Submitted: 15 June, 2022 Accepted: 03 August, 2022 Published: 08 July, 2023 DOI:10.22514/sv.2023.041

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SYSTEMATIC REVIEW

Prone positioning in awake COVID-19 patients: a systematic review and meta-analysis

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Abstract

Prone positioning is a well-established treatment in mechanically ventilated patients with acute respiratory distress syndrome. Although recommended by guidelines, limited evidence exists on the benefits of prone positioning in awake Corona Virus Disease 2019 (COVID-19) patients. Aim of our systematic review was to provide an overview of all published evidence on this intervention in the setting of COVID-19. Moreover, we aimed to investigate feasibility, efficacy and safety of awake prone positioning in COVID-19 patients with acute respiratory failure. Inclusion criteria were: adult hospitalized, awake, COVID-19 patients, lying in the prone position for respiratory failure. All kind of studies were included without language restriction. Eighty manuscripts involving 3226 patients were included. Need for mechanical ventilation was reported in 26.8% of patients. No periprocedural death or severe adverse events were reported. During prone positioning, a significant improvement in peripheral capillary oxygen saturation (SpO_2) and ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) was obtained, together with a reduction in respiratory rate. These improvements persisted after resupination. Awake prone positioning in non-intubated COVID-19 patients is safe and improves oxygenation both during and after the end of proning cycles. Large, high-quality, randomized clinical trials are warranted to determine the impact of prone positioning on survival.

Keywords

Prone positioning; Systematic review; COVID-19; SARS-CoV-2; Meta-analysis

1. Introduction

Prone positioning is a well-established, evidence-based treatment in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) [1]. Studies performed in mechanically ventilated patients with ARDS from different causes showed that early application of prone positioning was associated with improvement in gas exchanges and clinically relevant outcomes [2, 3]. From a physiological point of view, prone positioning reduces regional differences in alveolar inflation, ventilation distribution and pleural pressure gradient, thus improving respiratory mechanics and oxygenation [4].

Scarce evidence exists in awake patients undergoing prone non-invasive mechanical ventilations or conventional oxygen therapy. Although recommended in recent guidelines by the UK Intensive Care Society and international health care professionals [5, 6], little evidence exists on the benefits of prone positioning in awake coronavirus disease of 2019 (COVID-19) patients. COVID-19 patients are a large and not uniform population and might particularly benefit from this inexpensive intervention which might reduce the need for mechanical ventilation. This is especially true in limited resources settings or during pandemic outbreaks.

In spite of the limited available evidence-based medicine, since a high number of COVID-19 patients with respiratory failure required to be treated outside the intensive care unit (ICU), the use of prone position in awake, spontaneously breathing patients spread around the world with promising result [7, 8].

We decided to perform a systematic review and meta-analysis of all published studies on awake proning in COVID-19 patients in order to give the reader an overview of all the published evidence on this intervention in the setting of COVID-19. Moreover, we investigated feasibility, efficacy and safety of awake proning in COVID-19 patients with ARDS.

2. Methods

2.1 Search strategy

Electronic searches in Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTri-

als.gov used different keywords and vocabulary terms (*i.e.*, medical sub-heading (MeSH) terms, EMTREE terms). Keywords included both patient-related terms (acute respiratory distress syndrome, COVID-19, SARS-Cov-2), and treatment-related terms (pronation; prone positioning) (Supplementary Material). In addition, hand searches of the reference lists of suitable studies and review articles were conducted. No restrictions on language were applied.

2.2 Study selection and inclusion criteria

All references derived from database and literature searches were individually examined at title and abstract level by two investigators and different opinions were managed by consensus or by adjudication of a third author. If suitable, full text papers were studied. The following inclusion criteria were used: hospitalized awake COVID-19 patients; $\geq$18 years old; with or without sedation; lying in the prone position for respiratory failure. Exclusion criteria were: duplicate publications (in this case we included the paper reporting the longest follow-up or the largest cohort); pediatric patients; studies with overlapping cohorts; no COVID-19 patients; patients intubated before pronation; out-of-hospital setting; case reports; studies not reporting outcomes of interest.

