Clinical benefits of prone positioning in the treatment of non-intubated patients with acute hypoxic respiratory failure: a rapid systematic review

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ABSTRACT

Background The COVID-19 pandemic has led to a surge in critically unwell patients with type 1 respiratory failure. In an attempt to reduce the number of patients requiring mechanical ventilation, prone positioning (PP) of non-intubated patients has been added to many hospital guidelines around the world. We set out to conduct a systematic review of the evidence relating to PP in the non-intubated patient with type 1 respiratory failure secondary to COVID-19 and other causes.

Methods The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. A literature search of major databases and grey sources was conducted. Studies were assessed for inclusion by two authors according to prespecified criteria. Data collection processes, analysis and risk of bias assessment were planned.

Results 31 studies were included for analysis. These consisted of prospective and retrospective case series, cohort studies and case reports. None of the studies included a comparison group. No statistical analysis was performed. Descriptive data of included studies and narrative synthesis are presented.

Conclusions No high-quality randomised controlled trials were found and thus evidence in relation to PP as a treatment for non-intubated patients with type 1 respiratory failure is lacking.

Key messages

What is already known on this subject

- Prone positioning (PP) in intubated, mechanically ventilated patients has been demonstrated to reduce mortality, particularly in patients with severe acute respiratory distress syndrome (ARDS).
- PP has been used extensively during the COVID-19 pandemic in awake, non-intubated patients despite the lack of robust evidence of benefit.

What this study adds

- In this systematic review, we found no high-quality evidence that PP in awake, non-intubated patients reduces rates of subsequent intubation or decreases mortality.
- There was some signal that PP may improve hypoxia.
- However, randomised controlled trials are needed to assess whether PP in awake, non-intubated patients confers patient benefit.

INTRODUCTION

Acute respiratory failure is a leading reason for endotracheal intubation, mechanical ventilation and referral to the intensive care unit (ICU). Patients have traditionally been cared for in a recumbent or semirecumbent position. Prone positioning (PP) refers to the practice of positioning patients on their ventral surface. Theoretically, the reasons why PP might convey substantial physiological benefit include improved gas exchange via more homogeneous matching of ventilation and perfusion, increased cardiac output from optimisation of right ventricular preload and afterload, and improved drainage of secretions via the general dorsal lung to ventral trachea drainage vector.[1–3]

In 2013, the Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA) Trial demonstrated that PP, for a minimum of 16 hours continuously, conveyed a mortality benefit at 28 days, for mechanically ventilated patients with moderate to severe acute respiratory distress syndrome (ARDS) (ie, P/F ratio <150 mm Hg). Prior to the publication of PROSEVA, several trials demonstrated no significant benefit in clinically relevant outcomes when PP was applied across a broader group of patients. This is despite evidence that PP improved oxygenation across all groups of mechanically ventilated patients with ARDS. This contrast demonstrates the importance of randomised controlled trials (RCTs) in determining whether improvement in physiological markers translates to improvement in patient-oriented outcomes, as well as in determining specific protocols that are effective, and which patient groups stand to benefit.

PP in patients who are not intubated has been less well studied. The capacity for awake patients to modulate their own position, cough and exercise voluntary control makes them a physiologically distinct population from heavily sedated intubated patients. Therefore, it is not clear that the benefit conveyed by PP on intubated patients is transferable. Potential harms of PP in non-intubated patients are yet to be elucidated but may include dislodged venous access or O_2 delivery devices, delay to intubation and pressure injuries. Tolerance

of PP, especially for prolonged periods, is considerably more variable in awake patients than in those who are deeply sedated.

