/Abstract]
2. 'Prone' [Title/Abstract], OR 'Prone position' [Title/Abstract]
3. 'Oxygenation' [Title/Abstract], OR 'Cell Respiration' [Title/Abstract], OR 'Cell Respirations' [Title/Abstract]
4. 'Respiratory Distress Syndrome' [Title/Abstract], OR 'Acute respiratory distress syndrome' [Title/Abstract] OR 'Hypoxemic' [Title/Abstract], OR 'Respiratory Insufficiency' [Title/Abstract], OR 'Dyspnea' [Title/Abstract]
5. 1 AND 2
6. 1 AND 2 AND 3
7. 2 AND 3 AND 4
8. 1 AND 2 AND 3 AND 4

Population, Intervention, Comparators, Outcomes (PICO) criteria for this study includes (P): patients with COVID-19. (I): prone position. (C): no intervention, (O): respiratory parameters and outcome.

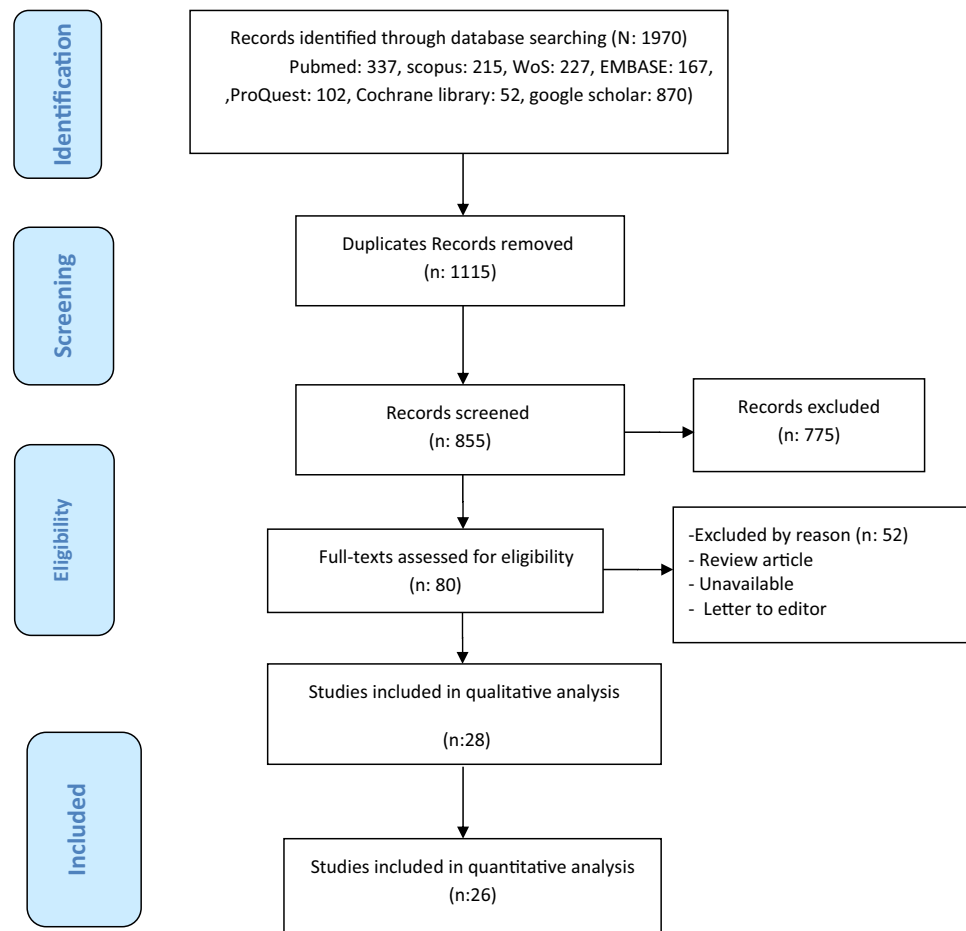


Figure 1. PRISMA diagram for searching resources.

Inclusion and exclusion criteria. *Type of studies.* Studies including quasi-experimental and before–after designs were included if the effects of prone position on respiratory parameters were reported as an outcome. Also, studies met the inclusion criteria if they were published until 1st January 2021. There was no language filtering. The case report, case series, reviews, and studies with incomplete data were excluded.

Type of participants. The studies were selected if participants were patients with Reverse transcription polymerase chain reaction (RT-PCR) confirmed test or if imaging findings showed evidences of COVID-19, patients with COVID-19 need oxygenation (face mask, nasal cannula, invasive mechanical ventilation, non-invasive mechanical ventilation). Pregnant women, patients who have prone positioning contraindication such as skeletal fractures were excluded.

Type of intervention. Patients were instructed to stay in the prone position based on the proning protocol of each study for at least 30–60 min and then return to the supine position. Standard prone position was considered for 16 h/day (some studies considered the duration of prone position ≥ 3 –4 h, or until the patient is uncomfortable). The average time of prolonged sessions was considered up to 36 h. However, in one study, a 5-min protocol was used. Respiratory parameters were measured three times in most studies (before positioning, during prone position, and after prone position).

Type of outcomes measure. The primary outcome was the respiratory parameters and respiratory status. The secondary outcomes were death rate and intubation rates (Supplementary 1).

Study selection. Two authors independently evaluated the eligibility of these articles, and any disagreements were resolved by consensus. Several articles were excluded due to being irrelevant or duplicated. Finally, 28 full-text articles were included in the systematic review and 26 articles in the meta-analysis (Fig. 1).

Risk of bias and quality assessment. The methodological quality of the included studies in this review was conducted by the Mixed Methods Appraisal Tool (MMAT). The quality assessment was conducted independently by two authors. The MMAT was developed to appraise different empirical studies categorized into

five categories: qualitative, randomized controlled trial, nonrandomized, quantitative descriptive, and mixed methods studies²². This tool consists of five items for each category, each of which could be marked as Yes, No, or cannot tell. Based on the scoring system, score one is assigned to Yes and score 0 to all other answers. In other words, the total score would be the percentage of affirmative responses. To evaluate the final scores qualitatively, the scores above half (more than 50%) were considered high quality.

Data extraction. Data were collected as follows: reference, location, type of study, sample size, age, duration of the prone position, proning protocol, timing of measurement, and respiratory parameters.

Unification of units. All respiratory parameters converted to mmHg. For conversion of respiratory parameters to get from SI units (KPa) to mmHg was multiplied by 7.501.

Statistical analysis. All analyses were conducted with Stata software version 14.0 (College Station, Texas). For each study, the mean and standard deviation (SD) of respiratory parameters in the prone position and supine position was extracted and if Median and IQR was reported; we changed it to mean with $[(\min + \max + 2 \times \text{Median})/4]$ or $[(\text{med} + q1 + q3)/3]$ and SD with $[\text{IQR}/1.35]$. Then mean difference (MD) of respiratory parameters for each study was calculated by mean1 minus to mean 2. Due to different studies design (Before–After or Quasi-Experimental design), in the before–after design, we calculated the change score MD (mean after prone position minus mean before prone position), and in Quasi-Experimental design, we calculated MD (mean in supine position minus mean in prone position). Then Standard deviation in Before–After design and Quasi-Experimental design was calculated based on formulas (1) and (2):

$$SD_{\text{change score}} = \sqrt{SD_{\text{before}}^2 + SD_{\text{after}}^2 - (2 \times r \times SD_{\text{before}} \times SD_{\text{after}})} \quad (1)$$

where SD_{before} , SD_{after} , and Corr is the standard deviation in before prone position, standard deviation after prone position, and correlation coefficient between before and after

$$SD_{\text{pooled}} = \sqrt{\frac{(n_1 - 1)SD_{\text{prone position}}^2 + (n_2 - 1)SD_{\text{supine position}}^2}{n_1 + n_2 - 2}} \quad (2)$$

where $SD_{\text{prone position}}$, $SD_{\text{supine position}}$, n_1 , and n_2 is the standard deviation in prone position group, the standard deviation in supine position group, the sample size in the prone position and supine position groups. Then pooled MD (PMD) was calculated by the “Metan” command^{23,24}. Heterogeneity was determined using Cochran’s Q test of heterogeneity, and the I^2 index was used to quantify heterogeneity. In accordance with the Higgins classification approach, I^2 values above 0.7 were considered as high heterogeneity. To estimate the PMD for respiratory parameters and subgroup analysis (study design and ventilation), the fixed-effect model was used, and when the heterogeneity was greater than 0.7, the random-effects model was used. The meta-regression analysis was used to examine the effect of study design, sample size, BMI, age and prone position (PP) duration as factors affecting heterogeneity among studies. The “Meta bias” command was used to check for publication bias, and if there was any publication bias, the PMD was adjusted with the “Metatrim” command using the trim-and-fill method. In all analyses, a significance level of 0.05 was considered.

