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.
## Authorship and Committee Members

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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 (≤10LPM)
      iii. Those without absolute contraindications to prone positioning, which are: respiratory distress (RR ≥ 35, PaCO2 ≥ 48, accessory muscle use), immediate need for intubation, hemodynamic instability (SBP < 90mmHg) 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 ≥4h, 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

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Sample Size</th>
<th>Inclusion Criteria (I); Exclusion Criteria (E)</th>
<th>O2 Delivery Protocol</th>
<th>Prone Positioning Protocol</th>
<th>Study Outcome</th>
<th>Analysis – details</th>
<th>Duration and tolerability of PP</th>
<th>Intervention Description</th>
<th>Adverse Event Reporting and Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor (2020)</td>
<td>N=40</td>
<td>I: Adults, admitted by study team, suspected or confirmed COVID-19, or either: 1) SpO2 &lt;93% on RA or (i) O2 requirement of ≥3LPM without mechanical ventilation</td>
<td>RA, NP, HFNC, BiPAP</td>
<td>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.</td>
<td>SpO2:FiO2, Intubation, Mortality</td>
<td>Evaluated outcomes for both intention-to-treat and as-treated groups.</td>
<td>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.</td>
<td>Intubation, Pressure ulcer, 4% loss of PIV, 0% anterior pressure wound, 0 died</td>
<td></td>
</tr>
<tr>
<td>C-RCT Pilot</td>
<td>N=144</td>
<td>I: Age ≥ 18 years, COVID-19, no previous invasive MV or NIV use before starting HFNO, and SpO2 &lt; 93% with a non-rebreather face mask at 15 L/min</td>
<td>HFNC</td>
<td>Intubation, PaO2:FiO2</td>
<td>NO: Discharge from ICU</td>
<td>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.</td>
<td>Patients only included in PP group for analysis if they were able to PP &gt;16h/day.</td>
<td>PaO2:FiO2: 92.5 (77-125.5); SpO2: 89% (86-92); Max RR: 27 [24-32]</td>
<td>Not reported</td>
</tr>
<tr>
<td>Non-ICU, Medical unit</td>
<td>N=144</td>
<td>I: Adults, admitted by study team, suspected or confirmed COVID-19, or either: 1) SpO2 &lt;93% on RA or (i) O2 requirement of ≥3LPM without mechanical ventilation</td>
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<td>PC ICU</td>
<td>N=144</td>
<td>I: Age ≥ 18 years, COVID-19, no previous invasive MV or NIV use before starting HFNO, and SpO2 &lt; 93% with a non-rebreather face mask at 15 L/min</td>
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<td>Intubation, PaO2:FiO2</td>
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**Adverse Event Reporting and Mortality**
- Intubation rate: 40% in the original (1.0 vs 2.0 days, p = 0.054) and adjusted (2.0 vs 4.1 days, p = 0.054) samples.
- No loss of PIV, 0% anterior pressure wounds, 0 deaths.
positioning group had higher baseline median PaO2/FiO2 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 (SpO2 and ROX index)

1: COVID-19, hypoxemia (SpO2 < 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, immuno-suppression, 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 30minPP

SpO2, RR, ROX F/U: 90 days Unadjusted comparison between two groups

Median 9 h [8–22] Not reported SpO2 91.1 (1.5), RR 28.2 (3.1) ROX 3.35 (0.46) SpO2 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)

1: COVID-19 ARDS, 18–80 years, requiring supplemental O2
E: Pregnant, uncooperative, altered LOC, COPD requiring home NIV or O2

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 PaO2:FiO2 and SpO2:FiO2 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.


Jagan (2020) RC Rural hospital N=105 (40/105 PP) Patients in the supine group included those who did not meet these minimum

1: 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

patients. 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.

Padrão (2020)

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

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.

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.