The current COVID-19 pandemic has resulted in hospitals and ICUs being overwhelmed with patients in respiratory failure. COVID-19 is a viral pneumonia caused by SARS-CoV-2 infection often leading to severe hypoxia, ARDS and respiratory failure.[4] About 15% of patients with COVID-19 require oxygen therapy and about 5% require mechanical ventilation.[5] Despite a lack of strong supporting evidence, PP in non-intubated patients has been recommended in guidelines and advocated by influential FOAMed sites as a means to avoid endotracheal intubation for COVID-19-associated respiratory failure.[6]

If PP is shown to be beneficial in non-intubated patients, this cost-effective intervention could have a substantial impact on preserving hospital resources. Despite the pressures the COVID-19 pandemic has placed on healthcare systems, it remains important to ensure that this intervention is supported by quality evidence.

The objective of this review was to identify and synthesise the evidence related to PP in non-intubated patients with type 1 respiratory failure from all aetiologies.

METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was prospectively registered on the PROSPERO website (PROSPERO 2020 CRD42020184705).

Outcomes

The primary outcome was endotracheal intubation due to progressive respiratory failure. Secondary outcomes included change in oxygenation (PaO_2/FiO_2), need for escalation of respiratory support without requiring intubation, admission to ICU, mortality, adverse effects of PP, length of hospital stay and ventilator-free days.

Patient and public involvement

Patients and the public were not involved in the design, evaluation or dissemination of this research.

Literature search

A literature search was designed with the assistance of a medical librarian and performed on 14 August 2020. The following databases were searched:

1. PubMed.
2. Google Scholar.
3. WHO COVID-19 database.
4. Cochrane Clinical Trials Register.
5. Grey sources.

The search was conducted from inception of databases to 14 August 2020 and had no language restriction. Grey sources included Google and Google Scholar, FOAMed sites, reference lists of articles, clinical trial registries and conference abstracts. Titles and abstracts were reviewed, and full text of relevant and potentially relevant articles were obtained. The search strategy for MEDLINE is included as online supplemental appendix 1.

Inclusion and exclusion criteria

Articles for inclusion were limited to those available in English, with no restrictions on the country of origin. Studies included were those conducted on adult patients with acute type 1 respiratory failure, who were spontaneously breathing, and who underwent PP of any duration as a therapeutic intervention. Studies on paediatric patients, or on patients intubated at study commencement, were excluded.

Controlled trials and observational studies that included a comparison group were to be included in the final quantitative review. Case series and cohort studies were also reviewed for their narrative value. Editorials, commentaries and opinion pieces were excluded.

Study selection, data extraction and synthesis

Studies were screened for relevance and independently reviewed by two authors who assessed the studies against the inclusion/exclusion criteria. Arbitration was provided by a third author when required.

An electronic tool was designed to facilitate data extraction by two independent investigators. We also planned to assess the quality of included studies using the Cochrane risk of bias tool by two authors independently, with arbitration by a third author if required.

Analysis

Descriptive data about study characteristics are presented. Our plan for statistical analysis was to use RevMan, V.5.4, The Cochrane Collaboration, 2020, presenting risk ratios for the dichotomous outcomes (eg, primary outcome of endotracheal intubation) and difference in means (or standardised mean difference) for continuous outcomes. We planned to use the inverse variance approach to meta-analysis with either fixed or random effects meta-analysis. Heterogeneity was to be assessed with I^2.

Changes from protocol

Small changes were required from the published protocol. The original search was conducted from 1995 to present; however, this was subsequently extended to the inception of databases. No meta-analysis was performed as no suitable studies were identified. The planned quality assessment was changed from the Cochrane risk of bias tool to the methodological index for non-randomised studies (MINORS) tool,[7] a validated tool for non-randomised studies, as this was better suited to the types of studies found.

RESULTS

The PRISMA flow diagram is presented in figure 1. The search strategy identified 725 records. After removing duplicates, 561 abstracts were screened. We obtained 57 full-text articles for detailed review. Thirty-one records were agreed to have data that could contribute value to the review.[8–38] Excluded full-text articles are listed in online supplemental appendix 2. No identified studies included an appropriate comparator and therefore no statistical analysis was performed.

The articles reviewed and their major findings are summarised in online supplemental table 1 and 2. The design of the studies reviewed is summarised in table 1.