2.3 Data abstraction

Study details, baseline patients' clinical characteristics, and outcomes were collected by three investigators. If important data were missing, at least two attempts were conducted to contact the corresponding authors (*e.g.*, by email). The primary endpoint of our study was intubation rate. Differences in peripheral arterial oxygen saturation (SpO_2), the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and respiratory rate before/during and before/after pronation were also analyzed together with the occurrence of side effects.

2.4 Data analysis and synthesis

Categorical data were presented as absolute numbers and percentage. Continuous measurements were presented as means and standard deviations. When required, medians (interquartile ranges) were converted in means using the Wan's method [9].

Before/during and before/after pronation variations in gas exchange, respiratory rate and oxygen saturation were analysed with Review Manager (RevMan) (Computer program), version 5.4, The Cochrane Collaboration, 2020 using the generic inverse variance method. Mean differences (MD) and 95% confidence interval (CI) were calculated. The Cochrane Q test was used to measure statistical heterogeneity and the level of statistical significance was set at 0.10 (for a two-tailed test). I^2 was used to calculate statistical consistency, considering the formula: $I^2 = 100\% \times$ (Cochran's Q, heterogeneity statistic—degrees of freedom). If statistical inconsistency was low ($I^2 < 25\%$) a fixed effect model was used. Otherwise, we chose a random-effect model. Moreover, in case of high heterogeneity, subgroup analyses according to the type of study design were performed.

Unadjusted p values were reported and $p < 0.05$ were considered statistically significant. Funnel plots were used to visually assess the presence of publication bias.

The study was registered on PROSPERO (registration ID: CRD42020199858) and performed in compliance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10, 11].

3. Results

3.1 Study characteristics

Searches in different databases and snowballing identified 1309 articles. Excluding 1198 non-suitable titles or abstracts, we collected and assessed 111 papers in complete form, according to the inclusion criteria (Fig. 1). Thirty-one studies were later excluded because of the presence of exclusion criteria (Fig. 1). Therefore, 80 manuscripts involving 3226 patients were finally included. References of all included manuscripts are presented in the Supplementary Material. Median (range) age of studies population was 58 (21–75) years and 73.5% of patients were male.

Characteristics of included manuscripts are presented in **Supplementary Table 1**. Clinical heterogeneity was mainly ascribable to inclusion criteria and respiratory support during proning (**Supplementary Table 1**).

3.2 Qualitative and quantitative data synthesis

Need for mechanical ventilation was reported in 725/2704 (27%) patients. No death or severe adverse events were reported during pronation. Few authors reported mild adverse events related to prone positioning, in particular back pain, emesis, discomfort and anxiety (**Supplementary Table 1**). Mortality was reported in 550/3078 (18%).

During prone positioning, a statistically significant improvement in SpO_2 (MD 3.07; 95% CI 4.05; 2.09; P for effect $<$0.001; I^2 90%) and PaO_2/FiO_2 (MD 66.11; 95% CI 90.39; 41.83; P for effect $<$0.001; I^2 96%) was obtained, while reducing respiratory rate (MD 2.88; 95% CI 2.11; 3.64; P for effect $<$0.001; I^2 59%) (Table 1, Fig. 2). Beneficial effects persisted after resupination (Table 1, Fig. 3). Visual inspection of funnel plots suggests the presence of small publication biases (**Supplementary material**).

Subgroup analyses including only randomized clinical trials (RCTs) were not possible because of missing data on the outcomes of interest. When performing subgroup analyses including only retrospective studies or prospective studies the high heterogeneity was confirmed.