Result

Overall, 1970 studies were found through databases. After excluding redundant papers, 855 studies remained. After reading abstracts, 775 studies were excluded from the list. Then, the full text of the remaining 80 studies was reviewed, and 52 studies were excluded. Finally, 28 studies included in qualitative analysis and 26 studies with a total sample size of 1272 participants were included in the quantitative analysis. The flowchart of this selection process is shown in Fig. 1. Studies were published during 2020–2021, most studies were done in the UK, China, and Spain with three studies and range participants age were 17–83 years old (Tables 1 and 2). Supplementary 2 shows risk of bias assessment for included studies. All studies were high quality (more than 50% scores).

Pooled mean difference of respiratory parameters in total and based on subgroups. Figure 2 showed the forest plot for MD of $\text{PaO}_2/\text{FIO}_2$ Ratio in included studies. The minimum and maximum reported MD of $\text{PaO}_2/\text{FIO}_2$ reported by Abou-Arab et al. (MD: 0.00; 95% CI 7.21–7.21 mmHg) in France²⁵ and by Mittermaier et al. (MD: 187.90; 95% CI 156.14–199.66 mmHg) in Germany³⁰. Based on Fig. 2 using the random-effects model approach; the PMD in the study with before–after design, quasi-experimental design and in total was 55.74 (95% CI 28.13–83.35) mmHg, 56.38 (95% CI 8.47–104.29) mmHg, and 56.20 (95% CI 33.16–79.24) mmHg; respectively. This means that in general, the prone position in COVID-19 patients leads to significant improvement of $\text{PaO}_2/\text{FIO}_2$ Ratio, so that in before–after design, quasi-experimental design, and in total, the mean of $\text{PaO}_2/\text{FIO}_2$ Ratio significantly increased 55.74, 56.38, and 56.20 mmHg; respectively.

Figure 3 and Table 3 showed the PMD of other respiratory parameters in included studies. The PMD of SPO_2 (Sao_2) in the study with before–after design, quasi-experimental design, and in total was 3.38 (95% CI 1.68–5.09), 17.03 (95% CI 12.19–21.88), and 7.58 (95% CI 4.93–10.23); respectively. This means that the prone position in COVID-19 patients leads to significant improvement corresponding to Spo_2 (Sao_2). Also the PMD of Paco_2 in COVID-19 patients was significantly decreased in quasi-experimental design (PMD: –18.49; 95% CI –34.50 to –2.47 mmHg) and in total (PMD: –8.69; 95% CI –14.69 to –2.69 mmHg). No significant change was observed for PMD of PaCo_2 in the before–after design. The PMD of other respiratory parameters showed in Table 3 and

ID	Author (Ref.)	Recruitment period	Country	Study type	Population/SS	Gender/age (year) Mean (SD)/median (IQR)/range	Duration of PP	Proning protocol/ timing of measurement (hour)
1	Abou Arab ²⁵	1 March to 30 April, 2020	France	Before–after	Mechanically venti- lated COVID-19 T: 25	Male/female	At least one 16-h PP session	H ₀ : Before PP H ₁ : At the end of the first 16-h PP session
2	Coppo ⁵	20 March to 9 April, 2020	Italy	Before–after	COVID-19-related pneumonia T: 56	Male: 44 Female: 12 Age: 18–75	At least 3 h	H ₀ : before PP H ₁ : 10 min after pronation H ₂ : 1 h after return- ing to the supine position
3	Ferrando ²⁶	12 March to 9 June, 2020	Spain and Andorra	Quasi-experimental	COVID-19 patients with ARF Case: 55 Control: 144 T: 199	Male/female	16 h/day during 3 consecutive day	Case: HFNO + awake PP Control: only receive HFNO H ₀ : Before PP H ₁ : After PP
4	Caputo ²⁷	1 March to 1 April, 2020	USA	Before–after	COVID-19 Hypoxemia (SpO ₂ < 90%) T: 50	Male/female Age: 59 (50–68)	5 min	Awake self proning with supplemental oxygen H ₀ : At triage H ₁ : With Supple- mental oxygenation H ₂ : After 5 min of proning
5	Ni ⁴	31 January to 15 February, 2020	China	Quasi-experimental	COVID-19 Case: 17 Control: 35 T: 52	Male/female Age: 62 (12)	At least 4 h/day for 10 days	G ₁ : Standard care G ₂ : Position care (prone or lateral)
6	Elharrar ²⁸	27 March to 8 April, 2020	France	Before–after	COVID-19 T: 24	Male/female Age: 66.1 (10.2)	PP subgroup: Between less than 1 h to more than 3 h based on tolerability < 1 h (n: 4) 1 to < 3 h (n: 5) ≥ 3 h (n: 15)	H ₀ : Before PP H ₁ : During PP H ₂ : 6 to 12 h after resupination
7	Retucci ²⁹	March and April 2020	Italy	Quasi-experimental	COVID-19 with spontaneous breathing/T: 26	Male/female Age: ≥ 18	1 h session/39 ses- sions: Case: 12 prone session Control: 27 lateral session	Prone (case) and lateral position (control) in Nonin- vasive Helmet CPAP Treatment H ₀ : Before interven- tion H ₁ : During interven- tion H ₂ : 45 min after resupination
8	Mittermaier ³⁰	15 March to 11 April, 2020	Germany	Quasi-experimental	Mechanically venti- lated COVID-19 T: 15	Male/female Age: 26–81	15 ± 2.5 h for 6.2 days	G ₁ : Intubation G ₂ : PEEP G ₃ : PP
9	Taboada ³¹	31 March to 11 April, 2020	Spain	Before–after	COVID-19 T: 29	Male/female Age: 64 (12)	1 h	H ₀ : Before PP H ₁ : During PP H ₂ : After PP
10	Taboada ¹⁷	15 March to 15 April, 2020	Spain	Before–after	COVID-19 T: 50	Male/female Age: 63 (53–71)	30–60 min	H ₀ : Supine position H ₁ : PP H ₂ : Resupination
11	Zang ⁴²	1 February to 30 April, 2020	China	Before–after	COVID-19 Case: 23 Control: 37 T: 60	Male/female	Median: 9 h (8–22)	H ₀ : Before PP H ₁ : 10 min after PP H ₂ : 30 min after PP
12	Dong ¹⁹	5 February to 29 February, 2020	China	Before–after	COVID-19 T: 25	Male/female Age: 54.4 (16.1)	PP session > 4 h/day Mean (SD): 4.9 (3.1) h	Lateral positioning if PP not tolerated H ₀ : Before PP H ₁ : After sessions of PP
13	Shelhamer ¹¹	25 March to 2 May, 2020	USA	Quasi-experimental	Mechanically ventilated patients with moderate to severe ARDS due to COVID-19 Case: 62 Control: 199 T: 261	Male/female Age: 64 (55–73)	At least 16 h	Case: Prone Control: Not prone
14	Thompson ³³	6 April to 14 April, 2020	USA	Before–after	COVID-19 with severe hypoxemic respiratory failure T: 25	Male/female	At least 1 awake session of the prone position lasting longer than 1 h	H ₀ : Supine position H ₁ : 1 h after initia- tion of PP

