SYSTEMATIC REVIEW

# Awake Proning for Nonintubated Adult Hypoxic Patients with COVID-19: A Systematic Review of the Published Evidence

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## Abstract

**Objective:** Awake proning is an intervention that is being advocated for COVID-19 patients and has been suggested to improve the oxygenation, thereby decreasing oxygen requirements. We performed this systematic review with the aim of appraising the latest published evidence on the clinical effectiveness of awake proning in COVID-19 patients.

**Data sources:** PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Google Scholar, and one trial registry were searched until September 23, 2020, for studies on the use of awake proning for nonintubated COVID-19 patients.

**Study selection:** Published or in-press peer-reviewed randomized control trials, case-control trials, and prospective or retrospective cohort studies in English language only were sought, assessing the effectiveness of awake proning for nonintubated patients diagnosed with COVID-19.

**Data results:** We included 21 published studies (19 single arm and 2 with comparison group). Twenty-three registered clinical trials were identified. No randomized clinical trial has been published so far.

**Conclusions:** Awake proning is probably safe and effective in enhancing oxygenation in nonintubated COVID-19 patients; however, there is insufficient evidence. Further high-quality clinical trials are urgently needed to assess the effectiveness of awake proning on a variety of patient-centered outcomes.


**Keywords:** Awake proning, Coronavirus disease 2019, COVID-19, Intubation, Mortality, Oxygenation, Prone position.

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## Introduction

The coronavirus disease (COVID-19), which has become a pandemic, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spectrum of COVID-19 pneumonia patients stretches from asymptomatic to mild disease to hypoxemic respiratory failure to multisystem organ failure,[1] thereby putting an enormous strain on health-care delivery services globally, especially in intensive care unit (ICU) services. Continuous increase in demand for ICU beds warrants the strategies for COVID-19 pneumonia patients who are safe, effective, and practical to be utilized outside the ICU as well.

Awake proning is one such strategy for the management of patients with COVID-19 pneumonia that has been recommended in various protocols. UK Intensive Care Society (ICS) has also advocated awake proning of patients with suspected or confirmed COVID-19 infection and requiring more than 28% of the fraction of inhaled oxygen ($FiO_2$).[2] These recommendations are generalized on the basis of clinical evidence obtained from the clinical trials on patients with severe acute respiratory distress syndrome (ARDS) managed with invasive mechanical ventilation. Mechanisms proposed are the elimination of compressive constraint on the regions of the dependent lung by the weight of the heart[3] and enhanced ventilation in the regions of the lung that were originally dorsal.[4] With improvement in ventilatory homogeneity and relatively constant perfusion pattern, a reduction in intrapulmonary shunt is observed.[2,4]

Prone positioning of the patients suffering from acute hypoxemic respiratory failure has been shown to have significant mortality benefits in numerous trials.[5–7] A study has shown even more favorable physiological redistribution of ventilation and perfusion associated with proning in nonintubated patients compared to patients receiving invasive mechanical ventilation, and thus, prone positioning by circumventing invasive mechanical ventilation and complications associated with it may prove favorable in even awake patients with hypoxemic respiratory failure.[8]

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**Authorship statement:** Dr Samiksha Parashar (SP) conceived the study, Dr Karthik AR (KA), and Dr Ravi Gupta (RG) contributed to the design and protocol. SP and KA searched the databases. SP, KA, and RG screened the studies. SP wrote the first draft of the manuscript, and KA, RG, and Dr Deepak Malviya (DM) contributed substantially to its revision. All authors approved the final version of the manuscript.

However, the use of awake proning in nonintubated patients is a new area of research, and the literature is scarce, especially from the perspective of incomplete knowledge of COVID-19 physiology. Awake proning of nonintubated patients could prove to be a promising treatment strategy in patients with COVID-19. The purpose of this review is to systemically appraise and summarize the available literature regarding the role of awake proning in the management of COVID-19 novel coronavirus pneumonia.

## Materials and Methods

The review was registered prospectively with PROSPERO (International Prospective Register of Systematic Reviews) and available under the identifier #CRD42020199034 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020199034). The preferred reporting items for systematic reviews and meta-analyses (PRISMA guidelines) were adopted while conducting this review.[9] No ethical committee approval was required.

The research question was: In patients with confirmed COVID-19, is awake proning of patients in addition to other standards of care effective in improving clinical outcome?

PICO Question

Population (P): Adult patients with confirmed COVID-19 requiring oxygen therapy.

Intervention (I): Awake proning

Comparison (C): Other standards of care.

Outcomes (O): Clinical improvement of COVID-19 patients.

The predetermined primary outcome was the clinical improvement rate (in terms of improved oxygenation) in nonintubated patients with COVID-19 pneumonia undergoing awake proning. Other outcomes were need for mechanical ventilation, death rate, and length of hospital stay.

### Search Strategy and Inclusion Criteria

We carried out a systematic literature search following electronic databases: PubMed, EMBASE, Web of Science, Cochrane Library (Central Register of Controlled Trials), and Google Scholar from December 31, 2019 (first report of COVID-19) to September 23, 2020, using free-text terms, keywords, and controlled vocabulary terms [i.e., medical subheading (MeSH) terms]. Keywords were translated into a controlled vocabulary for the individual database (Appendix 1).

In addition, we conducted the search for ongoing trials using the U.S. National Library of Medicine Register of Clinical Trials (ClinicalTrials.gov). The last search was performed on September 23, 2020. Reference lists of the included papers were also explored for additional potentially relevant studies. We did not attempt to identify any grey literature.

Studies published in English language only were looked at during the search strategy and were included.

We sought to include published or in press peer-reviewed randomized control trials, case-control trials, and prospective or retrospective cohort studies assessing the effectiveness of awake proning for nonintubated patients diagnosed with COVID-19. Patients with confirmed COVID-19 as detected by real-time reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal or oropharyngeal samples were included. Doubtful cases of COVID-19 without positive RT-PCR, intubated patients, or patients in need of impending intubation were excluded from the study. Furthermore, studies on animals, pregnant women, and children with COVID-19 were also excluded. The control group included patients treated with other standards of care.