4. Discussion

This systematic review and meta-analysis which included 80 manuscripts and 3226 COVID-19 patients who were managed with awake prone positioning showed that failure rate (need for endotracheal intubation) was 27%. Moreover, it showed that awake prone positioning was safe since no severe adverse

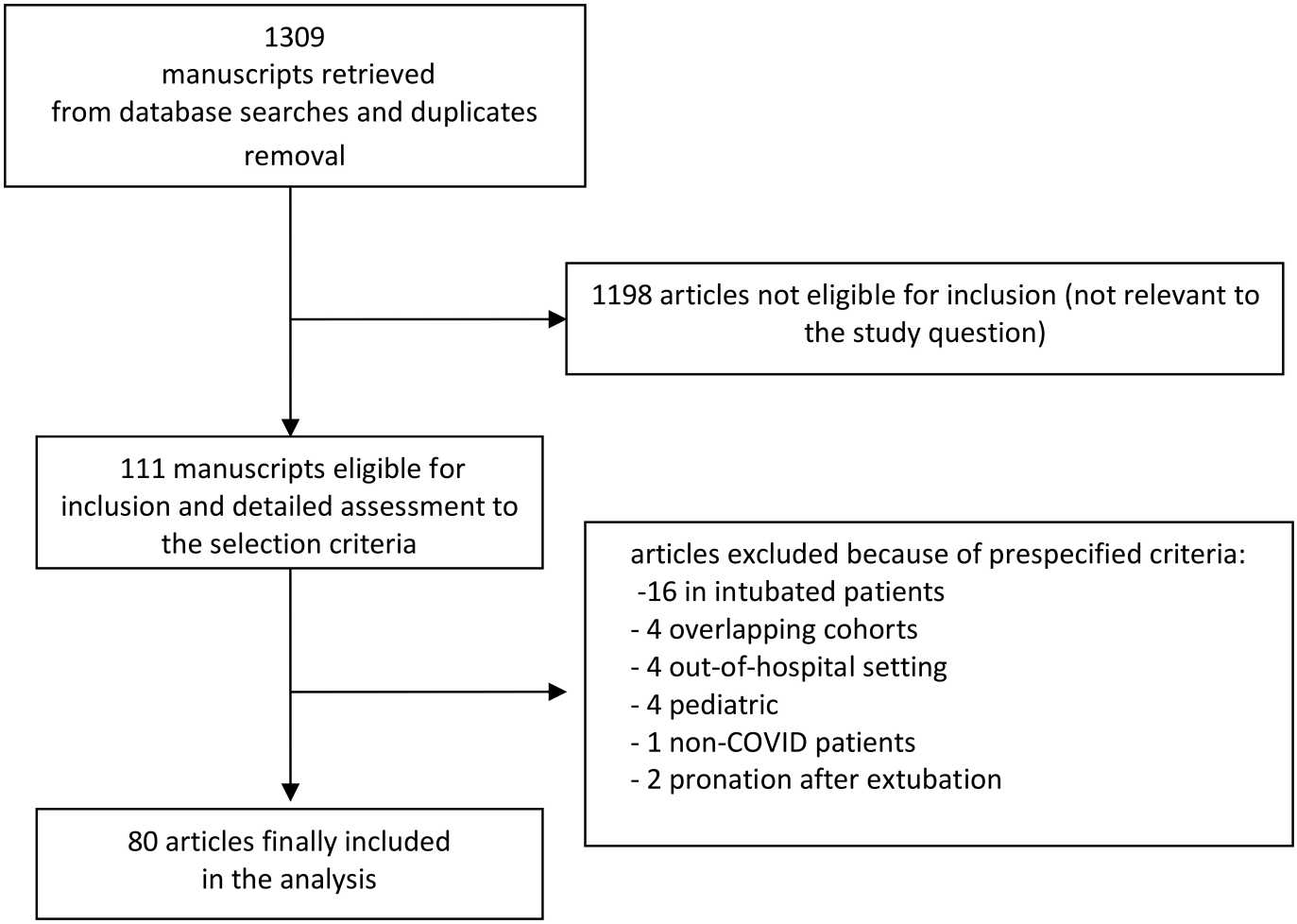


FIGURE 1. Flow-chart for manuscript selection. COVID: Corona Virus Disease 2019.