Continued

ID	Author (Ref.)	Recruitment period	Country	Study type	Population/SS	Gender/age (year) Mean (SD)/median (IQR)/range	Duration of PP	Proning protocol/ timing of measurement (hour)
15	Tu ³⁴	1 February to 10 March, 2020	China	Before–after	COVID-19 T: 9	Male/female Age: 51 (11)	Median of 5 (IQR: 3–8) procedures per subject (twice daily). The median duration was 2 (IQR: 1–4) h	PP in HFNC H ₀ : before PP H ₁ : after PP
16	Weiss ¹⁶	18 March to 31 March, 2020	USA	Before–after	Mechanically ventilated patients with COVID-19 T: 42	Male/female Age: 58.5 (51.8–69.3)	Several sessions lasting for 16 h	First PP session H ₀ : Pre-prone (in 1 h) H ₁ : Post-prone (in 2 h) H ₂ : Post-prone (4 h after) H ₃ : Pre-supine (0.5–2 h before) H ₄ : Post-supine (0.5–2 h after)
17	Winearls ³⁵	8 April to 31 May, 2020	UK	Before–after	COVID-19 T: 24	Male/female Age: 62 (13)	Mean duration of PP was 8 ± 5 h for a mean of 10 ± 5 days	PP combined with CPAP H ₀ : Prior to CPAP initiation H ₁ : On CPAP prior to PP H ₂ : During PP on CPAP (15 min after PP initiation) H ₃ : 1 h after PP while on CPAP
18	Khullar ⁸	March and May 2020	USA	Before–after	Mechanically ventilated SARS-CoV-2-positive adults/Living (n = 6) deceased (n = 17) T: 23	Male/female Age: 57 (25–75)	≥ 16 h, ≥ 1 day	H ₀ : Before PP H ₁ : Post proning H ₂ : 48 h after PP
19	Sharp ³⁶	12 March to 20 April, 2020	UK	Quasi-experimental	Mechanically ventilated COVID-19 pneumonia T: 12	Male/female Age: 30–76	Two or more full proning cycles	H ₀ : Supine position H ₁ : Prone position
20	Wendt ³⁷	30 March to 4 April, 2020	USA	Before–after	Spontaneously breathing COVID-19 with hypoxic respiratory distress T: 31	Male/female Age: 31(5)	At least 2 h	H ₀ : Room air H ₁ : Before PP with supplemental O ₂ H ₂ : With PP
21	Berril ¹²	23 March to 7 May, 2020	UK	Before–after	Mechanically ventilated COVID-19 T: 34	Female: 34 Age: (Med ± SD) 58.5 ± 11.1	The average duration was 16.5 ± 2.7 h/patient Proning done on average for 4 ± 2.4 separate sessions Total session: 131	H ₀ : Before PP H ₁ : After 3 h of PP
22	Burton-Papp ³⁸	4 March to 11 May, 2020	UK	Before–after	COVID-19 G ₁ : 13 G ₂ : 7 T: 20	Male/female Age: 53.4 (8.3)	5 prone cycles (each cycle lasted up to 3 h)	PP inconjunction with NIV G ₁ : Only NIV G ₂ : NIV and IMV T: All NIV and PP
23	Carsetti ¹	NR	Italy	Before–after	Mechanically ventilated SARS-CoV-2 T: 10	Male: 10 Age: 58 (50–64)	Standard duration: 16 h Prolonged duration: 36 h	H ₀ : Before pronation H ₁ : During pronation H ₂ : Resupination
24	Jagan ³⁹	24 March to 5 May, 2020	Grand Island	Quasi-experimental	COVID-19 G ₁ : 40 G ₂ : 65 T: 105	Male/female Age: G ₁ : 56.0 (14.4) G ₂ : 65.8 (16.3)	1 h	G ₁ : Proning G ₂ : Not proning
25	Padrao ⁹	1 March to 30 April, 2020	Brazil	Quasi-experimental	COVID-19 hypoxemic respiratory failure/case: 57 Control: 109 T: 166	Male/female Age: 58.1 (14.1)	Between 30 min and 4 h	Case: PP Control: Not PP H ₀ : Before PP H ₁ : After PP
26	Sartini ³²	April 2, 2020	Italy	Before–after	Hypoxemic COVID-19 (SpO ₂ < 94%) T: 15	Male/female Age: 59 (6.5)	Median 3 h (IQR, 1–6 h)	PP for NIV patients H ₀ : Before NIV H ₁ : During NIV in pronation (60 min after start) H ₂ : 60 min after NIV end

Continued

ID	Author (Ref.)	Recruitment period	Country	Study type	Population/SS	Gender/age (year) Mean (SD)/median (IQR)/range	Duration of PP	Prone protocol/ timing of measurement (hour)
27	San ⁴⁰	1 April to 31 May, 2020	Turkey	Before–after	COVID-19 pneumonia (SpO ₂ < 93%) T: 21	Male/female Age: 71 (60–76.5)	G ₁ = 15 min or below (N = 7) G ₂ = Above 1 min (N = 14)	PP on the ambulance stretcher H ₀ : Before transport H ₁ : After transport
28	Solverson ⁴¹	1 April to 25 May, 2020	Canada	Before–after	Non-intubated COVID-19 patients T: 17	Male/female Age: Median (range) 53 (34–81)	The median number of daily prone positioning sessions was 2 (1–6) with a duration of 75 (30–480) min for the first session G ₁ = < 75 min (n = 8) G ₂ = ≥ 75 min (n = 9)	H ₀ : Supine position H ₁ : Prone position H ₂ : Respiration

Table 1. Overview of all included studies in systematic review. *SS* sample size, *PP* prone position, *H* hour, *min* minutes, *G* group, *T* total, *O*₂ oxygen, *NIV* non invasive ventilation, *IMV* intermittent mandatory ventilation, *HFNO* high flow nasal oxygen, *PEEP* positive end expiratory pressure, *CPAP* continuous positive airway pressure, *SD* standard deviation, *IQR* interquartile range.

Fig. 3. It should be noted that prone position leads to improvement of PaO₂ but does not have any effects on the respiratory rate in general, especially in the quasi-experimental design. The pooled estimate and 95% CI for death rate and intubation rate were 19.03 (8.19–32.61) and 30.68 (21.39–40.75); respectively (Fig. 4).

Figure 5 showed PMD of respiratory parameters based on ventilation status. PMD of SpO₂ (Sao₂) in Intubation and Non-intubation subgroup was 10.56 (95% CI – 18.15 to 39.26) and 8.57 (95% CI 3.47–13.67); respectively. This means that the prone position in COVID-19 patients with non-intubation leads to significant improvement corresponding to SpO₂ (Sao₂) but Intubation have no effects on SpO₂ (Sao₂) improvement. Also PMD of PaO₂/FIO₂ in Intubation and non-intubation subgroup was 65.03 (95% CI 6.06–123.99) and 49.56 (95% CI 26.56–72.56); respectively. This means that the prone position in COVID-19 patients leads to significant improvement of PaO₂/FIO₂ Ratio, but this value for Intubated patients was higher than non-intubated groups. Situation of other parameter was showed in Fig. 5.

Publication bias. Based on Egger's test results, significant publication bias was observed for PaO₂/FIO₂ Ratio (Coefficient: 5.63; 95% CI 0.91–10.35; *p*: 0.024). Therefore, the fill- and trim-adjusted PaO₂/FIO₂ Ratio (PMD: 57.41, 95% CI 32.19–81.01 mmHg) was generated, which was not significantly different from the original PaO₂/FIO₂ Ratio (PMD: 56.20; 95% CI 33.16–79.24 mmHg). It means that the result of the meta-analysis was robust. No significant publication bias was observed for other respiratory parameters.

