

COVID-19 Scientific Advisory Group Rapid Evidence Report

**PRONE POSITIONING FOR AWAKE, NON-INTUBATED PATIENTS
WITH SARS-COV-2 PNEUMONIA**

February 3, 2021



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Lay Summary

- Prone Positioning is a potentially life-saving treatment in intubated, mechanically ventilated patients with severe pneumonia, as can be seen in people with COVID-19. This has raised hope that it may improve breathing and reduce the need for intubation and breathing support in people with COVID-19 pneumonia in hospital wards
- In prone positioning, patients lay on their stomach rather than their back, which changes both the amount of lung receiving oxygen entry, and lung blood flow
- These guidelines are intended for clinicians who care for patients with severe shortness of breath and low oxygen levels who are hospitalized but not in the ICU, a patient group where there is less evidence of benefit and harms.
- In this review, we noted that having patients who are awake and not intubated take a prone position may temporarily improve oxygen numbers, but has not been shown to affect overall survival, or the need for intubation or ICU admission.
- This practice can also have risks particularly in patients who are doing poorly and evolving to need ICU care, as monitoring and urgent interventions are more difficult in prone patients
- Current experience reported in over 700 COVID-19 patients exposed to awake prone positioning has shown that this is possible within acute care settings but that it is often poorly tolerated by awake, non-intubated patients and it is rare to be able to have patients stay prone for the duration of time that has shown benefits in ICU patients
- Also, in the published studies to date, there is a lack of comparison to similar patients (who have similar lung disease, other conditions, and ability to stay prone). Therefore it is hard to say that the patients who were able to stay in a prone position in the studies didn't do better because they were less ill and less complicated.
- Therefore to help tell if this is truly beneficial, patients should be enrolled in a clinical trial for awake, non-intubated prone positioning wherever trials are available (two are currently enrolling patients in Alberta).
- Currently, prone positioning may be implemented with caution on medical wards in patients who are low-risk for requiring escalating care (ICU or intubation), with appropriate protocols for monitoring in place.
- Prone positioning should not be implemented on medical wards in patients who are high-risk for requiring escalating care (ICU or intubation), as the potential harms associated with delaying intubation could outweigh the possible benefits.
- If prone positioning is used outside of a clinical trial, all complications and adverse events should be documented using the AHS Report & Learning (RLS) system.

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Key Research Questions:

In awake non-intubated patients with SARS-COV-2 pneumonia who are being cared for in acute care facilities, is prone positioning safe and/or effective at improving patient outcomes?

Updated February 3, 2021

Context

- Prone Positioning is a non-pharmacological therapy for hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) where patients lay on their stomach rather than their back (Kallet et al. 2015, Scholten et al. 2017)
- Prone positioning intubated and mechanically ventilated patients with moderate-severe ARDS within an intensive care unit (ICU) is a proven life-saving intervention.
 - The PROSEVA trial demonstrated a 16% absolute risk reduction in mortality (number needed to treat of 6 to save one life) for patients with moderate-severe ARDS when patients were prone positioned for 16 hours or longer at a time (Guerin et al. 2013).
 - Although many patients demonstrated an improvement in oxygenation in PROSEVA when in the prone position, this improvement had no association with the survival benefit demonstrated. The effect was likely mediated through a reduction in ventilator induced lung injury not improved oxygenation (Albert et al. 2014)
- Prone positioning non-intubated patients has gained attention as a potential treatment through small case reports and uncontrolled case series, social media, and conventional media reports.
- Awake prone positioning non-intubated patients has been attempted on hospital wards outside of the ICU in every zone in the province, without a formal protocol, oversight, or a detailed evaluation of the risks and benefits.
- These guidelines are intended for clinicians who may be responsible for patients with hypoxemic respiratory failure who are hospitalized and not requiring the ICU.
- The original version of this report included three cohort studies and two case reports. This updated version adds 28 cohort studies and one cluster randomized trial.

Key Messages from the Evidence Summary

- While awake prone positioning of non-intubated patients admitted with acute hypoxemic respiratory failure secondary to COVID-19 may transiently improve oxygen saturation levels, its effect on clinical outcomes such as hospital survival, intubation or need for ICU admission has not been defined.
- The risks of awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure secondary to COVID-19 have not been established,

but previous studies in patients with ARDS raise concerns about aspiration, hemodynamic instability, pressure ulcers, cardiac arrest, and delayed intubation.

- Careful assessment of patient indications and contraindications, as well as the identification of the appropriate care setting is required prior to consideration for awake prone positioning of patients admitted with COVID-19.
- Current experience reported in over 700 COVID-19 patients exposed to awake prone positioning in a variety of settings has shown that this is possible within acute care settings but lack of true control populations with equivalent disease severity, comorbidities and capacity to prone limits ability to measure its impact on key patient-centric outcomes including intubation, ICU length-of-stay or mortality.
- There is no current evidence to suggest a duration of prone positioning that may be of benefit. Prone positioning is not tolerated in all patients, with reported complications including pain/ discomfort, nausea and anxiety.
- Current reported experience with awake prone positioning in COVID-19 patients to date in these cohorts does not suggest significant adverse effects; however, variability in patient selection and care setting as well as variability in monitoring of these outcomes may underestimate these events.

Committee Discussion

The committee reached consensus on the recommendations.

Recommendations

1. The efficacy and safety of awake prone positioning of non-intubated COVID-19 patients with hypoxemic respiratory failure is not established and hence this practice is not recommended for routine application in this population of patients. Ongoing clinical trials (some of which are active in Alberta) should inform the best utility of this practice in the future.

Practical Considerations

1. Where available, enroll eligible patients in a clinical trial for awake, non-intubated prone positioning. Information on ongoing and upcoming clinical trials in Alberta can be found under “Evolving Evidence” below.
2. If being considered for awake prone positioning outside of a clinical trial, COVID-19 patients should be assessed to determine their risk for escalating care:
 - a. LOW-RISK patients, where prone positioning may be implemented with caution on a medical ward, include:
 - i. Those with the ability to communicate and cooperate with procedures and adjust position independently
 - ii. Those with relatively low oxygen requirements (≤ 10 LPM)
 - iii. Those without absolute contraindications to prone positioning, which are: respiratory distress ($RR \geq 35$, $PaCO_2 \geq 48$, accessory muscle use), immediate need for intubation, hemodynamic instability ($SBP < 90$ mmHg) or arrhythmia,

- agitation or altered mental status, unstable spine/thoracic injury/recent abdominal surgery
 - iv. Those without relative contraindications: facial injury, neurological issues (e.g. frequent seizures), morbid obesity, pregnancy (2/3rd trimesters), pressure sores / ulcers
 - b. HIGH-RISK patients, where prone positioning should not be implemented outside of a highly monitored unit, include:
 - i. Those who are unable to prone position independently
 - ii. Those with high oxygen requirements (>10LPM, high-flow nasal cannula, or non-invasive ventilation)
 - iii. Those with anticipated need for intubation or intensive care, with R1 or R2 goals of care
 - iv. All those with the contraindications listed in 2) a. iii and iv
- 3. There is some evidence to suggest that prone positioning can delay intubation and intensive care intervention in a safe environment. For this reason, HIGH-RISK patients described above should not be placed in a prone position outside of a highly monitored unit, such as the ICU.
- 4. If awake prone positioning for COVID-19 patients is being considered for use outside of a clinical trial, health systems should be assessed to identify the required setting including equipment, staffing, and monitoring required.
- 5. If awake prone positioning for COVID-19 patients is being considered for use outside of a clinical trial, clinicians should monitor for potential complications and adverse events.
 - a. Potential adverse events include, but are not limited to: clinical deterioration, potential line or tube loss (peripheral IV lines, etc), pain/discomfort, nausea and anxiety.
 - b. All patients who prone position should have all adverse events properly documented using the AHS Report & Learning (RLS) system for quality improvement surveillance and monitoring.
- 6. If awake prone positioning for COVID-19 patients is being considered for use outside of critical care, health care providers should follow the guidance tool being developed for use within AHS. This documents the required training, monitoring, documentation and outcomes measurement and includes appropriate thresholds for discontinuation and escalation to the next level of care.
- 7. Prone positioning for prolonged periods of time in awake, non-intubated patients is often not tolerated due to pain, discomfort, nausea and anxiety. Outside of a clinical trial, patients should not be encouraged to continue prone positioning if these complications are observed.