TABLE 1. Difference in respiratory parameters before and during prone positioning cycles and before and after prone positioning cycles.

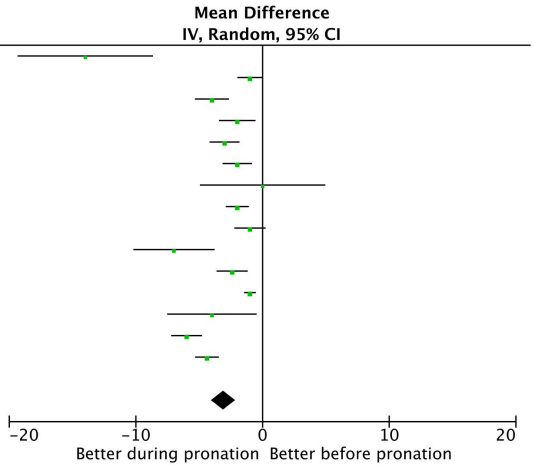
Outcome	Number of included studies	Number of included patients	MD	95% CI	P for effect	I^2 (%)
ΔSpO_2						
during pronation	15	1192	3.07	4.05, 2.09	<0.001	90
after pronation	11	636	4.85	7.12, 2.58	<0.001	96
$\Delta PaO_2/FiO_2$						
during pronation	11	671	66.11	90.39, 41.83	<0.001	96
after pronation	16	948	37.10	51.40, 22.80	0.010	82
ΔRespiratory rate						
during pronation	13	760	2.88	2.11, 3.64	<0.001	59
after pronation	11	994	2.11	0.58, 3.64	0.007	79

MD: mean difference; CI: confidence interval; P: p-value; SpO_2: peripheral arterial oxygen saturation; PaO_2/FiO_2: the ratio of arterial oxygen partial pressure to fractional inspired oxygen.

SpO_2

Study or Subgroup	During pronation Mean	SD	Total	Before pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bahloul M	82	12	21	96	3	21	2.5%	−14.00 [−19.29, −8.71]
Coppo A	97.2	2.8	56	98.2	2.2	56	8.0%	−1.00 [−1.93, −0.07]
Damarla M	94	1.48	10	98	1.48	10	7.5%	−4.00 [−5.30, −2.70]
Dubosh NM	94	2.97	22	96	1.48	22	7.4%	−2.00 [−3.39, −0.61]
Duenas-Castell C	91	5.93	212	94	5.93	212	7.7%	−3.00 [−4.13, −1.87]
Jha A	93	2	25	95	2	25	7.8%	−2.00 [−3.11, −0.89]
Kelly NL	22	9	17	22	5	17	2.7%	0.00 [−4.89, 4.89]
Padrao EMH	92	1.48	57	94	2.97	57	8.1%	−2.00 [−2.86, −1.14]
Retucci M	95	1.48	12	96	1.48	12	7.7%	−1.00 [−2.18, 0.18]
Solverson K	91	5.93	17	98	2.97	17	4.6%	−7.00 [−10.15, −3.85]
Sryma PB	92.4	2.8	30	94.8	1.7	30	7.7%	−2.40 [−3.57, −1.23]
Taboada M	94	1.48	50	95	0.01	50	8.5%	−1.00 [−1.41, −0.59]
Tatlow C	90	5	13	94	4	13	4.1%	−4.00 [−7.48, −0.52]
Wendt C	90	1.48	31	96	2.97	31	7.7%	−6.00 [−7.17, −4.83]
Zang X	91.09	1.4	23	95.48	1.65	23	8.1%	−4.39 [−5.27, −3.51]
Total (95% CI)			**596**			**596**	**100.0%**	**−3.07 [−4.05, −2.09]**