After removing the duplicates, screening of titles and abstracts were carried out in a spreadsheet. All articles were screened by two authors independently (S.P. and K.A.) to identify the relevant studies based on prespecified inclusion criteria. Of those articles selected by at least one of the reviewers, each of the reviewer (S.P., K.A., and R.G.) independently applied an inclusion and exclusion criteria checklist to decide if the study meets our selection criteria. Disagreements were resolved by discussion between the reviewers, with a fourth person (D.M.) available if consensus cannot be reached.

### Data Extraction and Risk of Bias Assessment

Reviewers team developed a standardized data abstraction form, pilot tested it, and then used a piloted form to independently extract the following information from an individual study: Year of publication, country of origin, study design, sample size, inclusion or exclusion criteria, COVID-19 confirmation, intervention, follow-up duration, and outcome data.

Risk of bias of the included studies was evaluated by two of the reviewers (S.P. and K.A.) independently. Any difference in opinion was resolved by consensus or, if necessary, by discussion with the third (D.M.) reviewer.

The methodological quality of the included studies was assessed by Newcastle-Ottawa scale (NOS) (Appendix 2). The NOS is a nine-point scale that assesses patient selection (four points), comparability of cohorts (two points), and the ascertainment of outcomes (three points).[10,11]

## Results

### Search Results and Study Characteristics

A PRISMA flow diagram is represented in Figure 1. Initial database search found 1707 articles, including 557 duplicates, leaving 1150 to be screened. After exclusion by title and abstract of 988 articles, 162 full-text articles were reviewed, of which 21 studies[12–32] were included in this review. Reviewers reached a complete agreement regarding the inclusion of all studies. In addition, 23 registered clinical trials were retrieved from the trial registries. Characteristics of these clinical trials are tabulated in Appendix 3.

Out of 21 included studies, 5 were from Italy,[17–20,29] 3 each from China[12,13,27] and Spain,[24–26] 2 each from France,[14,28] Iran,[15,16] New York,[21,22] United Kingdom,[31,32] and 1 each from Singapore[23] and Maryland.[30] All included studies were done in different hospitals and universities except two studies reported from the same hospital and also done during the overlapping time period,[25,26] thereby causing duplicate analysis of the same cohort.

The study design included 14 prospective cohort studies,[13–26] 6 retrospective cohort studies,[27–32] and one pilot study.[12] Included studies had varying durations of follow-up, mostly following till discharge from hospital[15,18,22,25,27,29,30,32] or ICU.[20,24] Six studies had no mention of follow-up duration.[12,16,19,21,28,31] All studies were single arm without any control group except two studies that had a control group and an intervention group.[13,24] Prone positioning was the intervention in all studies except one study that reported outcomes for two interventions, prone position and lateral position.[19] Duration of participant recruitment in these studies was from February 1, 2020 to June 9, 2020.

Outcome data for a total of 698 patients admitted to mainly non-ICU settings were reported in these studies. The median (IQR) number of patients was 24 (49-10). All included patients

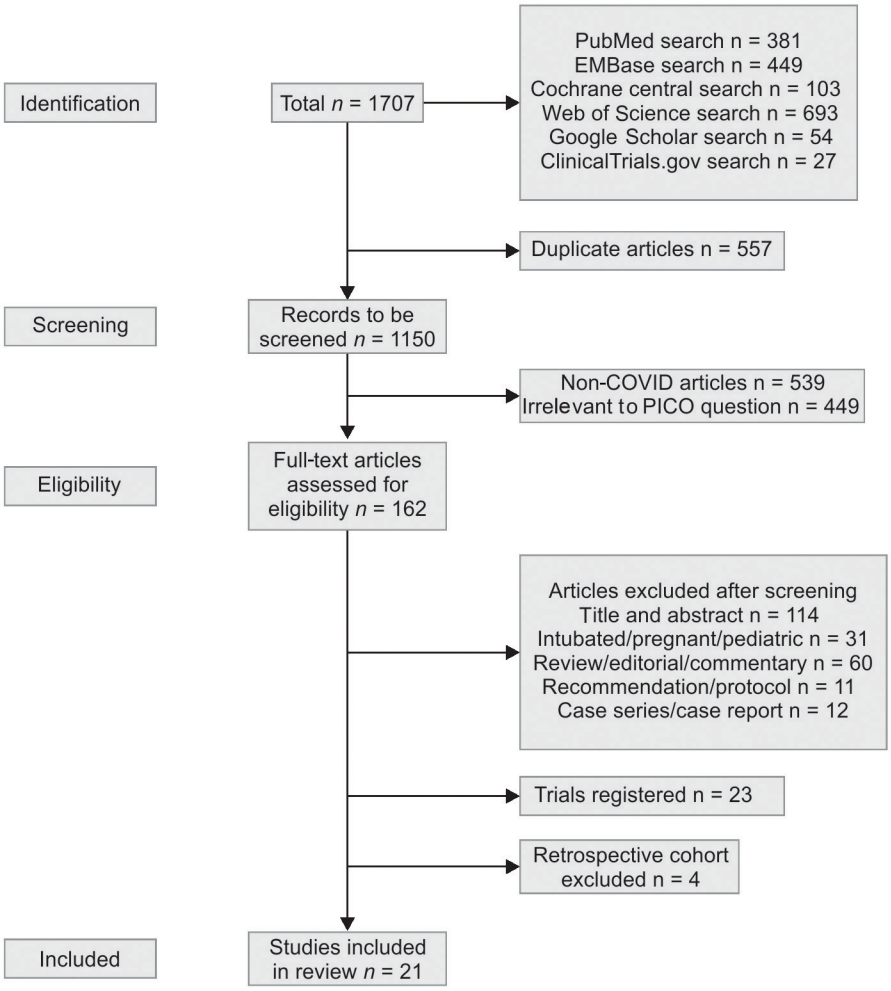


**Fig. 1:** PRISMA flowchart of included and excluded studies. PRISMA: preferred reporting items for systematic reviews and meta-analyses, n: number of articles