Research Gaps

Future studies will need to address the current gaps in research to be able to change the strength of evidence and recommendations.

1. Future studies with randomization and allocation concealment are needed to eliminate confounding factors and minimize selection bias, respectively.
2. Future studies should be adequately powered to detect meaningful differences in clinically meaningful outcomes.

3. Future studies should determine factors associated with tolerability of awake prone positioning.
4. Future studies should evaluate the optimal frequency and duration of prone positioning.

Strength of Evidence

1. The strength of the evidence to support awake prone positioning of non-intubated COVID-19 patients with hypoxemic respiratory failure with the goal of sustained improving oxygen saturations is **WEAK**. The transient increases noted in oxygen saturations with prone positioning have not been linked to key outcomes including preventing intubation, ICU length of stay, or mortality.
2. The strength of the evidence to support the effectiveness of awake prone positioning of non-intubated COVID-19 patients with hypoxemic respiratory failure with the goal of improving patient survival, reducing the need for intubation, or reducing hospital length of stay is **UNDETERMINED** due to lack of randomized control trials as well as a lack of standardized description of risks and their quantification.

Limitations of this review

This review is limited by several things:

COVID-19 is a novel disease and thus limited studies exist on the use of non-pharmacological therapies such as awake prone positioning. Current available literature for COVID-19 includes several prospective and retrospective cohorts that are heterogenous in their inclusion and exclusion criteria, prone positioning protocols, and outcome measurements. Only two prospective and two retrospective cohorts had control groups. Differences between intervention and control groups in these studies may bias findings.

Summary of Evidence

A total of 32 primary studies (including 17 prospective cohort studies, 14 retrospective cohort studies, and one cluster randomized control trial) with 1090 patients in total (777 exposed to prone positioning, 313 as controls) describe the use of awake prone positioning for hypoxic respiratory failure in patients with COVID-19. Two cohort studies used inverse probability of treatment weighting to account for baseline differences between groups. One cohort study adjusted for severity of illness scores. Studies are summarized in Table 1.

Appraisal of notable studies:

The Taylor et al. (2020) study presents a cluster randomized control trial (pilot) that randomized five inpatient medical service teams to 1) usual care or 2) the Awake Prone Positioning Strategy (APPS) plus usual care. Included patients (n=40) had suspected or confirmed COVID-19, SpO₂ <93% or O₂ requirements ≥3LPM. The usual care group (n=13) and the APPS group (n=27) did not have different median nadir S/F ratios (SpO₂/FiO₂) over the 48-hour study period (p=0.11). It is important to note that only 37% of the patients in the APPS group attempted prone positioning, as did 23% of

patients in the usual care group. In the as-treated populations, there was also not a statistically significant difference in the median nadir S/F ratios. Patients who did not attempt prone positioning were more frequently male, Black, with chronic lung disease or heart failure, and smokers, compared to those who attempted prone positioning. There were no serious adverse events; one patient in the APPS group accidentally lost a peripheral IV line. It is important to note, from a feasibility perspective, that although 6/7 (86%) of clinicians endorsed 12-16 hours of prone positioning, patients reported that they were only able to prone position for 10-120 minutes per day. This study is notable as it provides knowledge that can be used to inform the design and conduct of future trials evaluating PP for non-intubated patients.

The Ferrando et al. (2020) study presents a prospective cohort of 199 patients admitted to hospital with COVID-19 acute respiratory failure requiring high-flow nasal canula (HFNC). Patients were classified into two groups: 1) patients who received HFNC + awake prone positioning; and 2) patients who only received HFNC. It is important to note that patients were only considered for the first group if the duration of prone positioning was >16h/day. The HFNC + prone positioning group had a sample size of 55 (27.6%). At baseline, the groups were fairly comparable; the HFNC + prone positioning group had higher baseline median PaO₂/FiO₂ (p=0.037). Inverse probability of treatment weighting was used to account for baseline differences between the HFNC and HFNC + prone positioning groups. The use of prone positioning did not reduce the risk of intubation (p=0.6), but the researchers concluded the time from HFNC initiation to intubation was longer in the HFNC + prone positioning group (1.0 vs 2.0 days, p=0.055). ICU length of stay did not vary between the two groups (p=0.27), nor did the 28-day mortality risk (p=0.23). These results must be interpreted with caution due to the observational study design. No results reached statistical significance.

The Zang et al. (2020) study presents a prospective cohort study including 60 patients with COVID-19, of which 23 were exposed to prone positioning and 27 were not (controls). The prone positioning group had a significant increase in mean SpO₂ after 10 and 30 minutes (p<0.01), had a significant decrease in mean RR after 30 minutes (p<0.01), and a significant increase in ROX index ([oxygen saturation/FiO₂]/respiratory rate) after 10 and 30 minutes (p<0.01). These measures were also statistically significant between the prone positioning and non-prone positioning groups (p<0.01). After 90 days, 43.5% of the prone positioning group had died, compared to 75.7% of the non-prone positioning group. The non-prone positioning group also had a significantly longer length of stay (p<0.01). The rate of intubation was not statistically significantly different between the two groups (p=0.54). These results must be interpreted with much caution due to significant baseline differences between the two groups, including their baseline SpO₂ (p=0.08) and ROX index (p=0.08).

The Oliveira et al. (2020)* study presents a prospective cohort study of 59 patients with COVID-19 and moderate ARDS admitted to ICU who underwent prone positioning. 44.1% of patients required intubation within 48h of prone positioning. Those requiring intubation had lower pre-prone positioning SpO₂ (p=0.006) and lower post-prone positioning SpO₂/FiO₂ and PaO₂/FiO₂ ratios (p=0.034, p=0.019), compared to those

who did not require intubation. In the group who did not require intubation, prone positioning resulted in a lower RR ($p=0.012$) and pH ($p=0.016^{**}$), increased SpO₂ ($p<0.001$), PaO₂ ($p=0.030$), SpO₂/FiO₂ ratio ($p=0.001$) and PaO₂/FiO₂ ratio ($p=0.009^{**}$). Complications associated with prone positioning included anxiety, low back or abdominal pain, decreased SpO₂/worsening dyspnea, coughing crisis and malaise. These results must be interpreted with caution due to the observational study design and the lack of control group (non-prone positioning).

*currently preprint

** article table 2 p-values differ from text; here we have reported from the text

The Jagan et al. (2020) study presents a retrospective cohort of 105 adult patients admitted to a rural hospital in the United States with COVID-19, of which 40 (38.1%) were able to self-prone position. Patients who were able to prone position were younger with lower disease severity (SOFA and APACHE II) than the controls who could not. The prone positioning group had 0 deaths, compared to 24.6% of controls. The intubation rate was lower in the prone positioning group (10% vs 27.7%, $p=0.031$), and time to intubation was longer in the prone positioning group. After adjusting for SOFA and APACHE II scores, the risk for intubation remained significantly lower (adjusted hazard ratio [SOFA] 0.30, $p=0.043$; [APACHE II] 0.30, $p=0.034$). The collection of SpO₂:FiO₂ (S/F) ratios was not protocolized, so unknown if measurement was made while patients were supine or prone. The length of time patients were prone positioned was inconsistent. These results must be interpreted with caution due to the observational study design and the baseline differences between the intervention and control groups.