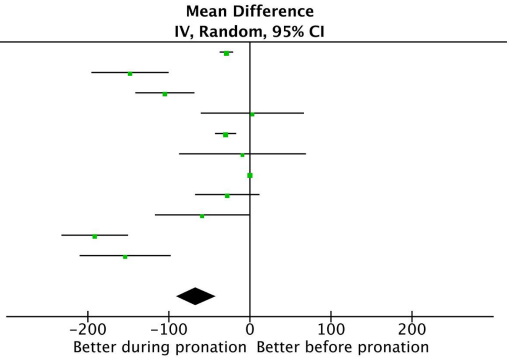
Heterogeneity: $Tau^2 = 2.89$; $Chi^2 = 146.46$, df = 14 ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 6.14$ ($P < 0.00001$)



PaO_2/FiO_2

Study or Subgroup	Before pronation Mean	SD	Total	During pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bastoni D	68	5	6	97	8	6	12.2%	−29.00 [−36.55, −21.45]
Chiumello D	166	85.99	40	314	124.54	40	8.4%	−148.00 [−194.90, −101.10]
Coppo A	180.5	76.6	56	285.5	112.9	56	9.7%	−105.00 [−140.73, −69.27]
Dubosh NM	298	80.06	22	295	81.54	9	6.7%	3.00 [−59.91, 65.91]
Fazzini B	140	30	46	170	30	46	11.9%	−30.00 [−42.26, −17.74]
Kelly NL	156.7	112.38	17	165.9	118.16	17	5.5%	−9.20 [−86.72, 68.32]
Nauka PC	95	2.97	41	95	4.45	41	12.3%	0.00 [−1.64, 1.64]
Padrao EMH	196	85.99	57	224	123.05	57	9.3%	−28.00 [−66.97, 10.97]
Retucci M	168.7	46.2	12	227.7	90.3	12	7.3%	−59.00 [−116.39, −1.61]
Simioli F	96.5	35	18	288	80	18	9.2%	−191.50 [−231.84, −151.16]
Wormser J	188.5	38.55	27	342.5	141.73	27	7.5%	−154.00 [−209.40, −98.60]
Total (95% CI)			**342**			**329**	**100.0%**	**−66.11 [−90.39, −41.83]**

Heterogeneity: $Tau^2 = 1247.59$; $Chi^2 = 262.64$, df = 10 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 5.34$ ($P < 0.00001$)



Respiratory rate

Study or Subgroup	Before pronation Mean	SD	Total	During pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bahloul M	31	10	21	21	4	21	5.7%	10.00 [5.39, 14.61]
Cherian SV	26.5	8.9	59	25	8.9	59	8.5%	1.50 [−1.71, 4.71]
Chiumello D	20	5.93	40	17	2.97	40	11.7%	3.00 [0.94, 5.06]
Coppo A	24.5	5.5	56	24.5	6.9	56	10.9%	0.00 [−2.31, 2.31]
Damarla M	31	11.86	10	22	4.45	10	2.6%	9.00 [1.15, 16.85]
Dubosh NM	26	5.93	22	25	4.45	22	8.8%	1.00 [−2.10, 4.10]
Fazzini B	35	10	46	28	5	46	8.4%	7.00 [3.77, 10.23]
Retucci M	23.5	6.3	12	21.3	5	12	5.8%	2.20 [−2.35, 6.75]
Ripoll-Gallardo A	32.15	8.89	13	29.31	8.84	13	3.2%	2.84 [−3.98, 9.66]
Solverson K	28	14.83	17	22	10.38	17	2.2%	6.00 [−2.60, 14.60]
Sryma PB	28.9	3.6	30	27.1	3.4	30	12.5%	1.80 [0.03, 3.57]
Wendt C	31	9	31	26	8	31	6.3%	5.00 [0.76, 9.24]
Zang X	28.22	3.06	23	24.87	1.84	23	13.4%	3.35 [1.89, 4.81]
Total (95% CI)			**380**			**380**	**100.0%**	**3.30 [1.92, 4.67]**