were adults and had laboratory-confirmed diagnosis of COVID-19. All patients were presented with hypoxia requiring supplemental oxygen by nasal prongs or face mask or high-flow nasal oxygen (HFNO) or noninvasive ventilation strategy. The intervention in each study was prone positioning of the patient, while the patient being still awake (except one study where morphine infusion was given for sedation).[20] The duration of proning session varied between studies from 1 hour to 8 hours/day, mostly without change in inspired oxygen concentration. Table 1 represents the baseline characteristics of the included studies. The time point for oxygenation status measurement ranged from 5 minutes to 1 hour after proning.

Parameter reported for assessing clinical improvement varied between studies and was oxyhemoglobin saturation of the peripheral blood ($SpO_2$),[12,13,15–17,21,22,25,26,30,31] ROX index (ROX index = $SpO_2/FiO_2 \times 1$/respiratory rate),[13,31] partial pressure of oxygen in arterial blood ($PaO_2$),[14] partial pressure of oxygen in arterial blood-fraction of inhaled oxygen ($PaO_2$:$FiO_2$),[17,18,20,25,27–29,31] alveolar to arterial oxygen gradient (A-$aO_2$),[19] and oxyhemoglobin saturation of peripheral blood-fraction of inhaled oxygen ($SpO_2/FiO_2$).[26] Oxygenation improvement was not assessed in three studies.[23,24,32]

A total of 495 patients underwent awake proning across included studies. Out of 495, 139 (27.1%) patients needed intubation and mechanical ventilation. Mortality rate was assessed in 18 studies. Fifty-five (13.3%) patients died among the four hundred and fourteen patients who were assessed for this outcome. Important findings of this review are summarized in Table 2.

### Risk of Bias Assessment

The median NOS quality score for risk of bias was 3/9, with 11 studies scoring below 4 (Table 3). Quality of studies was lowered by the lack of control group in majority of the studies.

## Discussion

This is the first systematic review assessing the outcomes of nonintubated COVID-19 patients undergoing awake proning. This review summarizes the clinical evidence available to date in the form of 21 studies. The cohort studies included in this review indicate a positive impression of awake proning on oxygenation status of the patients. The intubation rate was 27.1%, and the mortality rate assessed was 13.3%.

Outcome indicator chosen for improvement in oxygenation pre- and postintervention of prone positioning of patient varied among different studies. Most consistently reported parameter was an improvement in values of $SpO_2$ (and in some studies usually the only measurement that was actually

**Table 1:** Baseline characteristics of included studies

| *Author* | *Year of publication* | *Study type (country)* | *Patient (sample size)* | *Inclusion criteria* | *Exclusion criteria* | *Intervention* | *Comparison* | *Follow-up* | *Outcome* | *Main finding* |
|---|---|---|---|---|---|---|---|---|---|---|
| Tu et al. | 2020 | Pilot study (China) | Confirmed COVID-19 (9) | COVID-19 on HFNC for >2 days, and $PaO_2/FiO_2$ <150 mm Hg | Not mentioned | Prone positioning applied with a median of 5 (IQR: 3–8) procedures per subject (twice daily). The median duration of 2 (IQR:1–4) hr | Not mentioned | Not mentioned | Not mentioned | 1. Mean $SpO_2$ increased from 90% ± 2% to 96% ± 3% ($P < 0.001$), and the mean $PaO_2$ increased from 69 ± 10 to 108 ± 14 mm Hg ($p < 0.001$).<br>2. Two patients intubated: 1 extubated after 8 days, and other received venovenous extracorporeal membrane |
| Zang et al. | 2020 | Prospective cohort study (China) | COVID-19 diagnosed by nucleic acid detection (60) | 1. COVID-19 pneumonia<br>2. Severe hypoxia requiring oxygen, and whose $SpO_2$ can be maintained ≥90%<br>3. Ability to move independently<br>4. 18–80 years<br>5. Informed consent | 1. Contraindication to PP<br>2. Unstable hemodynamics or other organ failure<br>3. No hope of survival/deep coma/ no response to treatment within 3 hr | Prone position group (23) advised to spend 1–2 hr each in PP, 3–4 times/day for 5 consecutive days | Nonprone position group[37] | 90 days | 1. $SpO_2$<br>2. Respiratory rate<br>3. ROX index<br>4. CT scan-Chest<br>5. Outcome<br>6. Pressure sore<br>7. Emesis | 1. In PP group, $SpO_2$ increased from 91.09 ± 1.54% to 95.30 ± 1.72% ($p < 0.01$) after 10 min, 95.48 ± 1.73% after 30 min ($p < 0.01$), but no significant difference after 30 min compared with 10 min ($p = 0.58$)<br>2. The RR decreased from 28.22 ± 3.06/min to 27.78 ± 2.75/min after 10 min ($p = 0.20$), 24.87 ± 1.84/min after 30 min ($p < 0.01$), but no significant difference after 10 min compared with the baseline value ($p = 0.203$).<br>3. ROX index increased from 3.35 ± 0.46 after 10 min to 3.55 ± 0.47 ($p < 0.01$), 3.96 ± 0.45 after 30 min ($p < 0.01$). No significant difference in $SpO_2$, RR, and ROX index in nonprone position group.<br>4. Early PP can improve CT imaging performance.<br>5. 10 patients died in PP group and 28 patients in nonprone position group |
| Elharrar et al. | 2020 | Prospective cohort study (France) | Confirmed COVID-19 (24) | 1. Awake, nonintubated, spontaneously breathing<br>2. Hypoxemic acute respiratory failure requiring oxygen. | 1. Acute respiratory failure requiring intubation<br>2. Impaired consciousness | Not mentioned | No comparison group | 10 days | 1. Proportion of responders ($PaO_2$ increase ≥20% with PP)<br>2. $PaO_2$ and $PaCO_2$ variation<br>3. Feasibility (proportion of patients sustaining PP ≥1 hr and ≥3 hr)<br>4. Proportion of persistent responders ($PaO_2$ increase ≥20% between before PP and after resupination) | 1. 25% (95% CI,12%–45%) of responders<br>2. $PaO_2$ increased from a mean of 73.6 (SD, 15.9) mm Hg before PP to 94.9 (SD, 28.3) mm Hg during PP [difference, 21.3 (95%CI,6.3–36.3) mm Hg; $p = 0.006$]. No significant difference between $PaO_2$ before PP and $PaO_2$ after resupination ($p = 0.53$)<br>3. 40% (6/15) (95% CI, 20%–64%) of the responders who sustained PP for 3 hr or more<br>4. 3 patients persistent responders |
| Moghadam et al. | 2020 | Prospective cohort study (Iran) | Confirmed COVID-19 (10) | COVID-19 | 1. Tracheal intubation/mechanical ventilation. | Not mentioned | No comparison group | Till discharge | 1. $SpO_2$<br>2. Mean hospitalization duration | 1. Mean $SpO_2$% 85.6% and 95.9% before and after PP<br>2. All patients discharged. Mean hospitalization duration 4.8 days and no deaths |
| Golestani-Eraghi et al. | 2020 | Prospective cohort study (Iran) | COVID-19 (10) | 1. $PaO_2/FiO_2 < 150$, and awake<br>2. Nonagitated | Not mentioned | PP till they felt comfort; otherwise turned to supine position for almost 2 hr and thereafter procedure repeated | No comparison group | Not mentioned | 1. Oxygenation | 1. Oxygenation before and after PP was 46.34 ± 5.23 and 62.54 ± 4.57, respectively.<br>2. Sustained improvement in $SpO_2$ after 1 hr is 60%<br>3. Intubated 20% |