The Padrão et al. (2020) study presents a retrospective cohort study including 166 adult patients in the ED with suspected COVID-19, requiring supplemental O₂ (non-intubated) and a RR ≥ 24 . Intervention group consisted of 57 patients exposed to prone positioning; the control group consisted of 109 patients who were eligible for prone positioning but did not. At baseline, the groups were fairly comparable; the SpO₂/FiO₂ ratio was lower in the prone positioning group, but the RR was higher in the PP group. Propensity score matching and inverse probability of treatment weighting was used in the analysis to account for differences between the two groups. The hazard ratio for intubation between the two groups was non-significant ($p=0.39$). There were no significant differences in the 15-day outcomes between the two groups, including: mechanical ventilation-free days, need for dialysis or vasopressors, or ICU bed utilization. Gas exchange (SpO₂/FiO₂ ratios) improved in the prone positioning group ($p<0.001$), as did RR ($p<0.001$) and ROX index ($p<0.001$). 58% of patients tolerated prone positioning for ≥ 4 h, and adverse events attributed to prone positioning included: accidental peripheral intravenous line (PIV) removal ($n=2$) and cardiac arrest due to hypoxemia ($n=1$). It is important to note that the physiological measures (SpO₂/FiO₂, RR, etc) were measured immediately before prone positioning and then after (30 min to 4 hours). There was no evidence of long-term improvement from PP. These results must be interpreted with caution due to the observational study design and the baseline differences between the intervention and control groups.

Synthesis of the Evidence

In awake non-intubated patients with SARS-COV-2 pneumonia who are being cared for in acute care facilities, is prone positioning safe and/or effective at improving patient outcomes?

1. While awake prone positioning non-intubated patients may improve oxygen saturation levels, its effect on patient-centric clinical outcomes such as intubation, ICU admission or hospital survival remain undefined. This is primarily due to the lack of rigorously conducted randomized control trials to allow comparison between the intervention and usual care. Some additional points to note are as follows:
 - The majority of studies reported to date included patients in a highly monitored setting: ICU (n=12) and ED (n=6).
 - Prone positioning was attempted outside of the ICU or ED in 15 studies, including: medical wards (n=10), high-dependency units (n=4) and within a rural hospital (n=1).
 - The dose (duration of prone positioning) remains highly variable and is not standardized.
 - The majority of studies reported patients receiving oxygen via high flow nasal cannula (n=13) or non-invasive ventilation (n=13); 4 studies did not report the mode of oxygen delivery
 - Rates from intubation ranged from 0-69% of patients exposed to prone positioning. The follow-up period was unstandardized.
 - Rates of death ranged from 0-43% of patients exposed to prone positioning.
2. The risks of awake prone positioning non-intubated patients (which could include aspiration, hemodynamic instability, pressure ulcers, cardiac arrest, and delayed intubation) remain undefined with the exception of intolerance to prone positioning, musculoskeletal pain and loss of catheters/lines.
 - Studies reported loss of PIV as an adverse event (n=2).
 - Studies reported intolerance to prone positioning due to pain, discomfort, nausea, and anxiety; studies also reported patient refusal to prone position.
 - Reporting of safety or adverse events was not standardized.

Evolving Evidence

Several international multicenter trials are launching to examine the use of awake prone positioning. In the Calgary zone, the following two trials will be available:

COVI-PRONE – Examining the use of awake prone positioning in non-intubated COVID-19 patients with hypoxemic respiratory failure who are candidates for the ICU based on their goals of care (R1/R2).

CORONA - Examining the use of awake prone positioning in non-intubated COVID-19 patients with hypoxemic respiratory failure who are not candidates for the ICU based on their goals of care (R3/M1/M2).

Table 1:

Characteristics of studies examining awake prone positioning in non-intubated patients with hypoxic respiratory failure due to COVID-19

Study Description	Sample N=	Inclusion Criteria (I); Exclusion Criteria (E)	O2 Delivery Mode	Prone Positioning Protocol	Study Outcome	Analysis – details	Duration and tolerability of PP	Supine Oxygenation and Resp Rate mean (SD), median [IQR]	Prone Position Oxygenation and Resp Rate mean (SD), median [IQR]	Intubation Rate, No. (%) or time to intubation	Adverse Event Reporting and Mortality
Author (Year)	Description of groups (if control group used)				Duration of Follow-up (F/U)						
Study Type											
Setting											
<p>Taylor (2020)</p> <p>C-RCT Pilot</p> <p>Non-ICU, Medical unit</p>	<p>N=40 (27/40 PP)</p> <p>5 in-patient units randomly assigned to either a) usual care or b) the Awake Prone Positioning Strategy plus usual care.</p> <p>Patients and clinicians were unblinded to treatment allocation; data collection was blinded.</p>	<p>I: Adults, admitted by study team, suspected or confirmed COVID-19, either: i) SpO2 <93% on RA or ii) O2 requirement of ≥3LPM without mechanical ventilation</p> <p>E: Contraindications to PP (unable to self P, spinal instability, facial or pelvic fractures, open chest or abdomen, altered LOC, anticipated difficult airway, signs of respiratory fatigue, or EOL care)</p>	<p>RA, NP, HFNC, BiPAP</p>	<p>The APPS protocol combined 1) delivery of prone positioning education and explanation of risks and benefits to patients by bedside clinicians; 2) routine monitoring for worsening status; and 3) attempts to improve comfort as needed. Patients were encouraged to sustain the prone position as long as possible but were allowed to return to the supine position as necessary.</p>	<p>SpO2:FiO2, Intubation, Mortality</p> <p>F/U: Hospital discharge, median LOS for PP 6 [3-12]</p>	<p>Evaluated outcomes for both intention-to-treat and as-treated groups.</p> <p>Separation between the groups was evaluated by nadir S/F ratio and the time spent with S/F ratio < 315 in the first 48 hours following randomization.</p> <p>Median S/F ratios were plotted to visualize longitudinal trajectory of patient groups from baseline to 48 hours.</p> <p>Mixed methods used to explore feasibility of clinical trials for PP.</p>	<p>Patients reported they were only able to lie prone for 10-120 minutes per day, despite being encouraged to PP for 12-16 h/day.</p>	<p>Assigned usual care: SpO2:FiO2: 216 (95% CI: 95-303);</p> <p>Did not attempt PP: SpO2:FiO2: 225 (95% CI: 196-258)</p>	<p>Assigned PP: SpO2:FiO2: 253 (95% CI: 197-267);</p> <p>Attempted PP: SpO2:FiO2: 256 (95% CI: 185-284)</p>	<p>0 (0)</p>	<p>4% loss of PIV, 0% anterior pressure wound, 0 died</p>
<p>Ferrando (2020)</p> <p>PC ICU</p>	<p>N=144 (55/144 PP)</p> <p>Patients were classified into two groups: (1) patients who received HFNO + awake-PP and (2) patients who only received HFNO.</p> <p>At baseline the groups were fairly comparable; the HFNC + prone</p>	<p>I: Age ≥ 18 years, COVID-19, no previous invasive MV or NIV use before starting HFNO, and SpO2 < 93% with a non-rebreather face mask at 15 L/min</p> <p>E: No data on ventilation</p>	<p>HFNC</p>	<p>Only included in PP group if PP >16h/ day</p>	<p>Intubation, PaO2:FiO2</p> <p>F/U: Discharge from ICU</p>	<p>Inverse probability of treatment weighting used to account for baseline differences between HFNO and HFNO + awake-PP groups. Logistic regression models included: age, sex obesity, SOFA score, APACHE II, CPR, days from symptom onset to HFNO, RR, SpO2 and type of hospital</p>	<p>Patients only included in PP group for analysis if they were able to PP >16h/day.</p>	<p>PaO2:FiO2: 92.5 [77-125.5]; SpO2: 89% [86-92]; Max RR: 27 [24-32]</p>	<p>PaO2:FiO2: 103 [80-125]; SpO2: 88 [84-90]; Max RR: 27 [23-30]</p>	<p>22/55 (40%) in HFNO + PP group; 60/144 (41%) in HFNO (control) group.</p> <p>Time from HFNO to intubation was longer in the HFNO + awake-PP in the original (1.0 vs 2.0 days, p = 0.055) and adjusted (2.0 vs 4.1 days, p = 0.054) samples,</p>	<p>Not reported</p> <p>The 28-day mortality risk was not influenced by the use of awake-PP [RR 2.411 (95% CI 0.556–10.442), p = 0.23]</p>