Heterogeneity: $Tau^2 = 3.10$; $Chi^2 = 29.24$, df = 12 ($P = 0.004$); $I^2 = 59\%$
Test for overall effect: $Z = 4.71$ ($P < 0.00001$)

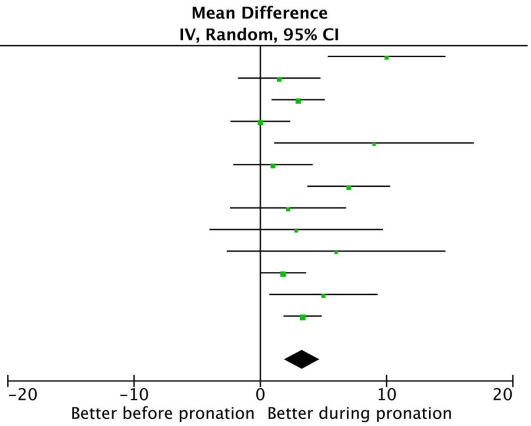
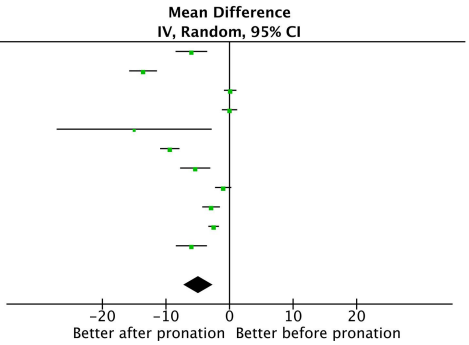


FIGURE 2. Forest plots for difference in peripheral capillary oxygen saturation (SpO_2) and ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) and respiratory rate before and during pronation. CI: confidence interval; SD: standard deviation.

SpO_2

Study or Subgroup	Before pronation Mean	SD	Total	After pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Altinay M	89	5.93	25	95	1.48	25	9.2%	−6.00 [−8.40, −3.60]
Caputo N	80.4	7.41	50	94	1.48	50	9.5%	−13.60 [−15.69, −11.51]
Coppo A	97.2	2.8	56	97.1	1.9	56	10.1%	0.10 [−0.79, 0.99]
Jha A	93	2	25	93	2	25	10.0%	0.00 [−1.11, 1.11]
Jouffroy M	60	25	40	75	30	40	2.6%	−15.00 [−27.10, −2.90]
Moghadam VD	86.5	0.7	10	95.9	2.2	10	9.9%	−9.40 [−10.83, −7.97]
Paternoster G	90.6	2.3	11	96	3.1	11	9.3%	−5.40 [−7.68, −3.12]
Retucci M	95	1.48	12	96	1.48	12	10.0%	−1.00 [−2.18, 0.18]
Sryma PB	92.4	2.8	30	95.3	2.3	30	9.9%	−2.90 [−4.20, −1.60]
Taboada M	94	1.48	50	96.5	2.22	50	10.2%	−2.50 [−3.24, −1.76]
Tu GW	90	2	9	96	3	9	9.3%	−6.00 [−8.36, −3.64]
Total (95% CI)			**318**			**318**	**100.0%**	**−4.85 [−7.12, −2.58]**

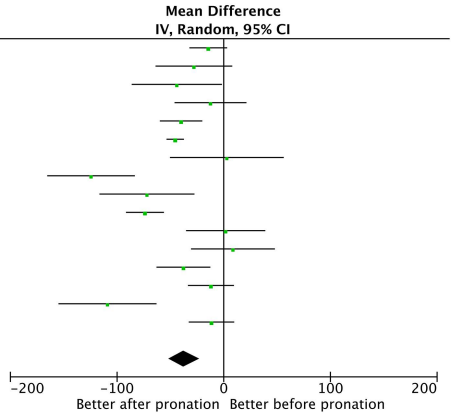
Heterogeneity: $Tau^2 = 13.02$; $Chi^2 = 281.80$, df = 10 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 4.19$ ($P < 0.0001$)