Padrão (2020)

RC

ED

Caputo (2020)

N=50

No control group

I: Hypoxemia (SpO2 < 90%)

E: NIV use, DNR order

Not reported

SpO2 5 min after PP, intubation rate within 24 h F/U: 3 days

Unadjusted comparison (pre/during PP)

Not reported

SpO2 84% [75–90]

13/50 (26.0)

22% required intubation within 60 min

Caputo (2020)

PC

ED

Coppo (2020)

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)

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 (6.9)

18/56 (32)

9% discomfort, 4% worsening oxygenation, 2% coughing, 5/56 died (9%)
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Control</th>
<th>I</th>
<th>E</th>
<th>F/U</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elharrar (2020) PC Non-ICU Medical unit</td>
<td>N=24</td>
<td>No control group</td>
<td>Hypoxemia, CT chest with COVID-19 and posterior lesions</td>
<td>Requiring intubation, altered consciousness</td>
<td>10 days</td>
<td>Unadjusted comparison (pre/post PP) 17% &lt;1 h 21% 1-3 h 63% &gt;3 h 42% backpain, 17% tolerated &lt;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</td>
</tr>
<tr>
<td>Golestani-Eraghi (2020) PC ICU</td>
<td>N=10</td>
<td>No control group</td>
<td>COVID-19, not mech ventilated, PaO2: FiO2 &lt; 150</td>
<td>Not reported</td>
<td>Not reported</td>
<td>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 3h</td>
</tr>
<tr>
<td>Moghadam (2020) PC Non-ICU Medical unit</td>
<td>N=10</td>
<td>No control group</td>
<td>COVID-19, not mech ventilated</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Unadjusted comparison (pre/post PP) Not reported Not reported SpO2 86% [0.7] SpO2 96% [2.2]</td>
</tr>
<tr>
<td>Ng (2020) PC</td>
<td>N=10</td>
<td>No control group</td>
<td>Hypoxemia</td>
<td>Drowsy, uncooperative, NP, HFNC, or Venturi mask</td>
<td>1 h sessions, 5 sessions/d spaced 3 h apart. Continued until onRAx24 h</td>
<td>Descriptive Median total duration 21 h (range 2-58)</td>
</tr>
<tr>
<td>Non-ICU, Medical unit</td>
<td>ophthalmic or cervical pathology, pregnancy, hemodynamic instability, FiO2 &gt; 0.5</td>
<td>F/U: Median 8 days, range 2-19 days</td>
<td>Some patients experienced mild side-effects, such as musculoskeletal discomfort, nausea or vomiting</td>
<td></td>
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</tr>
<tr>
<td>Paternoster (2020) PC HDU</td>
<td>N=11 No control group</td>
<td>I: COVID-19 ARDS who failed a one-hour helmet CPAP trial in supine position, with a persistent PaO2:FiO2 &lt;150. E: Excessive cough, hypotension, morbid obesity or patient refusal</td>
<td>Helmet CPAP Twelve hours helmet CPAP in prone position were followed by six hours helmet CPAP in supine position</td>
<td>SpO2, PaO2:FiO2, RR F/U: 28 days</td>
<td>Unadjusted comparison (pre/ 24h, 48h and 72h)</td>
<td>3 (1.2) hours Dexmedetomidine was given for comfort in PP (64%)</td>
</tr>
<tr>
<td>Retucci (2020) PC ICU</td>
<td>N=26 No control group</td>
<td>I: COVID-19, spontaneous breathing, GCS = 15, PaO2: FiO2 &lt; 250 after 48 h Helmet CPAP E: Requiring intubation, GCS &lt; 15, SBP &lt; 90, SpO2 &lt; 90% on FiO2 &gt; 0.8</td>
<td>Helmet CPAP Prone/lateral positioning based on CXR or CTscan, 1h sessions. 39 sessions: 12 prone, 27 lateral</td>
<td>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</td>
<td>F/U: Not reported</td>
<td>Unadjusted comparison (pre/ during/ post PP)</td>
</tr>
<tr>
<td>Sartini (2020) PC Non-ICU, Medical unit</td>
<td>N=15 No control group</td>
<td>I: Hypoxemia (SpO2 &lt; 94%), FiO2 &gt; 0.6 and CPAP 15 cm H2O E: Not reported</td>
<td>NIV</td>
<td>PaO2:FiO2, RR, patient comfort with NIV F/U: 14 days At 14 days, 9 had been discharged home, 4 remained hospitalized, 1 died</td>
<td>Unadjusted comparison (pre/ during/post PP)</td>
<td>Median 3 H (IQR 1-6) 73% reported improved comfort with PP</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Setting</td>
<td>Design</td>
<td>N</td>
<td>Control group</td>
<td>Inclusion criteria</td>
</tr>
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</tr>
<tr>
<td>Taboada (2020)</td>
<td>PC</td>
<td>Non-ICU, Medical unit</td>
<td>N=29</td>
<td>No control group</td>
<td>Adults, COVID-19, ARDS (mild or moderate), needing O2 therapy, able to PP</td>
<td>Face mask, NC</td>
</tr>
<tr>
<td>Taboada (2021)</td>
<td>PC</td>
<td>ICU</td>
<td>N=7</td>
<td>No control group</td>
<td>COVID-19 ARDS, 218 years, able to self-PP</td>
<td>Not reported</td>
</tr>
<tr>