Heterogeneity and meta-regression results. According to Cochran's Q test of heterogeneity, there was significant heterogeneity among studies (*p* < 0.001). Except for PaCO₂ in the before–after design, the heterogeneity amount was more than 85% based on the I² index, which indicates high heterogeneity. Table 4 presents the results of the univariate meta-regression; there are significant associations between study, results with study design corresponding to SPO₂ (Sao₂) percent (Coefficient: 12.80; *p* < 0.001). No significant associations were observed for other respiratory parameters with sample size, study design, BMI, age and PP duration (Table 4).

Discussion

This systematic review analyzed the effects of prone position on respiratory parameters, intubation, and death rate. We found that prone position initiation leads to improved oxygenation parameters (PaO₂/FiO₂ ratio, SpO₂, PaO₂, and PaCO₂) in patients with mild to severe respiratory failure due to confirmed COVID-19. However, the prone position did not change the respiratory rate in patients with hypoxemic respiratory failure suffering from COVID-19.

Most of the studies (18/28 studies) demonstrated significant improvement in PaO₂/FiO₂ ratio after prone positioning. Moreover, the improvement of SpO₂ (Sao₂) and PaO₂ has been shown in 15 and 7 studies, respectively. Although the effect of prone position after respiration has declined in five studies^{1,5,8,16,29}, early prone positioning should be considered as first-line therapy in ARDS patients⁴³. Initiation of prone position in ARDS patients by reducing shunt, and V/Q mismatch, brings about an increase in the recruitment of non-aerated areas of the lungs, secretion clearance, improvement work of breathing (WOB) and oxygenation, and reduction of mortality compared with the supine position^{44–46}. Prone position by enhancement in PaO₂/FiO₂ ratio not only leads to a decrease in the classification of respiratory failure but also prevents further complications due to ARDS, such as multi-organ failure (MOF), which is the most common cause of mortality in this devastating condition⁴⁷.

The efficacy of prone positioning may be affected by various protocols, such as different settings (ICU or emergency department), the timing of initiation (early or late), duration (prolonged or short sessions), positioning (prone position with or without lateral position), respiratory support in intubated or non-intubated patients (mechanical ventilation, NIV, nasal cannula, helmet, face mask) and the severity of ARDS⁴⁸. Even though in this study PaO₂/FiO₂ ratio was significantly higher in the prone-positioning group with mild to severe ARDS, a further meta-analysis need to assess the impact of prone position in a different classification of ARDS with mild

ID	Author	SPO ₂ (Sao ₂) (%) Mean (SD)/median (IQR)	PaO ₂ /FIO ₂ ratio or SPO ₂ /FIO ₂ ratio Mean (SD)/median (IQR)	PaCO ₂ (mmHg) Mean (SD)/median (IQR)	PaO ₂ (mmHg) Mean (SD)/median (IQR)	RR Mean (SD)/median (IQR)	Other variables
1	Abou-Arab	NR	H ₀ : 91 (78–137) H ₁ : 124 (97–149)	H ₀ : 49 (42–51) H ₁ : 49 (44–57)	NR	NR	NR
2	Coppo	H ₀ : 97.2 (2.8) H ₁ : 98.2 (2.2) H ₂ : 97.1(1.9)	H ₀ : 180.5 (76.6) H ₁ : 285.5 (112.9) H ₂ : 192.9 (100.9)	H ₀ : 35.3 (4.9) H ₁ : 35.6 (4.5) H ₂ : 35.5 (4.4)	H ₀ : 117.1 (47.4) H ₁ : 200.4 (110.9) H ₂ : 121.4 (69.6)	H ₀ : 24.5 (5.5) H ₁ : 24 (6.9) H ₂ : 23.9 (6.3)	Intubation rate 18/56
3	Ferrando	H ₀ Case: 90.4 Control: 90.4 H ₁ Case : 87.6 Control: 88.8	H ₀ Case: 148.2 Control: 123.9 H ₁ Case: 113.8 Control: 109.7	H ₀ Case: 34.0 Control: 34.7 H ₁ Case: 42.4 Control: 44.8	NR	H ₀ Case: 25.5 Control: 25.7 H ₁ Case Minimum: 20.8 Maximum: 27.7 Control Minimum: 19.7 Maximum: 27.1	Intubation rate Hazard ratio (95% CI); 1.002 (0.531, 1.890) 28-day mortality rate Hazard ratio (95% CI); 2.411 (0.556, 10.442)
4	Caputo	H ₀ : 80 H ₁ : 84 H ₂ : 94	NR	NR	NR	NR	Intubation rate 13/50
5	Ni	NR	H ₀ G ₁ : 128 (60) G ₂ : 142 (54) T: 133 (58) SpO ₂ /Fio ₂ 409 (95% CI 86–733)	NR	NR	H ₀ G ₁ : 26 (5) G ₂ : 23 (4) T: 25 (5)	NR
6	Elharrar	NR	NR	Total H ₀ : 34.1 (5.3) H ₁ : 32.8 (4.5) H ₂ : 32.3 (5.1)	Total H ₀ : 72.8 (14.2) H ₁ : 91 (27.3) H ₂ : 77.6 (11.5)	Total H ₀ : 18 (2.7)	Intubation rate 5/24
7	Retucci	Total H ₀ : 96 (95–98) H ₁ : 98 (97–98) H ₂ : 97 (95–98) Case H ₀ : 95 (93.5–96.0) H ₁ : 98 (98–99) H ₂ : 96 (95–98) Control H ₀ : 97 (96–98) H ₁ : 98 (96–98) H ₂ : 97 (96–98)	Total H ₀ : 182.9 (43.0) H ₁ : 220.0 (64.5) H ₂ : 179.3 (43.9) Case H ₀ : 168.7 (46.2) H ₁ : 227.7 (90.3) H ₂ : 166.9 (45.3) Control H ₀ : 189.7 (40.6) H ₁ : 216.2 (49.6) H ₂ : 185.0 (43.0)	Total H ₀ : 38 (35–40) H ₁ : 38 (35–39) H ₂ : 38 (35–40) Case H ₀ : 39 (35.5–40.5) H ₁ : 38 (34.5–41.0) H ₂ : 37 (35–41) Control H ₀ : 38 (34–39) H ₁ : 37 (35–39) H ₂ : 38 (35–40)	Total H ₀ : 86.9 (15.1) H ₁ : 104.5 (25.0) H ₂ : 85.4 (13.4) Case H ₀ : 83.6 (14.2) H ₁ : 112.3 (32.3) H ₂ : 85.6 (11.5) Control H ₀ : 88.4 (15.5) H ₁ : 100.8 (20.4) H ₂ : 85.8 (14.5)	Total H ₀ : 23.7 (4.7) H ₁ : 23.1 (4.5) H ₂ : 23.6 (4.7) Case H ₀ : 23.5 (6.3) H ₁ : 21.3 (5.0) H ₂ : 22.9 (6.0) Control H ₀ : 23.8 (.9) H ₁ : 23.9 (4.0) H ₂ : 24.0 (4.1)	Intubation rate 7/26 (26.9%) Death rate 2/26 (7.7%)
8	Mittermaier	NR	H ₀ G ₁ : 84.3(28) G ₂ : 80 ^a G ₃ : 140 ^a H ₁ G ₁ : 210.7 (86.6) G ₂ : 197.9 (43.0) G ₃ : 190 ^a	H ₀ G ₁ : 35.9(7) H ₁ G ₂ : 52.4 (9.7)	H ₀ NR H ₁ G ₂ : 79.5(7.8)	H ₀ G ₁ : 31 (2.6) G ₂ : 16 (2.6) H ₁ G ₂ : 15.7 (2.8)	Death rate G ₁ = 40% G ₂ = 42.9% G ₃ = 55.6%
9	Taboada	H ₀ : 93.6 (2.3) H ₁ : 95.8 (2.1) H ₂ : 95.4 (2.7)	H ₀ : 196 (68) H ₂ : 242 (107)	NR	H ₀ : 75 ^a H ₁ : 80 ^a	NR	Death rate 2/29 (7%)
10	Taboada	NR	NR	NR	NR	NR	Death rate 4%
11	Zang	Case H ₀ : 91.09 (1.54) H ₁ : 95.30 (1.72) H ₂ : 95.48 (1.73)	NR	NR	NR	Case H ₀ : 28.22 (3.06) H ₁ : 27.78 (2.75) H ₂ : 24.87 (1.84)	Death rate Case: 10/23 (43.5%) Control: 28/37 (75.7%)
12	Dong	NR	H ₀ : 194 (164–252) H ₁ : 348 (288–390)	NR	NR	H ₀ : 28.4 (3.5) H ₁ : 21.3 (1.3)	Death rate 0/25
13	Shelhamer	NR	PaO ₂ /FIO ₂ Case 0.10 (0.04, 0.17) + 11% improvement SPO ₂ /Fio ₂ – 0.28 (0.63, 0.08) + 24% improvement	NR	NR	NR	Death rate Case: 48 (77.4%) Control: 167 (83.9%)
14	Thompson	H ₀ : 65–95% ^a H ₁ : 90–100% ^a + (1–34%) [median [SE], 7% [1.2%]; 95% CI 4.6–9.4%)	NR	NR	NR	NR	Intubation rate 12/25 (48%) Death rate 3/25 (10%)
15	Tu	H ₀ : 90 (2) H ₁ : 96 (3)	NR	H ₀ : 47 (7) H ₁ : 39 (5)	H ₀ : 69 (10) H ₁ : 108 (14)	NR	Intubation rate 2/9
16	Weiss	H ₀ : 96 (93–99.0) H ₁ : 97.5(95–99) H ₂ : 97 (95.0–99.0) H ₃ : 98 (96–99.0) H ₄ : 96.5 (94.0– 99.0)	(KPa) H ₀ : 17.5 (11.6–19.2) H ₁ : 27.7 (19.5–35.7) H ₂ : NR H ₃ : NR H ₄ : 26.1 (17.9–33.1)	(KPa) H ₀ : 7.2 (5.7–7.9) H ₁ : 6.8 (6.0–7.7) H ₂ : NR H ₃ : NR H ₄ : 6.3 (5.5–6.8)	(KPa) H ₀ : 11.8 (9.3–14.2) H ₁ : 14.5 (10.2–20.4) H ₂ : NR H ₃ : NR H ₄ : 13.5 (10.3–17.3)	NR	Death rate 11/42
17	Winearls	H ₀ : 94 (3) H ₁ : 95 (2) H ₂ : 96 (2) H ₃ : 96 (2)	H ₀ : 143 (73) H ₁ : 201 (70) H ₂ : 252 (87) H ₃ : 234 (107)	NR	NR	H ₀ : 27 (6) H ₁ : 25 (6) H ₂ : 24 (6) H ₃ : 25 (6)	Death rate 4/24