	positioning group had higher baseline median PaO ₂ /FiO ₂									although differences did not reach statistical significance.	
Zang (2020) PC Not reported	N=60 (23/60 PP) 23 patients were exposed to prone positioning and 27 were not (controls). There were significant baseline differences between groups (SpO ₂ and ROX index)	I: COVID-19, hypoxemia (SpO ₂ < 90%), Age 18–80, consent E: Need for intubation, inability to self position, basal lung disease, unstable spine, high ICP, severe burns, abdo surgery, abdo HTN, cranial injury, tracheotomy, immunosuppression, pregnant, imminent death.	NP, HFNC, NIV	Evaluated muscle strength first, self position prone, 1-2 h sessions 3–4 times/day for 5 days. Vitals measured at 10 min and 30min in PP	SpO ₂ , RR, ROX F/U: 90 days	Unadjusted comparison between two groups	Median 9 h [8–22] Not reported	SpO ₂ 91.1 (1.5), RR 28.2 (3.1) ROX 3.35 (0.46)	SpO ₂ 95.5 (1.7) RR 24.9 (1.8) ROX 3.96 (0.45)	8/23 (35)	10/23 died (44%) in PP group; 28/37 died (76%) in control group
Oliveira (2020) PC ICU	N=59 All patients exposed to PP. Patients were divided into two groups according to whether the PP was successful (avoided intubation)	I: COVID-19 ARDS, 18-80 years, requiring supplemental O ₂ E: Pregnant, uncooperative, altered LOC, COPD requiring home NIV or O ₂	NP, HFNC, NIV or reservoir mask	Patients helped into PP, encouraged to PP ≥120 min, PP allowed following days according to clinician's judgement	1) Identify predictors of response to prone positioning; 2) Improvement of PaO ₂ :FiO ₂ and SpO ₂ :FiO ₂ with PP F/U: Hospital discharge	Multivariate Poisson regression model used to control for confounding. Authors do not address which confounders were included in the final model.	120 [80-120] minutes 62.7% tolerated PP; 12.3% reported anxiety; 15.5% received medication. 17 patients did not maintain PP for 60-120 min, due to low back pain (2%), SpO ₂ decrease (10%), coughing crisis (3%), abdominal pain (3%), dyspnoea (3%) and malaise (7%)	Not requiring intubation: RR: 28.9 (6), SpO ₂ : 93.6 (3.9), SpO ₂ :FiO ₂ : 105 [101-123], PaO ₂ :FiO ₂ : 94.6 [76-129] Requiring intubation: RR: 30.4 (7.2), SpO ₂ : 90.7 (3.9), SpO ₂ :FiO ₂ : 102 [95-152], PaO ₂ :FiO ₂ : 93.1 [70.7-156]	Not requiring intubation: RR: 24.8 (5.6), SpO ₂ : 96.6 (2.9), SpO ₂ :FiO ₂ : 119 [107-145]; PaO ₂ :FiO ₂ : 137 [107-169] Requiring intubation: RR: 26.7 (5.2), SpO ₂ : 95.5 (2.6), SpO ₂ :FiO ₂ : 107 [101-124], PaO ₂ :FiO ₂ : 87.2 [64-133]	26 (44.1%)	Not reported, 13/59 died (22%)
Jagan (2020) RC Rural hospital	N=105 (40/105 PP) Patients in the supine group included those who did not meet these minimum	I: All nonpregnant, COVID-19–infected patients greater than or equal to 19 years old. E: Intubation at the time of admission, repeat	Not reported	Patients educated on the benefits of awake PP and were instructed to self-prone intermittently.	Intubation, S/F ratio F/U: Hospital discharge	Time-to-intubation during the hospital stay was compared using Kaplan-Meier method, whereas risk of intubation was compared using univariable and multivariable Cox proportional-hazards models.	Included in PP group if ≥1h continuous hour on ≥5 occasions /day + ≥1 continuous hour overnight.	Not reported	Not reported	4/40 (10) Unadjusted risk of intubation was 69% lower in patients who were prone (hazard ratio [HR],	Adverse events not reported Patients who PP were 57% more likely to be discharged alive (HR, 1.57; 95% CI, 1.02–2.42; p = 0.039); however, this difference became non-statistically significant after

	frequencies and/or durations, those unable to tolerate the prone position, and those who refused. Patients who were able to prone position were younger with lower disease severity (SOFA and APACHE II) than the controls who could not.	admission, or incomplete records				Multivariable models included disease severity scores, which were estimated separately for SOFA and APACHE II scores given they are highly correlated but are calculated using different clinical variables.	Compliance with PP observed in 38% of patients.			0.31; 95% CI, 0.10–0.90; p = 0.032), an association that remained constant after adjusting for SOFA scores (adjusted HR [aHR], 0.30; 95% CI, 0.09–0.96; p = 0.043) or APACHE II score (aHR, 0.30; 95% CI, 0.10–0.91; p = 0.034).	adjusting disease severity using SOFA scores (aHR, 0.85; 95% CI, 0.47–1.53; p = 0.587) or APACHE II scores (aHR, 0.96; 95% CI, 0.56–1.66; p = 0.893).
Padrão (2020) RC ED	N=166 (57/166 PP) Intervention group consisted of 57 patients exposed to prone positioning; the control group consisted of 109 patients who were eligible for prone positioning but did not.	I: Age >18 years, COVID-19, non-intubated, requiring O2 (>3LPM) and tachypnea (RR>24) E: Intubated on arrival to ED or within 1h, hemodynamic instability, recent abdominal surgery, acute respiratory failure, unstable fractures, pregnancy or other contraindications to PP	NP, Venturi mask or NRB	Patients were asked to PP ≥4 hours in their first session; if some improvement was observed, patients were stimulated twice daily to maintain awake prone positioning sessions	Intubation; Mortality, SpO2, SpO2:FiO2 F/U: 15 days (from first prone)	Kaplan-Meier survival plot and a log-rank test for the univariate analysis; unadjusted and adjusted Cox model. Inverse probability of treatment weighting was used to control for differences between groups. Adjusted for age, S/F ratio, RR, obesity, 4C score.	Not reported 5% back pain limiting PP, 1 patient had a cardiac arrest due to hypoxemia.	In PP Group Prior to PP: SpO2: 92 [88-93]; RR 34 [30-38]; SpO2:FiO2: 196 [128-254]	In PP Group After PP: SpO2: 94 [92-96]; RR 29 [26-32]; SpO2:FiO2: 224 [159-307]	33/57 (58%) in PP; 53/109 (49%) non-PP In the univariate and multivariate models, the hazard ratios for intubation were not statistically significant.	4% accidental removal of PIV, 6/57 died (11%) in PP group; 22/109 died (20%) in control group There were no statistically significant differences between the two groups for risk of mortality, (both unadjusted and adjusted models). There were no significant differences in the 15-day outcomes between the two groups, including: mechanical ventilation-free days, need for dialysis or vasopressors, or ICU bed utilization.
Caputo (2020) PC ED	N=50 No control group	I: Hypoxemia (SpO2 < 90%) E: NIV use, DNR order	NP or facemask	Not reported	SpO2 5 min after PP, intubation rate within 24 h F/U: 3 days	Unadjusted comparison (pre/ during PP)	Not reported Not reported	SpO2 84% [75–90]	SpO2 94% [90–95]	13/50 (26.0)	22% required intubation within 60 min
Coppo (2020) PC	N=56 No control group	I: Age 18–75, confirmed COVID-19, hypoxemia consent E: Pregnant, uncollaborative, altered	Helmet CPAP, Reservoir mask, Venturi mask	Assisted PP, encouraged to maintain x 3 h, Repeat up to 8h/d	PaO2:FiO2 F/U: Hospital discharge	Unadjusted comparison (pre/ during PP) Sensitivity analysis evaluating differences between responders and non-responders to PP	Median 3 h [3, 4] Up to 7 sessions. PP unfeasible in 9 patients, reasons: discomfort (n=5),	PaO2:FiO2 180.5 (76.6) RR 24.5 (5.5)	PaO2:FiO2 285.5 (112.9) RR 24.5 (6.9)	18/56 (32)	9% discomfort, 4% worsening oxygenation, 2% coughing, 5/56 died (9%)