<td>Thompson (2020)</td>
<td>PC</td>
<td>Step-down unit</td>
<td>N=29</td>
<td>No control group</td>
<td>Confirmed COVID-19, Severe hypoxemia (RR&gt;30 and SpO2 &lt; 93% on 6 L O2 by NP and 15 L by NR)</td>
<td>NP or NR</td>
</tr>
<tr>
<td>Tu (2020)</td>
<td>PC</td>
<td>Not reported</td>
<td>N=9</td>
<td>No control group</td>
<td>COVID-19 confirmed, HFNC &gt;2 days, PaO2:FiO2 &lt; 150</td>
<td>HFNC</td>
</tr>
<tr>
<td>Bastoni (2020)</td>
<td>RC</td>
<td>ED</td>
<td>N=10</td>
<td>No control group</td>
<td>Receiving helmet NIV, awake &amp; able to prone</td>
<td>Helmet CPAP 10-20 cmH2O</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>N</td>
<td>Control Group</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Outcome Measures</td>
</tr>
<tr>
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<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Burton-Papp (2020)</strong></td>
<td>ICU</td>
<td>20</td>
<td>No control</td>
<td>COVID-19 hypoxemia, received CPAP or NIV E: Not reported</td>
<td>CPAP or NIV</td>
<td>Not described</td>
</tr>
<tr>
<td><strong>Damarla (2020)</strong></td>
<td>ICU</td>
<td>10</td>
<td>No control</td>
<td>Confirmed COVID-19, rapidly increasing O2 requiring ICU E: Requiring intubation</td>
<td>NP or NIV</td>
<td>Alternate prone/supine every 2 h, supervised first episode</td>
</tr>
<tr>
<td><strong>Despres (2020)</strong></td>
<td>ICU</td>
<td>6</td>
<td>No control</td>
<td>COVID-19, PaO2/FiO2 ≤ 300 E: Requiring intubation</td>
<td>NP or NIV</td>
<td>As long as tolerated</td>
</tr>
<tr>
<td><strong>Dong (2020)</strong></td>
<td>ICU</td>
<td>25</td>
<td>No control</td>
<td>COVID-19, severe disease (RR ≥ 30, SpO2 ≤ 93% or PaO2/FiO2 ≤ 300), or critical disease (Requiring ventilation, shock, organ failure) E: Patients who received PP but rapidly improved or who did not tolerate first session.</td>
<td>NP, mask, HFNC, NIV Daily session ≥4 h, nurse instructions, lateral positioning if PP not tolerated</td>
<td>Survival, intubation, PaO2/FiO2 F/U: Hospital discharge</td>
</tr>
<tr>
<td><strong>Kelly (2020)</strong></td>
<td>ICU</td>
<td>17</td>
<td>No control</td>
<td>Adult COVID-19 patients, requiring (FiO2) 0.28 to maintain peripheral oxygen saturations (SpO2) 92–96% E: Requiring intubation, cardiovascular instability, altered consciousness</td>
<td>Not reported</td>
<td>Patients were required to independently self-prone and free to cease at any stage. SpO2/FiO2 ratio, RR F/U: 49 days</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Control Group</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Helmet Type</td>
<td>CPAP, Face Mask, Face Shield</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Ripoll-Gallardo</td>
<td>Non-ICU, Medical unit</td>
<td>No control group</td>
<td>PaO2: Fio2 &lt; 150 E: Requiring intubation, hemodynamic instability, multiorgan failure</td>
<td>F/U: Hospital discharge</td>
<td>Not reported</td>
<td>113 [108–121]</td>
</tr>
<tr>
<td>Singh</td>
<td>HDU</td>
<td>No control group</td>
<td>COVID-19 confirmed, hemodynamically stable, SpO2 &lt;90%, able to PP</td>
<td>Face mask, NRB, NIV</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Solverson</td>
<td>Non-ICU, Medical unit, ICU</td>
<td>No control group</td>
<td>Suspected or confirmed COVID-19, ICU consult, Hypoxemia (5 L to maintain SpO2 ≥ 90%), at least 1 prone session</td>
<td>NP, HFNC</td>
<td>Encouraged as long as possible</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wendt</td>
<td>ED</td>
<td>No control group</td>
<td>Able to self PP and tolerate for 30 min, SpO2 ≤ 94% on O2</td>
<td>CPAP</td>
<td>Patients encouraged to prone for at least 2h</td>
<td>140 (47) minutes</td>
</tr>
<tr>
<td>Winearls</td>
<td>HDU</td>
<td>No control group</td>
<td>ARDS due to SARS-CoV-2 and on CPAP</td>
<td>Patients received verbal and written information on the rationale and practicalities of PP</td>
<td>8±5 hours in first 24h</td>
<td>2 patients unable to tolerate PP</td>
</tr>
<tr>
<td><strong>Xu (2020)</strong></td>
<td>N=20</td>
<td>No control group</td>
<td><strong>I:</strong> COVID-19 confirmed</td>
<td>HFNC</td>
<td>Target 16 h/d, target SpO2 &gt; 90%</td>
<td><strong>PaO2:FiO2</strong></td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>RC</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>Target 16 h/d, target SpO2 &gt; 90%</td>
<td>HFNC</td>
<td><strong>PaO2:FiO2</strong></td>
</tr>
</tbody>
</table>