Continued

ID	Author	SPO ₂ (Sao ₂) (%) Mean (SD)/median (IQR)	PaO ₂ /FIO ₂ ratio or SPO ₂ /FIO ₂ ratio Mean (SD)/median (IQR)	PaCO ₂ (mmHg) Mean (SD)/median (IQR)	PaO ₂ (mmHg) Mean (SD)/median (IQR)	RR Mean (SD)/median (IQR)	Other variables
18	Khullar	NR	Living H ₀ : 86.5 ^a H ₁ : 180 ^a H ₂ : 115 ^a Deceased H ₀ : 84.2 ^a H ₁ : 210 ^a H ₂ : 107 ^a Total H ₀ : 84.8 ^a H ₁ : 202 ^a H ₂ : 109 ^a	NR	Living H ₀ : 86.5 ^a H ₁ : 138 ^a H ₂ : 68.2 ^a Deceased H ₀ : 77.1 ^a H ₁ : 185 ^a H ₂ : 82.8 ^a Total H ₀ : 79.5 ^a H ₁ : 173 ^a H ₂ : 78.8 ^a	H ₀ : 27.2 H ₁ : 23.6	NR
19	Sharp	NR	H ₀ : 88.95 (19.34) H ₁ : 110.18 (28.11)	NR	NR	NR	30 day mortality rate 9/12
20	Wendt	H ₀ : 83% (IQR: 75–86%) H ₁ : 90% (IQR: 89–93%) H ₂ : 96% (IQR: 94–98%)	NR	NR	NR	H ₁ : 31 (SD = 9) H ₂ : 26 (SD = 8)	Intubation rate 14/31 Death rate 8/31
21	Berril	NR	(N: 89 session) H ₀ : 99.8 (37.5) H ₁ : 151.9 (58.9)	H ₀ : 47.3 (8.9)	NR	H ₀ : 18 (4.2)	Death rate 17/34 (50%)
22	Burton-Papp	NR	Δ PaO ₂ /FiO ₂ G ₁ : +40.8 (95% CI 28.8–52.7) G ₂ : +5.06 (95% CI –9.5 to 19.75) T: +28.7 mmHg [95% CI 18.7–38.6]	NR	NR	Δ RR G ₁ : –1.27 (95% CI –2.4 to –0.1) G ₂ : –0.09 ± 6.45 (95% CI –2.3 to 2.1) T: –0.98 [95% CI –2 to 0.04]	Intubation rate 7/20 (35%) Death rate 0%
23	Carsetti	NR	Standard pronation H ₁ vs. H ₀ H ₂ vs. H ₁ Prolonged pronation H ₁ vs. H ₀ H ₂ vs. H ₀	NR	NR	NR	NR
24	Jagan	NR	(95% CI 29.6 lower to 10.8 higher)	NR	NR	NR	Death rate G ₁ : 0 G ₂ : 24.6% Intubation rate G ₁ : 10% G ₂ : 27.7%
25	Padrao	Case H ₀ : 92 (88–93) H ₁ : 94 (92–96)	Case H ₀ : 196 (128–254) H ₁ : 224 (159–307)	NR	NR	Case H ₀ : 34 (30–38) H ₁ : 29 (26–32)	Intubation rate Case: 33/57 (58%) Control: 53/109 (49%) Death rate Case: 6 (11%) Control: 22 (20%)
26	Sartini	H ₀ : 93.5 ^a H ₁ : 118.6 ^a H ₂ : 95.3 ^a	H ₀ : 91 ^a H ₁ : 129 ^a H ₂ : 90.2 ^a	NR	NR	H ₀ : 26.6 ^a H ₁ : 23.5 ^a H ₂ : 23.1 ^a	Intubation rate 1/15 Death rate 1/15
27	san	G ₁ H ₀ : 90.1 (82.3–92.5) H ₁ : 91.0 (89.1–93.4) G ₂ H ₀ : 87.9 (5.6) H ₁ : 94.1 (3.5) Total H ₀ : 89.6 (83.6–91.8) H ₁ : 92.8 (89.9–97.1)	NR	G ₁ H ₀ : 38.5 (29.7–51.2) H ₁ : 36.7 (34.1–47.1) G ₂ H ₀ : 37.4 (33.6–41.0) H ₁ : 35.3 (31.3–43.9) Total H ₀ : 37.8 (32.7–44.5) H ₁ : 35.6 (33.2–44.7)	G ₁ H ₀ : 64.5 (18.2) H ₁ : 67.9 (13.4) G ₂ H ₀ : 53.3 (45.4–67.4) H ₁ : 71.0 (63.1–104.1) Total H ₀ : 53.5 (46.1–71.0) H ₁ : 70.0 (60.7–88.1)	NR	NR
28	Solverson	G ₁ H ₀ : 91 (87–95) H ₁ : 98 (94–100) G ₂ H ₀ : 91 (84–95) H ₁ : 96 (92–99) Total H ₀ : 91 (84–95) H ₁ : 98 (92–100)	G ₁ H ₀ : 138 (97–198) H ₁ : 155 (106–248) G ₂ H ₀ : 152 (97–233) H ₁ : 165 (106–240) Total H ₀ : 152 (97–233) H ₁ : 165 (106–248)	NR	NR	G ₁ H ₀ : 30 (24–38) H ₁ : 20 (15–33) G ₂ H ₀ : 26 (18–35) H ₁ : 24 (16–32) Total H ₀ : 28 (18–38) H ₁ : 22 (15–33)	Intubation rate 7/17 Death rate 2/17

Table 2. Respiratory parameters, intubation rate, and death rate in COVID-19 patients. *H* hour, *Spo*₂ pulse oximeter oxygen saturation, *Sao*₂ oxygen saturation (arterial blood), *Paco*₂ partial pressure of carbon dioxide, *Pao*₂ partial pressure of oxygen, *FIO*₂ fractional inspiratory oxygen, *RR* respiratory rate, *SD* standard deviation, *IQR* interquartile range, *mmHg* millimeter of mercury, *CI* confidence interval, *SE* standard error, *SHR* substidistribution hazard ratio, *SS* sample size, *NR* not reported. ^aData extracted from figures and charts.