The nine cohort studies identified were assessed for methodological quality with the MINORS tool[7] (table 2). Only two studies scored higher than 10 of a maximum 16 for non-comparative studies.

Heterogeneity of design and methodology was evident across all the included studies. For the larger studies, patients were selected via convenience sampling or cross-sectional survey. Protocols for PP varied with regard to level of ergonomic support and supervision. Some protocols combined PP with

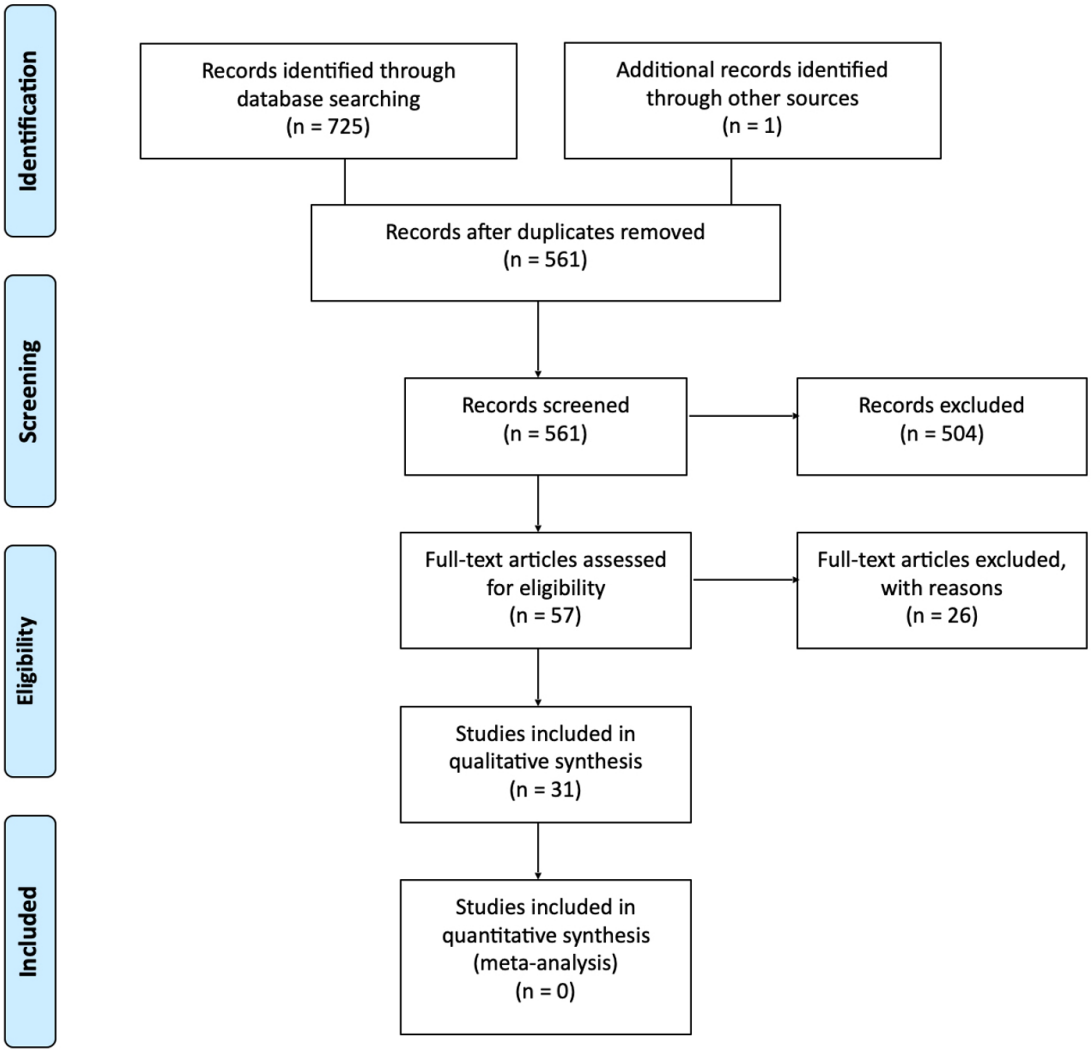

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

other postures. Duration and frequency also varied, and in some protocols was very limited due to poor patient tolerance. The devices used for respiratory support included standard nasal cannulae, Hudson masks, non-rebreather masks, high flow nasal cannulae, mask non-invasive ventilation and helmet continuous positive airway pressure (CPAP). In some studies, the mode of respiratory support was changed with the initiation of PP. The most common outcome measure was oxygenation (PaO_2/FiO_2). Other outcome measures included rate of intubation, dyspnoea, respiratory rate, haemodynamic parameters, tolerance, comfort and mortality. Some of the studies included data on adverse events. Limited documentation and missing data were noted in several studies.

Protocols for capturing data also differed between studies. To illustrate, SPO_2 and PaO_2/FiO_2 were measured at different times depending on the study, with examples including 5 min post PP, intervals from 10 to 60 min, post return to the supine position or as a single daily measurement. Rates of intubation were occasionally reported. Only a few studies reported time-to-event outcomes such as mortality or hospital discharge.

Table 1 Design of included studies

Study design	COVID-19 studies	Non-COVID-19 studies
Prospective observational cohort studies	5	1
Retrospective observational cohort studies	3	0
Case series/single case studies	16	6

Although meta-analysis was not possible, some comments can be made in relation to the available data. Of note, it appeared that PP resulted in improved oxygenation in many patients across the studies. This was observed as a consistent before-and-after effect following initiation of PP. While some patients maintained improved oxygenation with resupination, most did not. The findings in terms of other respiratory parameters like respiratory rate, work of breathing and dyspnoea were noted to either improve or remain unchanged.