(*Contd...*)

| *Author* | *Year of publication* | *Study type (country)* | *Patient (sample size)* | *Inclusion criteria* | *Exclusion criteria* | *Intervention* | *Comparison* | *Follow-up* | *Outcome* | *Main finding* |
|---|---|---|---|---|---|---|---|---|---|---|
| Sartini et al. | 2020 | Prospective cohort study (Italy) | COVID-19 (15) | Hypoxemia ($SpO_2$ <94%), $FiO_2$ >0.6 and CPAP 10 cm $H_2O$ | Not mentioned | Not mentioned | No comparison group | 14 days | 1. $SpO_2$<br>2. $PaO_2$:$FIO_2$<br>3. RR and patient's comfort | 1. $SpO_2$; $p < 0.001$ between before and during pronation and $p < 0.004$ between before and after pronation<br>2. $PaO_2$:$FIO_2$; $p < 0.001$ between before and during pronation and $p < 0.004$ between before and after pronation<br>3. RR; $p < 0.001$ between before and during pronation and $p < 0.001$ between before and after pronation. Nine patients discharged, one improved and stopped pronation, three continued pronation, one intubated, and one died |
| Coppo et al. | 2020 | Prospective cohort study (Italy) | COVID-19 diagnosed by RT-PCR using a nasal swab (56) | 1. 18–75 years<br>2. COVID-19 pneumonia<br>3. On oxygen or noninvasive CPAP | 1. Pregnant, uncollaborative or altered mental status<br>2. NYHA <II/ increased pro-BNP<br>3. COPD requiring NIV or $O_2$ at home<br>4. Impending intubation | Assisted prone positioning, encouraged to maintain for at least 3 hr, repeat up to 8 hr/day | No comparison group | Till hospital discharge | 1. Change in $PaO_2$/$FiO_2$<br>2. Safety and feasibility of prone positioning (for 3hrs)<br>3. Effect on $PaCO_2$ and dyspnea<br>4. Predictors of response to the prone position (i.e., differences between responders and nonresponders). Responders were patients with an increased $PaO_2$/$FiO_2$<br>5. Incidence and time to tracheal intubation | 1. $PaO_2$/$FiO_2$ difference (from supine to prone) of 104·9 mm Hg (95% CI 70.9–134.0)<br>2. Proning did not significantly decrease accessory muscle use [proning vs resupination difference–8.7% (95% CI –22.7 to 5.2)] or dyspnea [difference–10.8% (–23.8 to 2.1)]<br>3. No difference observed in $PaCO_2$ or respiratory rate at any time point<br>4. Improvement in oxygenation maintained in 23 [50% (95% CI 34.9–65.1)] responders<br>5. Proning done significantly earlier in responders than nonresponders [2.7 days (SD 2.1) vs 4.6 days [3.7] from hospital admission; difference of 1.9 days (95% CI 0.1–3.7)]. Incidence of intubation not significant between responders and nonresponders [7 (30%) vs 6 (26%); $p = 0.74$] |
| Retucci et al. | 2020 | Prospective cohort study (Italy) | Laboratory-confirmed COVID-19 pneumonia (26) | 1. >18 years with hARF receiving helmet CPAP<br>2. Glasgow coma scale of 15 with spontaneous breathing and not intubated | 1. Need for immediate intubation<br>2. Glasgow coma scale <15<br>3. SBP <90 mm Hg<br>4. $SpO_2$ <90% at $FIO_2 > 0.8$ | Either prone or lateral positioning according to standard operating procedures for 1 hr | No comparison group | Not mentioned | Success of the prone/lateral positioning trial, defined as:<br>1. A decrease in the alveolar–arterial gradient ($A\text{-}aO_2$) of at least 20%<br>2. Equal or reduced respiratory rate<br>3. Equal or reduced dyspnea<br>4. SBP>90 mm Hg | Among trials conducted in prone positioning (total 12), 33.3% succeeded; 41.7% showed a decreased $A\text{-}aO_2$ (<20%), whereas 25% failed.<br>7 of 26 patients (26.9%) intubated; two patients (7.7%) died |
| Bastoni et al. | 2020 | Prospective cohort study (Italy) | Positive nasopharyngeal swab for COVID-19 (10) | 1. Receiving helmet NIV CPAP without sufficient improvement in arterial gas exchange<br>2. Awake and collaborative | 1. Need for rapid intubation<br>2. End-stage comorbid disease | Nurse assisted PP; morphine infusion for sedation | No comparison group | Till discharge | 1. $PaO_2$:$FiO_2$<br>2. Intubation rate | 1. Improvement in $PaO_2FiO_2$ ratio for all patients (median 97 ± 8 mm Hg)<br>2. 40% did not tolerate PP or refused. Rest all 6 patients intubated. Four deaths (40%) |