Non-ICU Medical units, ED, ICU		mental status, NYHA < II, increased BNP, COPD on home NIV or O2, impending intubation					coughing (n=1), refusal (n=1), decrease in SpO2 (n=2, one required emergent intubation).				
Dubosh (2020) PC ED	N=22 No control group	I: Suspected or confirmed COVID-19, dependant on supplemental O2 via NP or NRB, able to self-prone E: Rapid deterioration, required intubation, or had variable FiO2 during pre-PP period	NP or NRB	Patient assisted into PP, encouraged to stay in PP until admitted to ward or ICU, unable to tolerate, or worsening resp status or SpO2	SpO2:FiO2, Intubation F/U: Hospital discharge	Unadjusted comparison (pre/ during PP) Sensitivity analysis (patients who had no change in O2 delivery during PP)	109 [65-159] minutes 1 patient excluded d/t abdo pain with PP	SpO2:FiO2 298 [264-352]; RR 26 [23-30]; SpO2: 94% [92-96]; FiO2: 31.5 [27-36]	SpO2:FiO2 295 [279-350]; RR 25 [23-38]; SpO2: 96% [95-98]; FiO2: 33 [27-33] Minutes 3-35 of PP	5/22 (23) within 48h; 7/22 (32%) total	None reported; 2/23 died (9%)
Elharrar (2020) PC Non-ICU, Medical unit	N=24 No control group	I: Hypoxemia, CT chest with COVID-19 and posterior lesions E: Requiring intubation, altered consciousness	NP, facemask, HFNC	Single episode, no goal, duration	Proportion of patients with PaO2 increase ≥20% from supine to PP F/U: 10 days	Unadjusted comparison (pre/ during/post PP) Sensitivity analysis (subgroups based on length of time tolerated in PP)	17% <1 h 21% 1-3 h 63% >3 h 42% backpain, 17% tolerated <1 h	PaO2 72.8 (14.2)	PaO2 91 (27.3) 25% had ≥20% increase PaO2. After PP, no significant difference between pre-PP PaO2 and post-PP PaO2	5/24 (20.8) 4/24 (17) required intubation within 72 h	None reported
Golestani-Eraghi (2020) PC ICU	N=10 No control group	I: COVID-19, not mech ventilated, PaO2: FiO2 < 150 E: Not reported	Helmet NIV	2h sessions	Not reported F/U: Not reported	Unadjusted comparison (pre/ post PP)	Mean 9h Not reported	PaO2 46.3 (5.2)	PaO2 62.5 (4.6) 60% had sustained improvement in PaO2 after 1h	2/10 (20)	No complications (hypotension or desaturation) 2/10 died (20%)
Moghadam (2020) PC Non-ICU, Medical unit	N=10 No control group	I: COVID-19, not mech ventilated E: Not reported	Not reported	Not reported	SpO2, RR, auxiliary muscle use F/U: Hospital discharge	Unadjusted comparison (pre/ during PP)	Not reported Not reported	SpO2 86% (0.7)	SpO2 96% (2.2)	0/10 (0)	Not reported
Ng (2020) PC	N=10 No control group	I: Hypoxemia E: Drowsy, uncooperative,	NP, HFNC, or Venturi mask	1 h sessions, 5 sessions/d spaced 3 h apart. Continued until onRAx24 h	Not reported	Descriptive	Median total duration 21 h (range 2-58)	SpO2 91.5 (range 88-95)	Not reported	1/10 (10)	1/10 died (10%)

Non-ICU, Medical unit		ophthalmic or cervical pathology, pregnancy, hemodynamic instability, FiO2 > 0.5			F/U: Median 8 days, range 2-19 days		Some patients experienced mild side-effects, such as musculoskeletal discomfort, nausea or vomiting				
Paternoster (2020) PC HDU	N=11 No control group	I: COVID-19 ARDS who failed a one-hour helmet CPAP trial in supine position, with a persistent PaO2:FiO2 <150. E: Excessive cough, hypotension, morbid obesity or patient refusal	Helmet CPAP	Twelve hours helmet CPAP in prone position were followed by six hours helmet CPAP in supine position	SpO2, PaO2:FiO2, RR F/U: 28 days	Unadjusted comparison (pre/ 24h, 48h and 72h)	13 (1.2) hours Dexmedetomidine was given for comfort in PP (64%)	SpO2: 90 (2.3); RR: 27 (4.3); PaO2:FiO2: 107.5 (20.8)	After 72h: SpO2: 97 (3.1); RR: 20 (4.7); PaO2:FiO2: 244.4 (106.2)	3/11 (27)	Not reported, 2/11 died (18%)
Retucci (2020) PC ICU	N=26 No control group	I: COVID-19, spontaneous breathing, GCS = 15, PaO2: FiO2 < 250 after 48 h Helmet CPAP E: Requiring intubation, GCS < 15, SBP < 90, SpO2 < 90% on FiO2 > 0.8	Helmet CPAP	Prone/lateral positioning based on CXR or CTscan, 1h sessions. 39 sessions: 12 prone, 27 lateral	Successful trial, defined as all 4 of: 1. decrease A-aO2 gradient ≥20%, 2. equal or reduced RR, 3. equal or reduced dyspnea 4. SBP ≥ 90 mmHg F/U: Not reported	Unadjusted comparison (pre/ during/ post PP) Sensitivity analysis (prone and lateral positioning subgroups)	1 h 5% discomfort 3% SBP < 90 mmHg 8% increased RR	PaO2:FiO2 182.9 (43) SpO2 96 [95-98] RR 23.7 (4.7)	During PP: PaO2:FiO2 220 (64.5) SpO2 98 [97-98] RR 23.1 (4.5) Post PP: PaO2:FiO2 179 (44) SpO2 97 [95-98] RR 22.9 (6)	7/26 (27)	2/26 died (8%)
Sartini (2020) PC Non-ICU, Medical unit	N=15 No control group	I: Hypoxemia (SpO2 < 94%), FiO2 > 0.6 and CPAP 10 cm H2O E: Not reported	NIV	Not reported	PaO2:FiO2, RR, patient comfort with NIV F/U: 14 days At 14 days, 9 had been discharged home, 4 remained hospitalized, 1 died	Unadjusted comparison (pre/ during/post PP)	Median 3 H (IQR 1-6) 73% reported improved comfort with PP	PaO2:FiO2 58–117* Supine RR: 21-31	During PP: PaO2:FiO2 114–122* RR: 18–27* Post PP: 80% had improvement in SpO2 and PaO2:FiO2 1h post PP; 13% had no change; 7% worsened	1/15 (6.6)	1/15 died (7%)