Two studies[22 28] reported lower than anticipated rates of intubation in patients prescribed PP, but in the absence of true comparator groups, no real conclusions can be drawn. Coppo *et al* noted that there was no difference in the rate of intubation between patients who responded to PP with improved oxygenation relative to non-responders.[16]

Nine studies reported on the outcome of tolerance. Two reported no intolerance (or 100% tolerance). In other studies, intolerance ranged from 8% to 40%. Only Coppo *et al* delineated reasons for intolerance—five for discomfort, one for coughing, one for non-cooperation and two for worsening of

Table 2 MINORS score for the identified PP cohort studies

Criteria	Burton-Papp *et al*[17]	Caputo *et al*[18]	Coppo *et al*[16]	Ding *et al*[22]	Dong *et al*[23]	Elharrar *et al*[24]	Lawton *et al*[28]	Retucci *et al*[32]	Sartini *et al*[34]
1. A clearly stated aim	1	1	2	2	1	2	1	2	1
2. Inclusion of consecutive patients	1	2	0	1	0	2	1	2	0
3. Prospective collection of data	0	2	2	2	0	2	0	2	1
4. Endpoints appropriate to the aim of the study	1	1	2	2	1	1	1	1	1
5. Unbiased assessment of the study endpoint	1	1	1	1	1	1	0	1	1
6. Follow-up period appropriate to the aim of the study	2	1	2	1	1	1	2	0	1
7. Loss to follow-up less than 5%	1	1	1	1	0	1	2	1	1
8. Prospective calculation of study size	0	0	2	2	0	0	0	0	0
9. An adequate control group	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
10. Contemporary groups	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11. Baseline equivalence of groups	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12. Adequate statistical analysis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total score	7	9	12	12	4	10	7	9	6

Each criteria is scored either: 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The ideal score is 16 for non-comparative studies and 24 for comparative studies.
PP, prone positioning.

respiratory parameters (from 56 patients enrolled).[16] Of the two studies that reported 100% tolerance, one prescribed PP sessions of 1-hour duration and excluded patients requiring FiO_2 >50%.[29] The other specified no standardised duration of PP.[34] Burton-Papp *et al* reported that poor tolerance seemed to correlate with increased risk of intubation.[17] No other adverse events were reported.