| Author | Year of publication | Study type (country) | Patient (sample size) | Inclusion criteria | Exclusion criteria | Intervention | Comparison | Follow-up | Outcome | Main finding |
|---|---|---|---|---|---|---|---|---|---|---|
| Caputo et al. | 2020 | Prospective cohort study (New York city) | SARS-CoV-2 infection, confirmed by RT-PCR (50) | 1. Age ≥18 years with $SpO_2$ <90% or $SpO_2$ >93% with oxygen<br>2. Patients able to self-proning | 1. DNR/DNI code status/cardiac arrest<br>2. On NIV intubated | Self-prone/change position | No comparison group | No mention | 1. Change in $SpO_2$<br>2. Rate of intubation within 24 hr | 1. Median $SpO_2$ improves from 80% (IQR 69–85) to 84% (IQR 75–90) with $O_2$. After 5 min of proning, median $SpO_2$ increased to 94% (IQR 90–95) ($p = 0.001$)<br>2. Thirteen patients (24%, 95% CI 14.6–40.3%) intubated for 24 hr and 5 later |
| Thompson et al. | 2020 | Prospective cohort study (New York) | Laboratory-confirmed COVID-19 (29) | COVID-19 with severe hypoxemic respiratory failure (RR ≥30 breaths/min and $SpO_2$ ≤93% on oxygen) | Altered mental status, inability to turn in bed without assistance, requiring immediate intubation, or oxygen requirements less than those specified in the inclusion criteria | Asked to lie on their stomach for as long as tolerated, up to 24 hr daily | No comparison group | Till discharge/death | 1. Change in $SpO_2$<br>2. Mean risk difference in intubation rates between $SpO_2$ ≥95% vs $SpO_2$ <95% 1 hr after P.P. | 1. Improvement in $SpO_2$ from 1% to 34% [median (SE), 7% [1.2%]; 95% CI, 4.6%–9.4%]<br>2. The mean difference in the intubation rate was 46% (95% CI, 10%–88%)<br>3. Among 12 patients who required intubation, three died. Among 13 patients who did not require intubation, 9 discharged, 2 transferred to ward, and 2 remained in step-down unit |
| Ng et al. | 2020 | Prospective cohort study (Singapore) | COVID-19 pneumonia (10) | COVID-19 pneumonia on oxygen | 1. Drowsy/uncooperative<br>2. Ophthalmic, cervical, or abdominal pathologies (including pregnancy)<br>3. Hemodynamically unstable or required oxygen ≥$FiO_2$ 50% | PP for 1 hr each session, five sessions/day, each spaced 3 hr apart during awake hours | No comparison group | Till patient is weaned to room air for at least 24 hr | 1. Oxygen saturation | 1. One required intubation and one mortality |
| Ferrando et al. | 2020 | Prospective cohort study (Spain) | Confirmed SARS-CoV-2 infection from a respiratory tract sample using PCR-based tests (199) | 1. ≥18 years<br>2. No previous invasive MV or NIV use before starting HFNO<br>3. $SpO_2$ <93% on non-rebreather face mask at 15 L/min | Nonconfirmed SARS-CoV-2 infection and patients with no data on ventilation strategies | Prone position considered only if duration was >16 h/day regardless of the number of sessions | Two groups: (1) patients who received HFNO+awake-PP, and (2) patients who only received HFNO | Till discharge from ICU | 1. Need for invasive mechanical ventilation<br>2. Days to intubation<br>3. ICU length of stay<br>4. ICU mortality | 1. No reduction in risk of intubation (hazard ratio (RR) of 0.87 (95% CI: 0.538–1.435), $p = 0.60$])<br>2. Time from HFNO to intubation longer in the HFNO + awake-PP (1.0 vs 2.0 days, $p = 0.055$)<br>3. ICU length of stay did not vary between groups (7.5 vs 8.0, $p = 0.27$)<br>4. The 28-day mortality risk not influenced by the use of awake-PP [RR 2.411 (95% CI: 0.556–10.442), $p = 0.23$)] |
| Taboada et al. | 2020 | Prospective cohort study (Spain) | Laboratory-confirmed COVID-19 (29) | 1. Adults with mild or moderate ARDS needing oxygen and able to do PP | 1. Unstable hemodynamic status<br>2. ARDS needing HFNO or NIV | Instructed to remain first in supine position, then in PP for 1 hr, and then again in supine position | No comparison group | Till discharge | 1. Impact on oxygenation<br>2. To describe outcomes | 1. $SpO_2$ significantly higher during PP (95.8 ± 2.1; $p = 0.0003$) and after PP (95.4 ± 2.7; $p = 0.0034$) compared with previous supine position (93.6 ± 2.3). $PaO_2/FiO_2$ higher following PP (242 ± 107; $p = 0.0072$) as compared to before PP (196 ± 68)<br>2. Two patients (7%) died, 26 (89.6%) discharged, and one still hospitalized. Five patients needed ICU admission. The median duration of ICU and hospital stay was 11 [8–18] days and 15 [11–29] days, respectively |
| Taboada et al. | 2020 | Prospective cohort study (Spain) | Laboratory-confirmed COVID-19 (50) | COVID-19 with mild or moderate ARDS needing oxygen | Not mentioned | Instructed to remain in supine position, then in PP for 30–60 min, and then again in SP | No comparison group | 45 days | 1. Improvement in oxygenation | 1. $SpO_2/FiO_2$ increased during PP [277 (234–342) $p < 0.0001$] and after PP [277 (237–345) $p < 0.0001$] compared with previous supine position [265 (233–342)]. $SpO_2$ increased during PP [95 (95–96) $p < 0.0001$] and following PP [96.5 (94.2–98) $p < 0.0001$] compared with previous SP [94 (92–95)]<br>2. Two (4%) patients died, 7 (14%) needed ICU admission, and 41 (82%) discharged |