(PaO₂/FiO₂ = 201–300 mmHg), moderate (PaO₂/FiO₂ = 101–200 mmHg), and severe (PaO₂/FiO₂ < 100 mmHg) condition. In this systematic review, the prone position time varied from less than 1 to 16 h in a day. In eight studies, the prone positioning has been implemented for about 16 h a day. The prolonged prone positioning (no less than 10–12 h and ideally for 16–20 h) leads to improved oxygenation and a significant reduction in mortality in patients with severe ARDS. On the other hand, reducing the number of turning in patients with critical conditions can decrease the risk of more complications⁴⁸. Although PaCO₂ did not demonstrate a difference in five studies^{5,16,25,29,40}, the PMD of PaCO₂ in COVID-19 patients significantly decreased totally. The prone position by increasing the dorsal recruitment, PaCO₂ clearance, and decreasing the dead space can also lead to better ventilation. Moreover, a higher PaCO₂ clearance due to the prone position is related to a significant decrease in

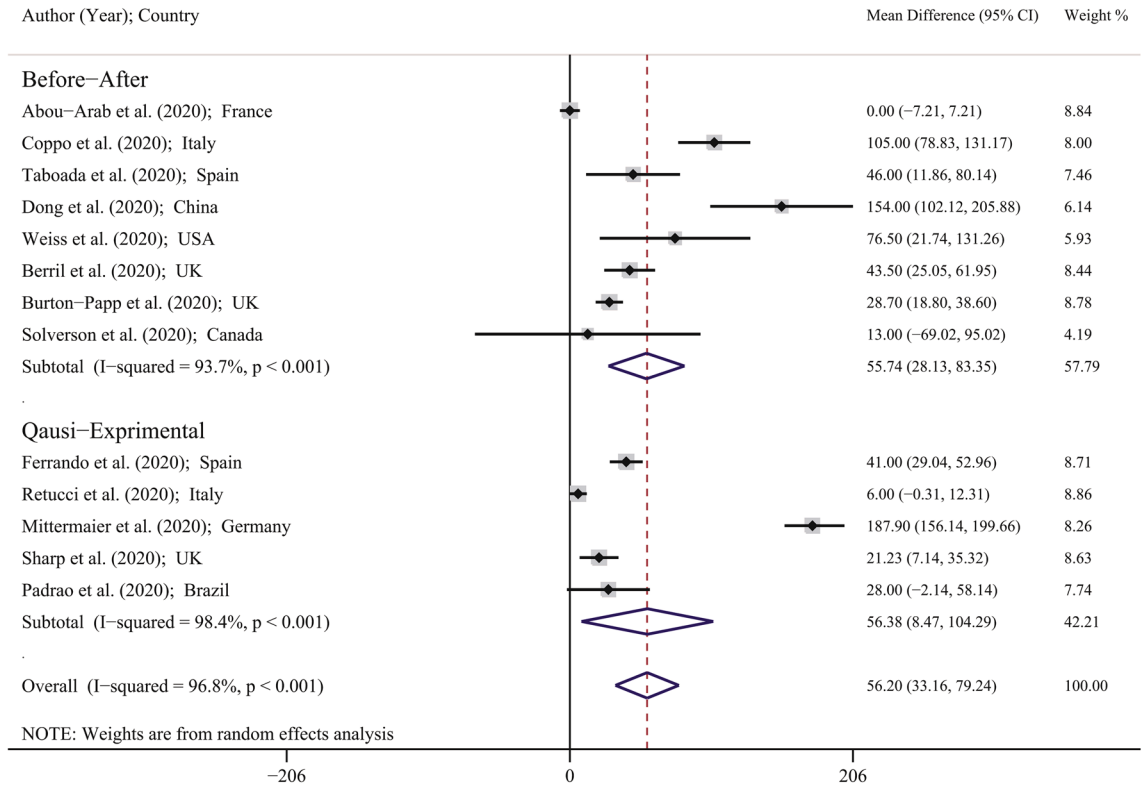


Figure 2. Forest plot for mean difference (MD) of PaO₂/FIO₂ Ratio (mmHg) based on random effects model. The midpoint of each line segment shows the MD, the length of the line segment indicates the 95% confidence interval in each study, and the diamond mark illustrates the pooled MD.

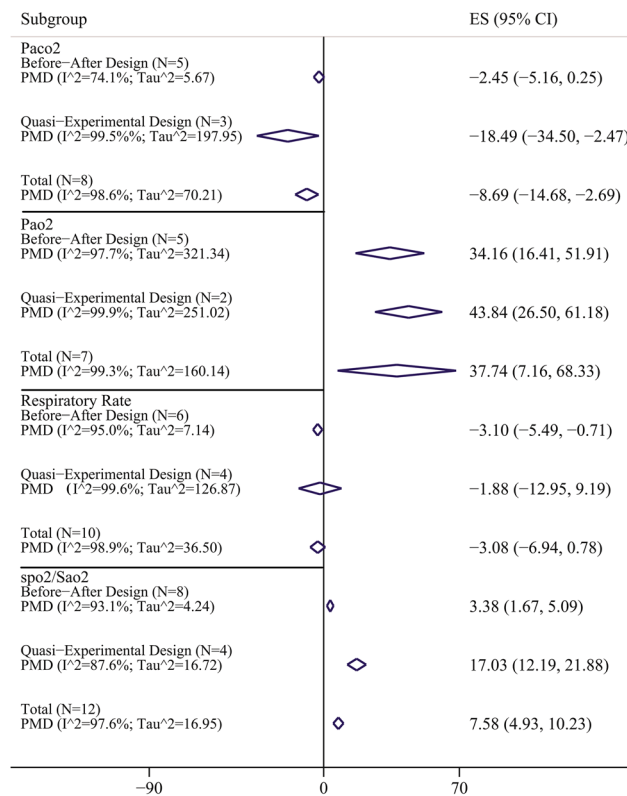


Figure 3. Pooled mean difference and 95% confidence interval of respiratory parameters based on the random effects model in total and in different study design. The diamond mark illustrates the pooled estimate.