DISCUSSION

Our systematic review found no high-quality evidence to support the use of PP in the management of awake, non-intubated, adult patients with respiratory failure, in terms of clinically relevant outcome measures. Despite this, the available data suggest that PP may improve oxygenation and appears to be sufficiently safe for further study.

Our review found that 24 of the 31 studies published on PP in non-intubated patients have been conducted during the COVID-19 pandemic. The context for these studies has been one of system overwhelm, need for innovation and diversion of resources to support the clinical workload. PP is distinguished from other therapies in that it is a cheap, non-pharmacological, behavioural intervention, conducted with the necessary cooperation of the patient. The same features that make PP attractive as a therapy make it difficult to study and more likely to be prescribed, even when high-quality evidence is lacking. These contextual factors may explain why we did not find any RCTs or uncontrolled observational trials with appropriate comparator groups which we could include in a quantitative analysis. The included papers consisted solely of case studies, case series and observational cohorts for qualitative or narrative review.

As is the nature of observational study design, the included studies were vulnerable to selection bias, favouring the inclusion of patients able to tolerate PP. Such patients are likely to be younger, less sick, have fewer comorbidities and better physiological reserve, thus inflating the apparent effectiveness of the intervention. For example, in one of the largest cohort studies of patients with COVID-19 in Italy, the included convenience sample was, on average, 10 years younger than that of patients not enrolled.[15] Age is known to be the most important factor associated with mortality for COVID-19.

Other confounding factors noted in many of the studies included the bundling of PP with cointerventions such as antiviral medications, hydroxychloroquine and steroids. Additionally, there was variation in the mode of respiratory support both within and between studies, including some studies where changing the mode of respiratory support coincided with commencement of PP. Lawton *et al* found that the relatively early application of mask CPAP and awake PP resulted in a lower than expected rate of ICU admission and intubation. This is despite the study population having a higher burden of risk factors for severe COVID-19 disease than the reference population of the UK ISARIC database, with the exception of age.[28] While the reported outcomes were impressive, the bundling of mask CPAP with PP, lack of detail as to how many patients received PP and the very small amount of PP prescribed limit the conclusions possible from this study. Future trials will ideally examine the effectiveness of PP as a standalone intervention, compared with 'standard care' determined by the broader evidence base at the time.

Significant heterogeneity was noted both across and within studies, in terms of the frequency, timing and duration of PP. Most protocols were designed and applied with a degree of pragmatism and allowed for broad variation in tolerance. For

example, many prescribed a minimum duration and frequency of PP, but no upper limit. At least one study excluded intolerant patients from the study group. Special note is also warranted on the subject of supervision, which likely increases compliance and safety, but also increases resource use. Given the presence of two nurses and a physician in one study, the purported resource savings are likely to have been negated. Researchers protocolising PP for future clinical trials need to consider the importance of cost, reproducibility and tolerance.

Outcome measures differed between studies. Many focused on short-term improvement in oxygenation. Indeed, in the studies that used oxygenation as an outcome measure, many patients exhibited a significant improvement, temporally related to the commencement of PP. In some cases, this improvement persisted after resupination. And yet, when Coppo *et al* then compared these 'responders' to the 'non-responders' in terms of subsequent rate of intubation, they found no difference.[16] This highly relevant observation illustrates the point that physiological endpoints can be poor surrogates for clinically relevant outcomes. Indeed, transient improvements in oxygenation from PP could delay inevitable intubation and lead to worse patient outcomes. Thus, future studies should focus on patient-oriented outcomes, such as avoidance of intubation and mortality.

Just 7 of the 34 reviewed papers looked at the effect of PP in the treatment of patients with respiratory failure from causes other than COVID-19. Aetiologies included bilateral pneumonia, viral pneumonia, drowning, thoracic trauma with pulmonary contusions, lupus pneumonitis, bone marrow transplantation and atelectasis. All these studies reported improvement in oxygenation, temporally associated with the initiation of PP, though again, the lack of comparator groups limits how much can be concluded. The findings do, however, raise the possibility that PP may have utility in respiratory failure due to a broad range of causes.