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| *Author* | *Year of publication* | *Study type (country)* | *Patient (sample size)* | *Inclusion criteria* | *Exclusion criteria* | *Intervention* | *Comparison* | *Follow-up* | *Outcome* | *Main finding* |
|---|---|---|---|---|---|---|---|---|---|---|
| Xu et al. | 2020 | Retrospective cohort study (China) | COVID-19 diagnosed using sputum or throat swab determined by RT-PCR (10) | Severe hypoxemia | Not mentioned | Target time of PP is >16 hr/day according to patient's tolerance | No comparison group | Hospital discharge | 1. $PaCO_2$ change<br>2. $PaO_2/FiO_2$ change<br>3. Need for intubation | 1. Median $PaCO_2$ increases [32.3 (29.3–34.0) vs. 29.7 (28.0–32.0), $p < 0.001$]<br>2. Median $PaO_2/FiO_2$ elevated significantly after PP<br>3. None of the patients needed endotracheal intubation |
| Depress et al. | 2020 | Retrospective cohort study (France) | Laboratory-confirmed SARS-CoV-2 infection (6) | 1. Spontaneously ventilated<br>2. No need for emergency intubation<br>3. No rapid worsening of dyspnea/oxygenation | Not mentioned | PP maintained depending on patient clinical tolerance and could be repeated if necessary | No comparison group | Not mentioned | 1. $PaO_2/FiO_2$<br>2. Intubation rate | 1. $PaO_2/FiO_2$ before and after proning was 18.17, 95% CI [–46.0721, 82.4121]<br>2. Intubation required in 50% of patients |
| Ripoll-Gallordo et al. | 2020 | Retrospective cohort study (Italy) | COVID-19 positive patients (13) | Moderate- to-severe ARDS | Not mentioned | PP maintained as long as it was well tolerated | No comparison group | Hospital discharge | 1. $PaO_2$:$FiO_2$<br>2. RR<br>3. Intubation rate | 1. Mean (SD) $PaO_2$:$FiO_2$ before PP was 115 (13). Improved $PaO_2$:$FiO_2$ compared to baseline in 12 patients ($p = 0.003$)<br>2. No difference in RR before and after PP ($p = 0.20$)<br>3. 4 patients (30%) needed intubation and 6 (46%) discharged |
| Damarla et al. | 2020 | Retrospective cohort study (Maryland) | Confirmed positive PCR testing results for SARS-CoV-2 RNA (10) | Confirmed SARS-CoV-2 RNA with increasing oxygen requirements | 1. Need for urgent intubation<br>2. Not eligible for proning | Asked to alternate every 2 hr between prone and supine position during the day and sleep in a prone position at night, as tolerated | No comparison group | 28 days | 1. $SpO_2$<br>2. RR<br>3. Incidence of intubation within 2 weeks of PP | 1. Median $SpO_2$ increased from 94% (IQR, 91–95%) to 98% (IQR, 97–99%)<br>2. Reduced median RR from 31 (IQR, 28–39) to 22 (IQR, 18–25) breaths/min<br>3. Two required intubation. All discharged from the hospital |
| Winearls et al. | 2020 | Retrospective cohort study (UK) | SARS- CoV-2 confirmed on nasopharyngeal swab (24) | On CPAP | 1. Imminent intubation<br>2. Reduced conscious level<br>3. Significant immobility or current pressure areas | Not mentioned | No comparison group | Not mentioned | 1. $SpO_2$<br>2. $PaO_2$:$FiO_2$<br>3. ROX index | 1. $SpO_2$ baseline 94% ± 3% vs PP on CPAP 96% ± 2%; $p < 0.005$, and difference sustained 1 hr after cessation of PP (baseline 94% ± 3% vs post-PP 96% ± 2%; $p < 0.05$)<br>2. $PaO_2$:$FiO_2$ increased (baseline 143 ± 73 mm Hg vs PP on CPAP 252 ± 87 mm Hg; $p < 0.01$). $PaO_2$:$FiO_2$ increase remained significant1hour after cessation of proning (baseline 143 ± 73 mm Hg vs post-PP 234 ± 107 mm Hg; $p < 0.05$)<br>3. Significant increase in ROX index on PP (baseline 7.0 ± 2.5 vs PP on CPAP 11.4 ± 3.7; $p < 0.0001$)18 discharged, 1 still inpatient. 1 intubated, and 4 died |
| Hallifax et al. | 2020 | Retrospective cohort study (UK) | COVID-19 (48) | 1. Increasing oxygen requirement, or either $FiO_2 \geq 40\%$ or ≥8 L/min via mask face | Requiring immediate ICU admission, or if deemed to be forward-based care | Prone or semiprone position as tolerated for periods of ≥2 hr at least twice daily | No comparison group | Till discharge | 1. Successful proning<br>2. Mortality<br>3. Intubation need | 1. Awake proning attempted in 30/48 (62.5%) patients. Successful proning achieved in 11/30 (36.7%), and semiproning in 17 (56.7%) patients<br>2. 12 patients died<br>3. 11 (22.9%) required intubation |