PaO_2/FiO_2

Study or Subgroup	Before pronation Mean	SD	Total	After pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Altinay M	175.7	25.95	25	190.2	35.29	25	7.8%	−14.50 [−31.67, 2.67]
Barker J	164	34	10	192	46	10	5.7%	−28.00 [−63.45, 7.45]
Cherian SV	103	129	59	147	100.82	59	5.0%	−44.00 [−85.78, −2.22]
Coppo A	180.5	76.6	56	192.9	100.9	56	6.0%	−12.40 [−45.58, 20.78]
Fazzini B	140	30	46	180	60	46	7.6%	−40.00 [−59.39, −20.61]
Hashemian SM	107.5	18	45	153	19	45	8.6%	−45.50 [−53.15, −37.85]
Jayakumar D	201.4	118.8	30	198.5	87.6	30	4.0%	2.90 [−49.92, 55.72]
Khanum I	188.7	59.7	23	313.1	79.3	23	5.2%	−124.40 [−164.97, −83.83]
Kharat A	318	34.1	10	390	62.27	10	4.8%	−72.00 [−116.00, −28.00]
Liu X	328	25.89	29	401.85	39.74	29	7.8%	−73.85 [−91.11, −56.59]
Retucci M	168.7	46.2	12	166.9	45.3	12	5.6%	1.80 [−34.81, 38.41]
Ripoll-Gallardo A	115	13.33	13	106.38	70.11	13	5.4%	8.62 [−30.17, 47.41]
Singh P	98.8	29.7	15	136.6	38.8	15	7.0%	−37.80 [−62.53, −13.07]
Taboada M	265	47.44	50	277	59.3	50	7.4%	−12.00 [−33.05, 9.05]
Winearls S	143	73	24	252	87	24	4.7%	−109.00 [−154.44, −63.56]
Wormser J	188.5	38.55	27	200	39.44	27	7.4%	−11.50 [−32.30, 9.30]
Total (95% CI)			**474**			**474**	**100.0%**	**−37.10 [−51.40, −22.80]**

Heterogeneity: $Tau^2 = 603.49$; $Chi^2 = 83.45$, df = 15 ($P < 0.00001$); $I^2 = 82\%$
Test for overall effect: $Z = 5.08$ ($P < 0.00001$)



Respiratory rate

Study or Subgroup	Before pronation Mean	SD	Total	After pronation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Coppo A	24.5	5.5	56	23.9	6.3	56	9.9%	0.60 [−1.59, 2.79]
Duenas-Castell C	25	10.38	212	23.5	4.45	212	11.1%	1.50 [−0.02, 3.02]
Elharrar X	18	2.7	24	18.5	3.1	24	10.9%	−0.50 [−2.14, 1.14]
Fazzini B	35	10	46	28	5	46	8.0%	7.00 [3.77, 10.23]
Kharat A	22	5.63	10	20	4.15	10	6.3%	2.00 [−2.33, 6.33]
Liu X	22.75	4.91	29	20.5	4.13	29	9.7%	2.25 [−0.09, 4.59]
Moghadam VD	21	2.6	10	22.1	1.7	10	10.4%	−1.10 [−3.03, 0.83]
Padrao EMH	34	5.93	57	29	4.45	57	10.4%	5.00 [3.08, 6.92]
Paternoster G	27.6	4.3	11	20.1	4.7	11	7.1%	7.50 [3.74, 11.26]
Retucci M	23.5	6.3	12	22.9	6	12	5.5%	0.60 [−4.32, 5.52]
Sryma PB	28.9	3.6	30	28.3	3.4	30	10.7%	0.60 [−1.17, 2.37]
Total (95% CI)			**497**			**497**	**100.0%**	**2.11 [0.58, 3.65]**

Heterogeneity: $Tau^2 = 4.95$; $Chi^2 = 48.48$, df = 10 ($P < 0.00001$); $I^2 = 79\%$
Test for overall effect: $Z = 2.69$ ($P = 0.007$)