Taboada (2020) PC Non-ICU, Medical unit	N=29 No control group	I: Adults, COVID-19, ARDS (mild or moderate), needing O2 therapy, able to PP E: Unstable hemodynamic status, requiring HFNC or NIV	Face mask, NC	Patients instructed to PP for 1h. Then, we recommended PP sessions for at ≥30min 3x/day	PaO2:FiO2, SpO2 F/U: Not reported	Unadjusted comparison (pre/ during/post PP)	Not reported	SpO2: 96.6 (2.3); 196 (68)	During PP: SpO2: 95.8 (2.1); After PP: SpO2: 95.4 (2.7), PaO2:FiO2: 242 (107)	Not reported	Not reported, 2/29 died (7%)
Taboada (2021) PC ICU	N=7 No control group	I: COVID-19 ARDS, ≥18 years, able to self-PP E: Inability to collaborate with PP or refusal, unstable hemodynamic status, patients with moderate or severe ARDS needing intubation, and mechanical ventilation.	Not reported	Patients were instructed to remain in PP until they felt too tired to maintain that position.	PaO2:FiO2 F/U: ICU discharge	Linear mixed-effects models were fit to estimate changes from baseline to account for the inherent within-patient correlation across the multiple measurements of the outcome (comparisons: pre/ during/ post PP)	Median: 10 hours All patients given dexmedetomidine for comfort	PaO2:FiO2: 114 [89-165]	PaO2:FiO2: 160 [101-204]	2/7 (29)	None reported
Thompson (2020) PC Step-down unit	N=29 No control group	I: Confirmed COVID-19, Severe hypoxemia (RR>30 and SpO2 < 93% on 6 L O2 by NP and 15 L by NRB) E: Altered mental status, inability to turn without help, immediate intubation needed, mild hypoxemia.	NP or NRB	Repeated episodes, up to 24 h per day, use a pillow under hips/pelvis.	Change in SpO2 at 1 hour F/U: Up to 49 days or Hospital discharge	Unadjusted comparison (pre/ 1h post PP) Sensitivity analysis (intubated and non-intubated subgroups)	Median 4 h (range 1–24) in not-intubated group, Median 6 h (range 1–24) in intubated group 25/29 tolerated PP ≥1h; 4 (13%) refused PP and required immediate intubation	SpO2 65–95%	SpO2 90–100%* Median SpO2 improvement 7% [4.6–9.4]	16/29 (55)	3/29 died (10%)
Tu (2020) PC Not reported	N=9 No control group	I: COVID-19 confirmed, HFNC >2 days, PaO2: FiO2 < 150 E: Not reported	HFNC	Repeated episodes, as long as tolerated	SpO2 PaO2 F/U: Hospital discharge; mean LOS 28 (10) days	Unadjusted comparison (pre/ post PP)	Median 2 h [1–4] per session, median 5 [3–8] sessions Not reported	SpO2 90% (2) PaO2 69 (10)	SpO2 96% (3) PaO2 108 (14)	2/9 (22)	1/9 required ECMO, 0 died (0%)
Bastoni (2020) RC ED	N=10 No control group	I: Receiving helmet NIV, awake & able to prone E: Need for rapid intubation & ICU, End-stage comorbid disease	Helmet CPAP 10-20 cmH2O	Nurse assisted, Morphine infusion for sedation.	PaO2:FiO2, Lung US signs F/U: Hospital discharge	Unadjusted comparison (pre/ during PP)	1 h 40% did not tolerate or refused. Lack of compliance (10%), pain (10%), refusal (20%)	PaO2:FiO2 68 (5)	PaO2:FiO2 97 (8) No change in lung US findings	6/10 (60)	4 deaths (40%)

Burton-Papp (2020) RC ICU	N=20 No control group	I: COVID-19 hypoxemia, received CPAP or NIV E: Not reported	CPAP or NIV	Not described	Δ P/F F/U: Hospital discharge	Unadjusted comparison (Δ P/F pre/during PP)	Median 3 [2] Median 5 cycles per patient [6.25] Not reported	Not reported	Δ PaO ₂ /FiO ₂ + 28.7 [95%CI 18.7–38.6] Δ RR -0.98 [95%CI -2-0.04]	7/20 (35)	None reported 2 intubated patients required ECMO 0 deaths
Damarla (2020) RC ICU	N=10 No control group	I: Confirmed COVID-19, rapidly increasing O ₂ requiring ICU E: Requiring intubation	NP or HFNC	Alternate prone/supine every 2 h, supervised first episode	SpO ₂ , RR at 1 h F/U: 28 days	Unadjusted comparison (pre/during PP)	2 h Not reported	SpO ₂ 94% [91–95] RR 31 [28–39]	SpO ₂ 98 [97–99] RR 22 [18–25]	2/10 (20)	None, 0 deaths
Despres (2020) RC ICU	N=6 No control group	I: COVID-19, PaO ₂ :FiO ₂ \leq 300 E: Requiring intubation	NP or HFNC	As long as tolerated	PaO ₂ :FiO ₂ F/U: Not reported	Unadjusted comparison (pre/during PP)	Median 2 h [1-7] Not reported	PaO ₂ :FiO ₂ 183 [144–212]	PaO ₂ :FiO ₂ 168 [156–225]	3/6 (50)	Not reported
Dong (2020) RC ICU	N=25 No control group	I: COVID-19, severe disease (RR \geq 30, SpO ₂ \leq 93% or PaO ₂ :FiO ₂ $<$ 300), or critical disease (Requiring ventilation, shock, organ failure) E: Patients who received PP but rapidly improved or who did not tolerate first session.	NP, mask, HFNC, NIV	Daily session $>$ 4 h, nurse instructions, lateral positioning if PP not tolerated	Survival, intubation, PaO ₂ :FiO ₂ F/U: Hospital discharge	Unadjusted comparison (pre/during PP) Sensitivity analysis (severe & critical disease severity subgroups)	Mean 4.9 h (SD 3.1) 16% Sternal pain, 4% Scrotal pain, 4% Lumbago, 4% Pruritis,	PaO ₂ :FiO ₂ 194 [164–252] RR 27 [26–30]	PaO ₂ :FiO ₂ 348 [288–390] RR 22 [20–22]	0/25 (0)	0/25 died
Kelly (2020) RC ICU, non-ICU medical ward	N=17 No control group	I: Adult COVID-19 patients, requiring (FiO ₂) 5 0.28 to maintain peripheral oxygen saturations (SpO ₂) 92–96% E: Requiring intubation, cardiovascular instability, altered consciousness	Not reported	Patients were required to independently self-prone and free to cease at any stage.	SpO ₂ /FiO ₂ ratio, RR F/U: 49 days	Unadjusted comparison (pre/during/post PP)	1–3 days with the total duration of 9.2 [5.2– 17.6] hours over five [2.8–10.0] sessions 1 patient refused subsequent PP after first session	SpO ₂ /FiO ₂ 156.7, [123.8–232.5]); RR 22.0 [19.8–27.3]	SpO ₂ /FiO ₂ increased (+27.8 [6.3–82.3] ; RR decreased -2 breaths/min, [-6–0] During PP Outcomes reverted to pre-PP levels when resupinated	2/17 (12%) (Both emergency intubations) 45% of patients who were for escalation failed PP, requiring intubation	6/17 died (35%)