ED, emergency department; $SpO_2$, oxyhemoglobin saturation of peripheral blood; DNR/DNI, do not resuscitate or do not intubate; NIV, noninvasive ventilation; RT-PCR, real-time reverse transcription-polymerase chain reaction; HFNO, high-flow nasal oxygen therapy; PP, prone position; PCR, polymerase chain reaction; CPAP, continuous positive airway pressure; COPD, chronic obstructive airway disease; NYHA, New York Heart Association; BNP, brain natriuretic peptide; hARF, hypoxemic acute respiratory failure; SBP, systolic blood pressure; IQR, interquartile range; CI, confidence interval; SD, standard deviation; MV, mechanical ventilation; $PaO_2/FiO_2$, partial pressure of oxygen in arterial blood-fraction of inhaled oxygen; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; ARDS, acute respiratory distress syndrome; SP, supine position; SE, standard error; RR, respiratory rate ; HFNC, high-flow nasal cannula

**Table 2:** Summary of assessed outcomes

| *Included studies (n = 21)* | *Prospective cohort,[14] retrospective cohort,[6] pilot study[1]* |
|---|---|
| Total number of patients in included studies | 698 |
| Median (IQR*) number of patient in each study | 24 (10–49) |
| Number of patients who underwent awake proning | 495 |
| Duration of proning session | 1 to 8 hr/day |
| Intubation rate | 139/495 (27.1%) |
| Mortality rate | 55/414 (13.3%) |

*IQR: interquartile range

recorded), probably because the intervention under evaluation is awake proning, which can easily be implemented outside the ICU,[33] thereby reducing the load on ICU services. Also, since arterial blood sampling facility may not be readily available in wards or emergency department units or non-ICU settings, $SpO_2$ monitoring proves itself as a prime noninvasive bedside indicator of oxygen saturation of the patient. $SpO_2$ is stated to be the most clinically relevant measure of oxygenation and most often used for decision-making in the emergency ward and other outpatient settings.[33]

Most studies demonstrated statistically significant improvement in oxygenation with the intervention of awake proning. Caputo et al. reported in their study of 50 patients that after 5 minutes of proning, comparison of the pre- and postmedian $SpO_2$ by the Wilcoxon rank sum test yielded a significant favorable response ($p = 0.001$).[21] Same results were reported by Coppo et al. in their study on 46 patients; they demonstrated a significant improvement in $SpO_2$ after 10 minutes of proning [mean difference (95% CI) 1.0 (0.3–2.0), $p = 0.01$].[18] Retucci also based on the analysis of variance and Friedman tests detected a statistically significant improvement in $SpO_2$ values pre- and one-hour postproning ($p < 0.0001$).[19] These studies demonstrated a significant improvement in oxygenation with early initiation of proning sessions, probably owing to a larger fraction of potentially recruitable alveoli in the early stages of ARDS.

Mostly, literature has used $PaO_2$-$FiO_2$ ratio (PFR) to establish the effectiveness of prone positioning in acute lung injury or ARDS.[34] PFR has traditionally been used to diagnose ARDS (Berlin criteria), but now $SpO_2$-$FiO_2$ ratio (SFR) can be used as a reliable noninvasive measure of oxygenation.[35,36] Hence, substituting SFR instead of PFR may allow attending physicians to point toward ARDS associated with COVID-19 without the need of blood gases, further strengthening the agreement toward $SpO_2$ being used as an outcome indicator.

The time points of measuring oxygenation outcome were different in included studies, thereby explaining the differences in the degree of improvement seen. Furthermore, to procure clinically significant benefits, the minimum duration of prone positioning needed to be maintained in awake patients remains undefined. Durations equivalent to those required for patients undergoing mechanical ventilation (12–16 hours/day) may be arduous to attain.[37,38] For instance, the maximum duration of prone positioning reported in included studies was 8 hours in a single session.[18] As alveolar recruitment by prone positioning is a time-dependent affair,[39] more studies appraising the outcome with prolonged duration of proning sessions are needed.

The persistence in improvement of oxygenation after resuming supine position would have been a better indicator of improvement; however, these data were missing in most of the studies. Coppo et al. mentioned that the improvement seen on proning was not sustained and on an average was not significant when supine position was resumed ($p = 0.87$).[18] Elharrar et al. also reported that oxygenation that improved in about one-fourth of the patients by awake proning worsened again on making the patient back to the supine position.[14]

Short-lived improvement in oxygenation with prone positioning has been shown in numerous studies, without any ill effects to patients.[8,34,40] Valter reported that four patients with hypoxemic respiratory failure with indications for mechanical ventilation had good tolerance when placed in prone position, thereby increasing oxygenation and avoiding intubation in all four patients.[8] Scaravilli et al. demonstrated that repeated prone positioning in nonintubated patients with acute hypoxemic respiratory failure, who were managed with noninvasive mode of ventilation, significantly improved oxygenation.[40] Thus, favorable results were observed with repeated sessions of prone positioning.