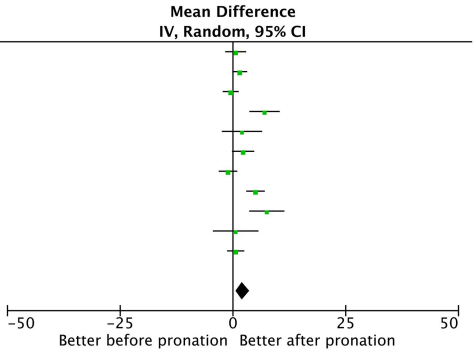


FIGURE 3. Forest plots for difference in peripheral capillary oxygen saturation (SpO_2) and ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) and respiratory rate before and after pronation. CI: confidence interval; SD: standard deviation.

events were recorded. When analyzing oxygenation variables (SpO_2, PaO_2/FiO_2 and respiratory rate) of included patients, we found that they all significantly improved during prone positioning and that this effect persisted thereafter.

In accordance with our results, previous studies showed positive effects on patients' oxygenation during proning. Ponnapa Reddy *et al.* [7], in a meta-analysis including 25 studies, showed that prone positioning, in non-intubated hypoxemic patients with COVID-19, significantly improved oxygenation. Touchon *et al.* [8] confirmed the positive effects of proning on gas exchanges during prone positioning, but the persistence after resupination remained undetermined. More recently, Fazzini *et al.* [9], in a meta-analysis including only studies with at least 20 patients, showed that prone positioning can improve oxygenation amongst non-intubated patients with ARDS when applied for at least 4 h over multiple daily cycles.

To the best of our knowledge, our meta-analysis, thanks to the high number of included studies (n = 80), is the first meta-analysis to demonstrate that improvement in oxygenation variables observed in COVID-19 patients undergoing awake prone positioning persisted after resupination. This finding is of great importance since it suggests that prone positioning does not just guarantee a transient improvement in oxygenation variables, but could be associated with clinical benefits, preventing the upgrading of required respiratory support and therefore improving patients' outcome. Nonetheless, despite

the increasingly published evidence, the role of awake prone positioning in reducing the need for endotracheal intubation in COVID-19 patients remains undetermined [9].

This study presents several limitations. First of all, most of the included studies were small, retrospective studies. Therefore, patient's selection biases cannot be excluded and a high heterogeneity was observed. In addition, considerably heterogeneity was confirmed in subgroup analysis performed according to the type of study design, probably because of the presence of high clinical variability of included patients. Nonetheless, the aim of our review was to give the reader a complete overview of published evidence on this intervention in the setting of COVID-19. Therefore, all kind of studies were included. Our findings on improved oxygenation are promising, but evidence on major clinical outcome, such as a reduction in the need for intubation or in mortality, is still lacking. Hopefully, ongoing trials will help to better clarify the role of prone positioning on clinically relevant outcomes.

In conclusion, awake prone positioning in non-intubated COVID-19 patients is safe and improves oxygenation both during and after the end of the proning cycles. Large, high-quality, randomized clinical trials with standardized intubation criteria and prone positioning practice are warranted to determine the impact of prone positioning on mortality of COVID-19 patients.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article (and supplementary material).

AUTHOR CONTRIBUTIONS

LP and GL—designed the research study, performed statistical analysis. LD, MC, SB, MM, CSRG and EB—searched for articles and collect data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni, Laura Pasin and Carolina Soledad Romero García are serving as the Editorial Board members of this journal. We declare that Giovanni Landoni, Laura Pasin and Carolina Soledad Romero García had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to ZZ.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1670686619036729344/attachment/Supplementary%20material.docx.

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How to cite this article: Pasin L, Dagna L, Consonni M, Boraso S, Munari M, Romero García CS, *et al*. Prone positioning in awake COVID-19 patients: a systematic review and meta-analysis. Signa Vitae. 2023; 19(4): 31-36. doi: 10.22514/sv.2023.041.