Ripoll-Gallardo (2020) RC Non-ICU, Medical unit	N=13 No control group	I: PaO ₂ : FiO ₂ < 150 E: Requiring intubation, hemodynamic instability, multiorgan failure	Helmet CPAP	Encouraged as long as possible	PaO ₂ :FiO ₂ F/U: Hospital discharge	Unadjusted comparison (pre/during PP)	Mean 2.4 h (SD 0.87) Not reported	PaO ₂ :FiO ₂ 113 [108–121]	PaO ₂ :FiO ₂ 138 [126–178]	9/13 (69)	None, 7/13 died (54%)
Singh (2020) RC HDU	N=15 No control group	I: COVID-19 confirmed, hemodynamically stable, SpO ₂ <90%, able to PP E: Hemodynamically unstable, drowsy or uncooperative	Face mask, NRB, NIV	Awake prone position was explained, encouraged to spend as much time in PP as tolerated. Target time was 10 to 12 hours per day.	PaO ₂ :FiO ₂ F/U: Not reported	Unadjusted comparison (pre/during PP) Sensitivity analysis (days 1-3, 4-6, 7-10 and 11-discharge)	Not reported Not reported	PaO ₂ :FiO ₂ : 98.8 (29.7) day 1-3, 142.4 (40.9) day 4-6, 178.3 (38.3) day 7-10, and 210.3 (37.9) day 11+	PaO ₂ :FiO ₂ : 136.6 (38.8.) day 1-3, 173.9 (46.6) day 4-6, 214.8 (44.2) day 7-10, and 218.6 (32.5) day 11+	2/15 (13)	2/15 died (13%)
Solverson (2020) RC Non-ICU, Medical unit, ICU	N=17 No control group	I: Suspected or confirmed COVID-19, ICU consult, Hypoxemia (5 L to maintain SpO ₂ ≥ 90%), at least 1 prone session E: Not reported	NP, HFNC	Encouraged as long as possible	SpO ₂ Tolerability F/U: Hospital discharge	Unadjusted comparison (pre/during/post PP) Sensitivity analysis (ability to PP <75min or ≥75 min)	Median PP sessions 2 [1-6], duration 75 [30-480] minutes Back or shoulder pain (12%), general discomfort (35%), delirium (6%). 8 patients (47%) had no tolerability problems.	SpO ₂ 91% (range 84–95) RR 28 (range 18–38) SpO ₂ :FiO ₂ 152 (range 97–233)	SpO ₂ 98% (range 92–100) RR 22 (range 15–33) SpO ₂ :FiO ₂ 165 (range 106–248)	7/17 (41)	No adverse events observed (including worsening dyspnea, intravenous catheter dislodgement, aspiration, pressure ulcers, oxygen cannula removal, or hemodynamic decompensation) 2 /17 died (12%)
Wendt (2020) RC ED	N=31 No control group	I: Able to self PP and tolerate for 30 min, SpO ₂ <90% on RA and pre-PP SpO ₂ ≤ 94% on O ₂ E: Not reported	NP or NRB	Patients encouraged to prone for at least 2h	SpO ₂ F/U: Hospital discharge	Unadjusted comparison (pre/during PP)	Mean 140 (47) minutes Not reported	SpO ₂ : 83 [75-86] on RA or 90 [89-93] with supplemental O ₂ ; RR: 31 (9)	SpO ₂ 96 [94-98]; RR 26 (8)	14/31 (45%)	Not reported, 8/31 died (26%)
Winearls (2020) RC HDU	N=24 No control group	I: ARDS due to SARS-CoV-2 and on CPAP E: Contraindications to PP (imminent intubation, reduced LOC, significant immobility or current pressure areas)	CPAP	Patients received verbal and written information on the rationale and practicalities of PP	SpO ₂ , PaO ₂ :FiO ₂ , RR F/U: 28 days post admission	Analysis of variance with post hoc correction for multiple testing was used to compare PaO ₂ :FiO ₂ indices at each time point.	8±5 hours in first 24h 2 patients unable to tolerate PP	RR: 27 (6); SpO ₂ : 94 (3); PaO ₂ :FiO ₂ : 143 (73)	During PP: RR 24 (6); SpO ₂ 96 (2); PaO ₂ :FiO ₂ 252 (87) Post PP: RR: 25 (6); SpO ₂ : 96 (2); PaO ₂ :FiO ₂ : 234 (107)	1/14 (7); denominator is subgroup of those appropriate for intubation	Not reported, 4/24 died (17%)

Xu (2020)	N=20	I: COVID-19 confirmed	HFNC	Target 16 h/d, target SpO2 > 90%	PaO2:FiO2	Unadjusted comparison (pre/ day 3 of PP)	4–6 h sessions	PaO2:FiO2 89–228	PaO2:FiO2 200–325** on day 3 of PP	0/10 (0)	Not reported
RC	No control group	E: Not reported			F/U: Hospital discharge; mean LOS 17.7 days		Not reported				
Not reported											

*Range estimated from a figure. Abbreviations: ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; CT, computed tomography; DNR, do not resuscitate; ECMO, extracorporeal membrane oxygenation; ED, emergency department; FiO2, fraction of inhaled oxygen; F/U: Follow up; GCS, Glasgow Coma Scale; HFNC, high-flow nasal cannula; HTN, hypertension; ICP, intracranial pressure; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; NIV, non-invasive ventilation; NP, nasal prongs; NRB, non-rebreather face mask; NYHA, New York Heart Association; PaO2, partial pressure of arterial oxygen; PC, prospective cohort; PP, prone position; RC, retrospective cohort; RA, room air; ROX, ROX index = SpO2/FiO2 x 1/respiratory rate; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; SpO2, oxygen saturation; US, ultrasound.

Appendix

List of Abbreviations

AHS: Alberta Health Services
ARDS: Acute Respiratory Distress Syndrome
COVID-19: Coronavirus Disease-2019
ED: Emergency Department
FiO₂: Fraction of inspired oxygen
HFNC: High-Flow Nasal Canula
ICU: Intensive Care Unit
MRP: Most responsible physician
PaCO₂: Partial pressure of carbon dioxide
PaO₂: Partial pressure of oxygen
PIV: Peripheral intravenous line
ROX index: ([oxygen saturation/FiO₂]/respiratory rate)
RR: Respiratory rate
SAG: Scientific Advisory Group
SBP: Systolic blood pressure
S/F ratio: SpO₂/FiO₂
SpO₂: Peripheral capillary oxygen saturation

Methods

Literature Search

A literature search was conducted by Nicole Loroff from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from January 1, 2020 to January 7, 2021 in English language, and included: MEDLIDE (Ovid), PubMed, Trip PRO, LitCOVID, WHO COVID-19 Research Database, Centre for Evidence-Based Medicine (CEBM), National Institute for Health and Care Excellence (NICE), medRxiv, and Google Scholar. Briefly, the search strategy involved combinations of keywords and subject headings including:

- SARS-COV-2 or COVID-19 or Coronavirus
- Awake or non-intubated
- Prone positioning

The full search strategy is listed in the Search Strategy section below.

Articles identified by KRS in their search were initially screened by title against the PICOS statement listed in Table 2 and the inclusion/exclusion criteria listed in Table 3 below. 68 articles were identified by KRS with references and abstracts provided for further review. An additional five articles were found by hand-searching review articles found in the search. 41 were excluded from the review in accordance with the inclusion/exclusion criteria stated below.

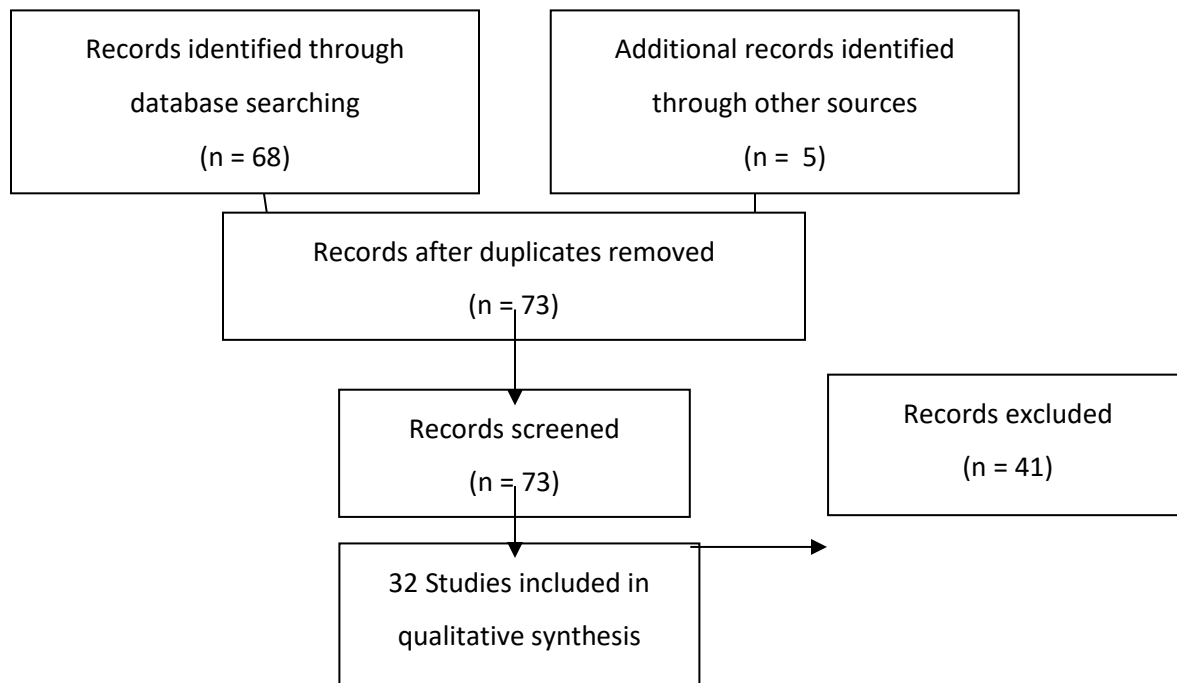


Figure 1: PRISMA Flow Diagram (Moher et al. 2009)

Table 2. Inclusion and exclusion criteria for results of the literature search

Population	Patients with hypoxemic respiratory failure who are not intubated.
Intervention	Prone positioning
Comparison	Usual management (supine position) – when available
Outcome	Including but not limited to: Clinical (intubation rates or survival), physiological (oxygen saturations), hospital resource utilization (length of stay in ICU or hospital), adverse events
Settings	Hospitalized patient in acute care facility

Table 3. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<p>[numerated list of inclusion criteria]</p> <ul style="list-style-type: none"> - Patients with SARS-COV-2, admitted to acute care facilities - Patients awake, non-intubated - Intervention: prone positioning - Jan 1, 2020 to Jan 7, 2021 - Primary research - English language 	<ul style="list-style-type: none"> - Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Review articles (not primary research) - Case reports or sample size <5 patients - Clinical guidelines or recommendations - Patients without COVID-19 - Does not include prone positioning - Does not include outcome measures

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 2 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al, 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 2. Narrative overview of the literature included in this review.