*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: MEDLINE (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 listed 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.
Table 2. Inclusion and exclusion criteria for results of the literature search

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Patients with hypoxemic respiratory failure who are not intubated.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Prone positioning</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Usual management (supine position) – when available</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Settings</strong></td>
<td>Hospitalized patient in acute care facility</td>
</tr>
</tbody>
</table>
Table 3. Inclusion and exclusion criteria for results of the literature search

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>[numerated list of inclusion criteria]</td>
<td>- Article is not from a credible source</td>
</tr>
<tr>
<td>- Patients with SARS-COV-2, admitted to acute care facilities</td>
<td>- Article does not have a clear research question or issue</td>
</tr>
<tr>
<td>- Patients awake, non-intubated</td>
<td>- Presented data/evidence is not sufficient to address the research questions</td>
</tr>
<tr>
<td>- Intervention: prone positioning</td>
<td>- Review articles (not primary research)</td>
</tr>
<tr>
<td>- Jan 1, 2020 to Jan 7, 2021</td>
<td>- Case reports or sample size &lt;5 patients</td>
</tr>
<tr>
<td>- Primary research</td>
<td>- Clinical guidelines or recommendations</td>
</tr>
<tr>
<td>- English language</td>
<td>- Patients without COVID-19</td>
</tr>
<tr>
<td></td>
<td>- Does not include prone positioning</td>
</tr>
<tr>
<td></td>
<td>- Does not include outcome measures</td>
</tr>
</tbody>
</table>

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 (Unwin, 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.

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
</tr>
<tr>
<td><strong>Consistency</strong></td>
</tr>
</tbody>
</table>

**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-pronning 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 SARS-CoV-2 or SARS-CoV2 or SARS-CoV19 or SARS-Cov-19 or SARS-CoV-19 or SARS-CoV2019 or SARS-Cov-2019 or SARS-CoV-2019 or "severe acute respiratory syndrome cov 2" or 2019 ncv 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)

3. or/1-2 (21110)

4. "wakefulness"[MeSH Terms] (18230)


6. or/4-5 (285048)

7. 3 and 6 (689)


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.**
Reference


COVID-19 in Wuhan: A Respective Cohort Study. medRxiv. doi:10.1101/2020.05.09.20091454