Variables	Subgroup	Meta-analysis	Heterogeneity		Egger's test for publication bias		Fill-and-trim
		PMD (95% CI)	I ² (%)	Tau ²	Coefficient (95% CI)	P-value	PMD (95% CI)
PaO ₂ /FIO ₂ ratio	Before-after design (N = 8)	55.74 (28.13–83.35)	93.7	121.01	5.63 (0.91–10.35)	0.024	57.41 (32.19–81.01)
	Quasi-experimental design (N = 4)	56.38 (8.47–104.29)	98.4	141.02			
	Total (N = 12)	56.20 (33.16–79.24)	96.8	99.04			
Spo ₂ (Sao ₂)	Before-after design (N = 8)	3.38 (1.68–5.09)	93.1	4.24	– 10.02 (– 25.04 to 5.01)	0.168	–
	Quasi-experimental design (N = 4)	17.03 (12.19–21.88)	87.6	16.72			
	Total (N = 12)	7.58 (4.93–10.23)	97.6	16.95			
Paco ₂	Before-after design (N = 5)	– 2.45 (– 5.15 to 0.25)	74.1	5.67	– 3.89 (– 16.71 to 8.94)	0.486	–
	Quasi-experimental design (N = 3)	– 18.49 (– 34.50 to – 2.47)	99.5	197.95			
	Total (N = 8)	– 8.69 (– 14.69 to – 2.69)	98.6	70.21			
Pao ₂	Before-after design (N = 5)	34.16 (16.41–51.91)	87.7	321.34	2.12 (– 18.16 to 22.40)	0.799	–
	Quasi-experimental design (N = 2)	43.84 (26.03–61.18)	99.9	251.02			
	Total (N = 7)	37.74 (7.16–68.33)	99.3	160.14			
RR	Before-after design (N = 6)	– 3.10 (– 5.49 to – 0.71)	95.0	7.14	1.52 (– 12.94 to 15.98)	0.815	–
	Quasi-experimental design (N = 4)	– 1.88 (– 12.95 to 9.19)	99.6	126.87			
	Total (N = 10)	– 3.08 (– 6.94 to 0.78)	98.9	36.50			

Table 3. Result of meta-analysis for calculation of pooled mean difference of respiratory parameters; publication bias and fill and trim method. *CI* confidence interval, *N* number of study, *PMD* pooled mean difference, *Pao₂* partial pressure of oxygen, *FIO₂* fractional inspiratory oxygen, *Sao₂* oxygen saturation (arterial blood), *RR* respiratory rate.

28-day mortality⁵⁴. In terms of respiratory rate, in few studies, the respiratory rate reduction was significant, but we found that respiratory rate did not change during the prone positioning in the overall analysis.

Our systematic review and meta-analysis demonstrated that prone positioning leads to a lower mortality rate in confirmed COVID-19 patients. Although in this systematic review and meta-analysis, many studies have assessed the impact of prone position on the short term (28 days) mortality, where they benefit from prone positioning protocols, the effect of prone positioning in the long-term (3 months or more) mortality is unclear. Therefore, further studies will be needed to demonstrate the relationship between prone positioning in COVID-19 patients and long-term mortality. Furthermore, this study confirmed that the improvement of oxygenation parameters due to the prone position might be associated with a lower intubation rate in COVID-19 patients.

Conclusions

In our systematic review of 28 studies, prone positioning has been compared with supine positioning in hypoxic adult patients with COVID-19. We found prone position by optimizing lung recruitment, and the V/Q mismatch can improve oxygenation parameters such as PaO₂/FIO₂ Ratio, Spo₂ (Sao₂), PaO₂, PaCO₂. Nevertheless, the prone position did not change their respiratory rate. Moreover, the initiation of prone position might be associated with a lower mortality and intubation rate. Since most patients demonstrated improved oxygenation and lower mortality and intubation rate, we recommend the prone position in patients COVID-19. Similar to other studies, our research had some limitations. (1) Some studies did not report values of the respiratory parameters in different groups and just reported significantly parameter (like that p-value); which we have to exclude this studies from the quantitative analysis that this limitation was not be resolved even by data requesting from corresponding authors. We would like to perform the gender-specific estimation, but it was not possible due to insufficient data in the primary studies; (2) also we tend to estimate the pooled MD in different geographical regions or country-specific estimation based on available methods⁵⁰, since the infrequent studies number, this estimation will not be robust.

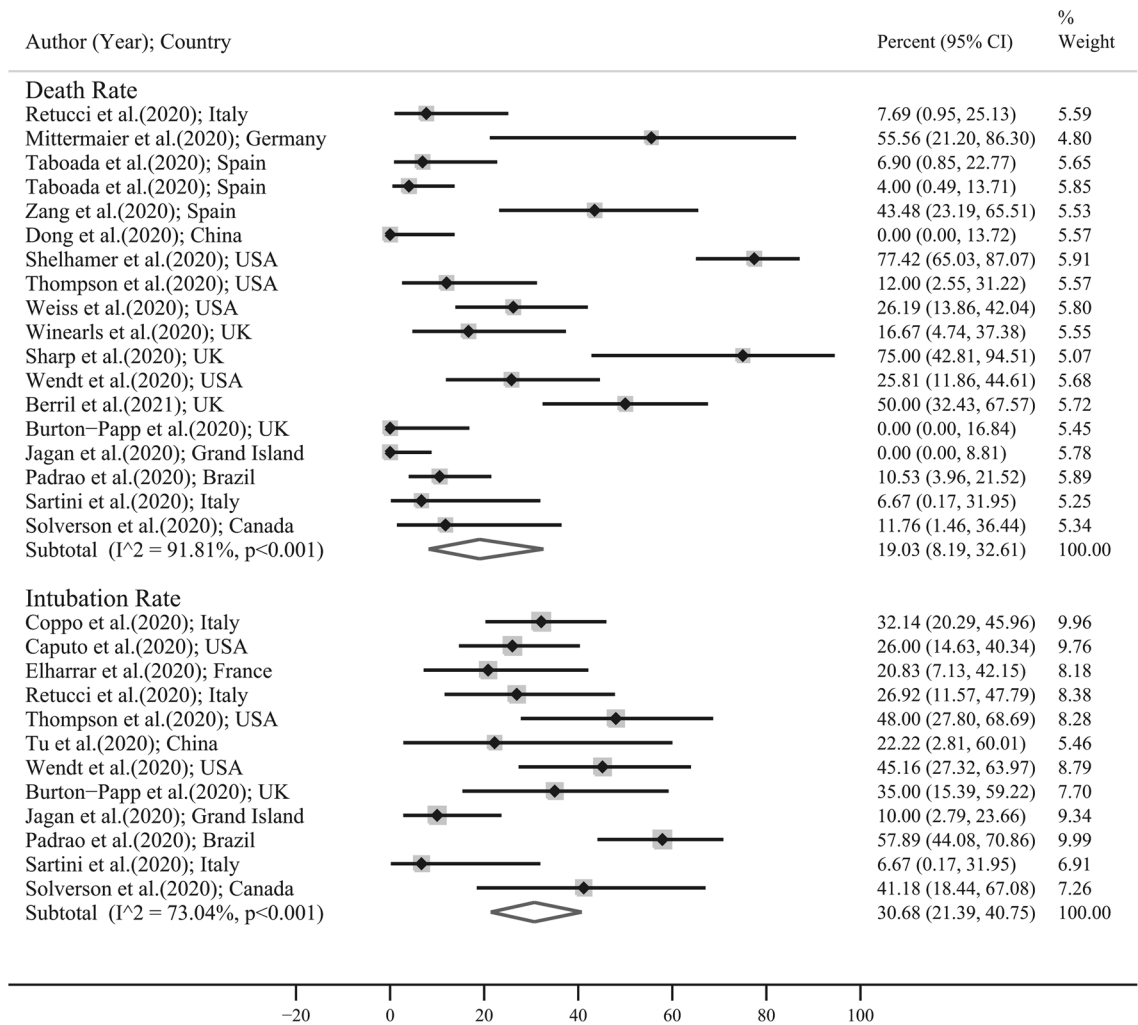


Figure 4. Forest plot for death rate and intubation rate in included studies. The diamond mark illustrates the pooled estimate and length of diamond indicates 95% confidence interval.