	Description
Volume	One cluster RCT was included, 17 prospective cohort studies were included (one is pre-review), and 14 retrospective cohort studies were included (one is pre-review). In total, this represents 1,090 patients, of which 777 were exposed to prone positioning and 313 were included as controls.

<p>Quality</p>	<p>Two of the prospective cohort studies and two of the retrospective cohort studies had control groups (usual care or did not prone position). Due to the study designs, there was a lack of similarity of controls to intervention groups. The controls were also not consistent from study to study. For example, Ferrando et al. (2020) classified patients as controls if they did not meet the > 16 hours of prone positioning per day, where Jagan et al. (2020) classified patients as controls if they did not meet the ≥1 hour on ≥5 occasions per day and ≥1 continuous hour overnight.</p> <p>The studies were unable to be synthesized due to heterogeneity in:</p> <ul style="list-style-type: none"> - inclusion and exclusion criteria - acuity of patients - therapies provided to patients, including oxygen delivery - prone positioning protocols, including duration and frequency - follow up time and evaluation of outcomes - outcome reporting including adverse events
<p>Applicability</p>	<p>14 studies included patients on a medical ward or high-dependency unit, 12 included patients in an ICU, and six included patients in an emergency department.</p> <p>The studies varied in settings, from hospitals with different volumes of patients and capacity for ICU and intubation. These studies also took place in settings with varying healthcare systems.</p> <p>The cluster RCT (Taylor et al. 2020) provides a mixed methods analysis using an implementation outcome framework with implications for future RCTs. This should be considered when designing and implementing future RCTs in this area.</p>
<p>Consistency</p>	<p>Consistent results suggesting improvements in oxygenation during prone positioning. However, in many studies, the improvements did not continue after the patient returned supine. Rates of intubation ranged from 0-69%, which is likely a result of the heterogeneity in included sample acuity, prone positioning protocols, and settings. Rates of mortality ranged from 0-43%, which is also likely a result of the heterogeneity in included sample acuity, prone positioning protocols, and settings.</p> <p>Studies did not consistently report adverse events, and when they did, the descriptions varied.</p>

Search Strategy

Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily 1946 to January 07, 2021

Date searched: January 8, 2021

Search strategy:

1. Patient Positioning/ or Prone Position/ (10353)
2. (proned or proning or pronat* or self-prone* or self-proning or self-pronat*).tw,kf,kw. (6181)
3. (prone* adj5 position*).tw,kf,kw. (7565)
4. ((abdominal or stomach) adj5 position*).tw,kf,kw. (1295)
5. or/1-4 (22260)
6. Wakefulness/ (18227)
7. non-intubat* or nonintubat* or "not intubat*" or non-ventilat* or nonventilat* or "not ventilat*" or unintubat* or noninvasive* or non-invasive* or conscious or awake or tubeless or awake-prone* or awake-proning or awake-pronat*).tw,kf,kw. (268585)
8. or/6-7 (281990)
9. 5 and 8 (749)
10. exp Coronavirus/ or exp Coronavirus Infections/ (55338)
11. (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or "severe acute respiratory syndrome cov 2" or 2019 ncov or 2019ncov).tw,kf,kw. (82250)
12. or/10-11 (90990)
13. 9 and 12 (87)
14. limit 13 to english language (87)
15. limit 14 to yr="2020 -Current" (87)

PubMed

Date searched: January 8, 2021

Search strategy:

1. "patient positioning"[MeSH Terms] OR "prone position"[MeSH Terms] (10822)

2. "prone position*" [Title/Abstract] OR proned [Title/Abstract] OR proning [Title/Abstract] OR pronat* [Title/Abstract] OR self-prone* [Title/Abstract] OR self-proning [Title/Abstract] OR self-pronat* [Title/Abstract] OR "abdominal position*" [Title/Abstract] OR "stomach position*" [Title/Abstract] (12916)
3. or/1-2 (21110)
4. "wakefulness" [MeSH Terms] (18230)
5. "non intubat*" [Title/Abstract] OR "nonintubat*" [Title/Abstract] OR "not intubat*" [Title/Abstract] OR "non ventilat*" [Title/Abstract] OR "nonventilat*" [Title/Abstract] OR "not ventilat*" [Title/Abstract] OR "unintubat*" [Title/Abstract] OR "noninvasive*" [Title/Abstract] OR "non invasive*" [Title/Abstract] OR "conscious" [Title/Abstract] OR "awake" [Title/Abstract] OR "tubeless" [Title/Abstract] OR "awake prone*" [Title/Abstract] OR "awake-proning" [Title/Abstract] OR "awake pronat*" [Title/Abstract] (271644)
6. or/4-5 (285048)
7. 3 and 6 (689)
8. "coronavirus" [MeSH Terms] OR "coronavirus infections" [MeSH Terms] (64627)
9. "covid" [Title/Abstract] OR "coronaviru*" [Title/Abstract] OR "corona viru*" [Title/Abstract] OR "ncov*" [Title/Abstract] OR "ncov*" [Title/Abstract] OR "novel cov*" [Title/Abstract] OR "COVID-19" [Title/Abstract] OR "COVID19" [Title/Abstract] OR "COVID-2019" [Title/Abstract] OR "COVID2019" [Title/Abstract] OR "SARS-CoV-2" [Title/Abstract] OR "SARSCoV-2" [Title/Abstract] OR "SARSCoV2" [Title/Abstract] OR "SARSCoV19" [Title/Abstract] OR "SARS-Cov-19" [Title/Abstract] OR "SARSCoV2019" [Title/Abstract] OR "SARS-Cov-2019" [Title/Abstract] OR "severe acute respiratory syndrome cov 2" [Title/Abstract] OR "2019 ncov" [Title/Abstract] OR "2019ncov" [Title/Abstract] (99858)
10. or/8-9 (108847)
11. 7 and 10 (100)
12. limit 11 to english language (100)

13. limit 12 to yr="2020 -Current" (100)

Trip Pro

Date searched: January 8, 2021

(covid OR coronavirus OR COVID-19 OR "corona virus" OR ncov OR n-cov OR covid-2019 OR covid2019 OR SARS-COV-2 OR sarscov-2 OR sarscov2 OR sarscov19 OR sars-cov-19 or sarscov-19 OR sarscov2019 OR sars-cov-2019 OR "severe acute respiratory syndrome cov 2") AND (prone or prone position or proned or proning or pronation or prone positioning or awake prone positioning or awake-proning or awake pronation or conscious proning or conscious pronation or self-proning or self-pronation)from:2020 (154)

LitCovid/WHO COVID-19 Research Database/Centre for Evidence Based Medicine (CEBM)/CADTH COVID-19 Evidence Portal/COVID-Evidence

Date searched: January 8, 2021

prone or prone position or proned or proning or pronation or prone positioning or awake prone positioning or awake-proning or awake pronation or conscious proning or conscious pronation or self- proning or self-pronation

medRxiv/Google Scholar

Date searched: January 8, 2021

(covid-19 or coronavirus or sars-cov-2) and (prone or proning or pronation or awake prone or awake proning or awake pronation)

**Citation tracking of key research was conducted in Google Scholar.

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