Although improvement in oxygenation with prone positioning of the patient is important, hypoxemia has not been shown to be a definitive proxy biomarker for mortality in ARDS. This review showed a mortality rate of 13.3% among the patients with the intervention of awake proning. Thirty out of forty-eight patients in a study by Hallifax et al. were made prone, and twelve patients died during the treatment. The high number of patient death could be attributed to their inclusion criteria; they included patients with increasing oxygen requirement and already on continuous positive airway pressure (CPAP) or HFNO support.[32] Twenty-one studies demonstrated a high need for intubation and mechanical ventilation. Four hundred and ninety-five patients underwent awake proning, and one hundred and thirty-nine (27.1%) were intubated. This intubation rate seen in patients with COVID-19 is similar to the one that is usually seen in patients with other causes of ARDS being treated with noninvasive ventilation (NIV). In a proportion meta-analysis by Agarwal et al., assessing the efficacy of NIV estimated the pooled intubation rate to be 48% (95% CI, 39–58%).[41] Another study by Thompson et al. in a similar cohort of 25 patients treated with conventional oxygen therapy found improvements in $SpO_2$ (in response to awake proning) ranging from 1 to 37%, but 48% of patients (12/25) needed intubation.[22] Better results were shown in a study by Ng et al. who demonstrated the need of intubation in only one out of 10 non-ICU patients with daily awake proning sessions of 5 hours.[23] Xu et al. applied HFNO with early awake prone positioning in ten patients with five (50%) requiring intubation.[27] In a prospective multicenter adjusted study of 199 COVID-19 patients with acute respiratory failure, contrasting results were seen. In this study, patients managed with awake proning and HFNO not only failed to show any reduction in intubation rate, but also awake proning could have negatively influenced the outcome by delaying intubation.[24]

## Strengths and Limitations

Very little literature is available currently, and lots of trials are currently under recruitment and trial process. Twenty-six trials are registered for assessing the effectiveness of prone positioning in COVID-19 pneumonia currently. Until these studies are available,

**Table 3:** Newcastle-Ottawa scale (NOS) score for quality assessment

| | *Selection* | | | | | *Outcome/exposure* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Study* | *Representativeness of exposed cohort* | *Selection of the nonexposed cohort* | *Ascertainment of exposure* | *Demonstration that outcome of interest was not present at the start of the study* | *Comparability* | *Assessment of outcome* | *Was followed up long enough for outcomes to occur* | *Adequacy of follow-up of cohorts* | *Overall rating (more stars = lower risk of bias)* | *Diseases* |
| Tu et al. | | | | | | * | | | * | COVID-19 |
| Zhang et al. | * | * | * | * | | * | * | | ****** | COVID-19 |
| Elharrar et al. | * | | | * | | * | | | *** | COVID-19 |
| Moghadam et al. | | | | * | | | * | * | *** | COVID-19 |
| Golestani-Eraghi et al. | | | | | | | * | * | ** | COVID-19 |
| Sartini et al. | | | | | | | * | * | ** | COVID-19 |
| Coppo et al. | * | | * | * | | * | * | * | ****** | COVID-19 |
| Retucci et al. | * | | | * | | * | | | *** | COVID-19 |
| Bastoni et al. | * | | | * | | * | * | * | ***** | COVID-19 |
| Caputo et al. | * | | | * | | | | | ** | COVID-19 |
| Thompson et al. | * | | | * | | * | * | * | ***** | COVID-19 |
| Ng et al. | | | * | * | | * | * | * | ***** | COVID-19 |
| Ferrando et al. | * | * | * | * | ** | * | * | * | ********* | COVID-19 |
| Taboada et al. | * | | * | * | | | * | * | ***** | COVID-19 |
| Taboada et al. | * | | | | | * | * | | *** | COVID-19 |
| Xu et al. | | | | | | | * | * | ** | COVID-19 |
| Depress et al. | | | | * | | * | | | ** | COVID-19 |
| Ripoll-Gallordo et al. | | | | | | | * | * | ** | COVID-19 |
| Damarla et al. | | | * | * | | * | * | * | ***** | COVID-19 |
| Winearls et al. | | | | * | | * | * | * | **** | COVID-19 |
| Hallifax et al. | * | | * | * | | * | * | * | ****** | COVID-19 |

our review represents the summary of the currently available evidence for the effectiveness of awake proning. However, this review has various limitations. Firstly, as all aspects of care were uncontrolled in a majority of studies, therefore, the result derived may actually be due to unidentified another intervention and not due to awake proning. Secondly, the time point for data collection varied across included studies making it difficult to estimate the true effectiveness of awake proning in patients with COVID-19. The timings and the technique of the prone positioning were nonuniform among different studies. Thirdly, these studies were carried out on a selected group of patients who could tolerate the intervention, thereby having much heterogeneity in both reporting the intervention delivered and the manner of assessing its effects. Fourthly and most importantly, most studies available were single-armed studies without a control group, some of which were retrospective, with low quality, high publication bias, and lack of hard outcomes, making it difficult to assess the true validity of outcomes and also, limiting conclusions that could be drawn from these studies. Since several studies are single arm, any improvements reported may also be just a reflection of natural history for that patient and may not imply anything about the intervention. No randomized clinical trials have been published so far regarding either the effectiveness or the safety of awake proning in the context of COVID-19. Lack of comparator cohort groups weakens the usefulness of these studies; thus, caution should be taken while interpreting the outcomes of these studies. High heterogeneity between each study has led to the inability to pool the data to come up with a meaningful assessment on the benefits of awake prone positioning. Thus, awake proning is an easy to execute intervention and also might show short-term benefits. But to assess the degree to which awake prone positioning may be beneficial and whether these translate into a useful clinical outcome or worse needs further high-quality studies. In paucity of high-level evidence, providing a blanket policy for awake prone positioning in COVID-19 may actually harm the patient by delaying intubation.

To conclude, we share preliminary evidence that proning the patient with COVID-19 pneumonia could prove to be an effective way to improve the clinical outcomes. However, further high-quality studies providing a better evidence base for the practice of awake prone positioning are warranted.

## Highlights

- Awake proning is commonly advocated in the management of patients with COVID-19.
- We evaluated the literature assessing the clinical effectiveness of awake proning.
- Awake proning of nonintubated patients with COVID-19 might improve oxygenation; however, high-quality studies to base this evidence are lacking.

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*Appendix 1:* Search strategy for the different databases

*Appendix 2:* NOS for cohort studies

*Appendix 3:* Characteristics of registered trials

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