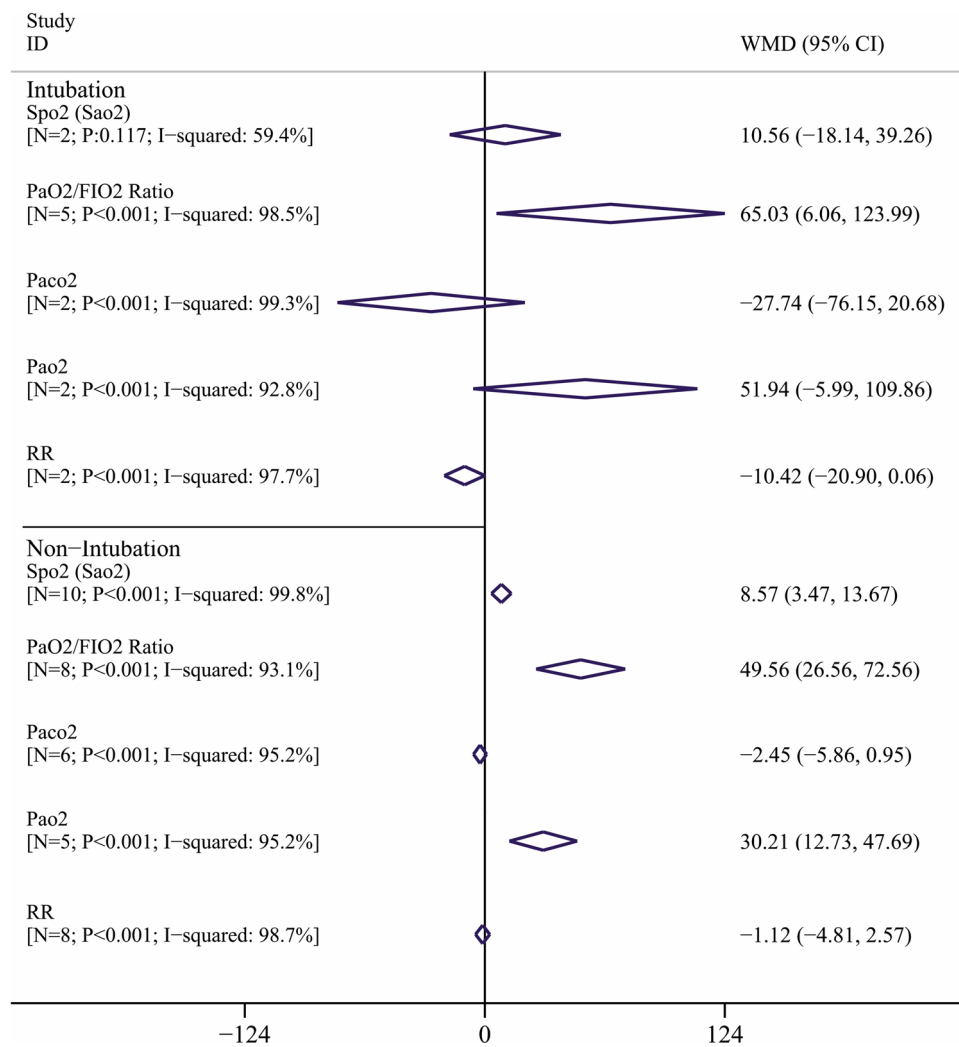


Figure 5. Pooled mean difference and 95% confidence interval of respiratory parameters based on the random effects model in different ventilation status. The diamond mark illustrates the pooled estimate.

Variables	SPO ₂ /Sao ₂ (%)	PaO ₂ /FIO ₂ ratio (mmHg)	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	RR (RPM)
Sample size					
Coefficient (95% CI)	0.04 (−0.01 to 0.14)	−0.15 (−0.79 to 0.4789)	0.05 (−0.23 to 0.33)	0.15 (−2.01 to 2.31)	0.01 (−0.11 to 0.15)
p-value	0.091	0.583	0.697	0.821	0.701
Study design					
Coefficient (95% CI)	12.80 (7.78 to 17.81)	−1.22 (−76.96 to 74.52)	−15.71 (−46.37 to 14.94)	8.80 (−62.74 to 80.34)	2.12 (−8.80 to 13.03)
p-value	<0.001	0.972	0.256	0.765	0.667
BMI					
Coefficient (95% CI)	−0.91 (−5.66 to 3.83)	−1.11 (−32.82 to 30.59)	0.34 (−22.74 to 23.43)	−10.24 (−50.94 to 30.47)	−1.37 (−55.51 to 52.76)
p-value	0.941	0.927	0.955	0.193	0.802
Age					
Coefficient (95% CI)	−0.04 (−1.35 to 1.26)	0.77 (−11.46 to 13.01)	0.05 (−2.97 to 3.07)	−1.69 (−6.90 to 3.52)	−0.39 (−1.42 to 2.20)
p-value	0.941	0.889	0.969	0.443	0.626
PP duration					
Coefficient (95% CI)	−0.08 (−1.22 to 1.05)	1.50 (−4.36 to 7.36)	−1.28 (−3.94 to 1.38)	1.40 (−4.94 to 7.73)	−0.70 (−1.52 to 0.13)
p-value	0.875	0.582	0.271	0.574	0.089

Table 4. Results of the univariate meta-regression analysis on the heterogeneity of the determinants. *CI* confidence interval, *mmHg* millimeter of mercury, *PMD* pooled mean difference, *PaO₂* partial arterial oxygen, *FIO₂* fractional inspiratory oxygen, *Sao₂* oxygen saturation (arterial blood), *RR* respiratory rate, *RPM* respiration per minute, *Study design* before–after design = 1; quasi-experimental design = 2.

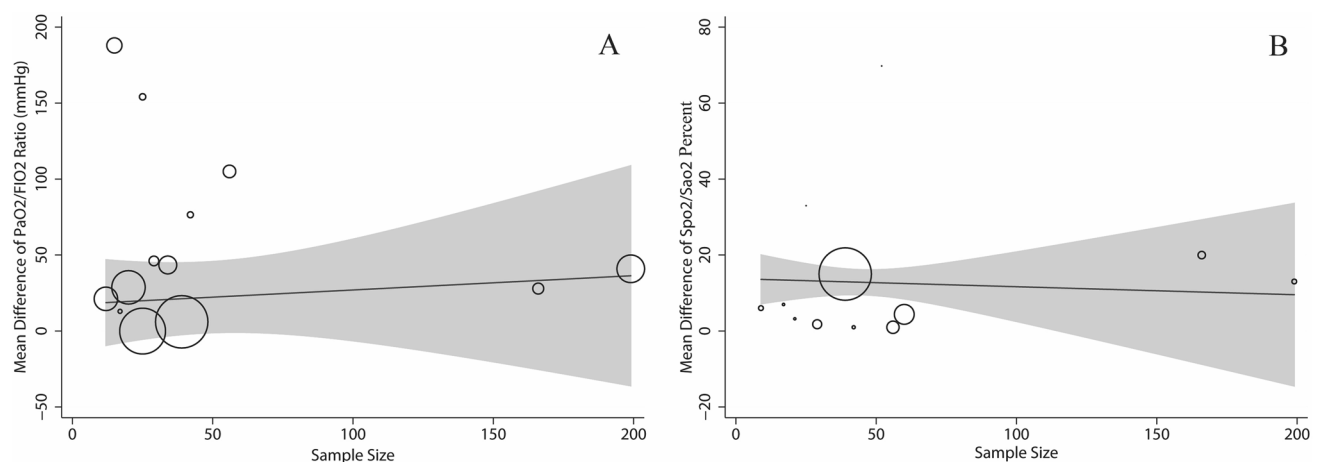


Figure 6. Association between sample size with mean difference (MD) of PaO₂/FIO₂ Ratio (mmHg) (A) and Spo₂ (Sao₂) (B) using meta-regression. Size of the circles indicates sample magnitude. There was no significant association between sample size with MD of PaO₂/FIO₂ Ratio and Spo₂ (Sao₂).

Received: 5 March 2021; Accepted: 29 June 2021

Published online: 13 July 2021

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Acknowledgements

We appreciate the reviewers comment.

Author contributions

F.B. and F.A. conceived the study, interpreted the data, drafted the manuscript and approved the final version of the paper. R.P. critically analyzed the data. M.G.H., F.Z., N.M. interpreted the data.

Funding

This study has no funding.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-021-93739-y>.

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