It is also plausible that any potential benefit of PP in non-intubated patients will be limited to certain subgroups. Indeed, this was revealed in the study of PP for mechanically ventilated patients with ARDS. A Cochrane review on this subject found that benefits were confined to patients with severe hypoxaemia in whom PP was implemented early and applied for a prolonged period.[3] The review found no convincing evidence of benefit nor harm from PP in a broader group of patients.[3] The same subgroup was shown to benefit from PP in the PROSEVA trial, where from 466 included patients, mortality in the prone group was 16.0%, compared with 32.8% in the supine group ($p<0.001$).[39] In non-intubated patients, there are insufficient data to inform which patients are likely to benefit from PP and which patients may be harmed.

Limitations

The review was restricted to full-text articles written in English. The abstracts of two Japanese case reports were found and not included as time constraints precluded their translation and it was decided they would not have affected our conclusions. Also, this is a fast-moving field and we expect further data to be available soon. It will be imperative to continue to evaluate new evidence to ensure patients are offered interventions that are supported by data.

CONCLUSION

Despite theoretical physiological advantages, we could not find any high level evidence to demonstrate the clinical effectiveness of PP in non-intubated patients with respiratory failure. Although many patients appear to respond to the intervention with improved respiratory parameters, the absence of any comparator groups limits the conclusions that can be drawn. RCTs or other comparative studies are required to determine if clinical benefits exist and, if they do, which patients will benefit most. Future investigation may also serve to inform the optimisation of protocols and implementation of the intervention.

Contributors Dr HR and Dr TO'B were primarily involved in the inclusion/exclusion and analysis of the reviewed papers. Dr KR-B and Dr GW created the protocol for the planned quantitative analysis of the included papers. JF provided oversight, guidance and arbitration throughout. All authors contributed to the writing and editing of the manuscript. Research librarian, SH, is acknowledged as an important contributor for assisting with the literature search.

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Appendix 1. Medline search strategy

(awake[tiab] OR noninvasive[tiab] OR non invasive[tiab] OR nonintubated[tiab] OR non intubated[tiab] OR selfproning[tiab] OR self proning[tiab] OR spontaneous breath*[tiab]) AND (((covid*[tiab] OR SARS-CoV-2[tiab] OR 2019-nCoV[tiab] OR coronavirus*[tiab] OR corona virus*[tiab] OR nCov 2019[tiab] OR sars[tiab] OR MERS[tiab] OR pneumoni*[tiab] OR lung inflammation*[tiab] OR Pulmonary Inflammation*[tiab] OR Severe Acute Respiratory Syndrome[tiab] OR Middle East respiratory syndrome[tiab] OR Shock Lung[tiab] OR ARDS[tiab] OR Acute Respiratory Distress Syndrome[tiab] OR Adult Respiratory Distress Syndrome[tiab] OR Respiratory disease*[tiab] OR Respiratory failure[tiab]) OR ((Respiratory tract diseases[mh] OR Respiratory tract infections[mh] OR Lung diseases[mh] OR Coronavirus[mh] OR COVID-19[Supplementary Concept]) NOT (animals[mh] NOT humans[mh]))) AND (Prone position[mh] OR (Prone[tiab] AND position*[tiab]) OR Proned[tiab] OR Proning[tiab] OR Pronation[tiab] OR prone ventilat*[tiab] OR (ventral[tiab] AND downward[tiab]) OR face down[tiab]))

Appendix 2. List of excluded full text papers

First Author	Study Name	Reason for Exclusion
Alhazzani	Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)	Guideline only
Bamford	ICS Guidance for the Prone Positioning of the Conscious COVID Patient 2020	Guideline only
Cordero	Soporte ventilatorio no invasivo y posición prono despierto en paciente con COVID-19	Narrative review
Dikmen	Prone position in nonintubated hypoxemic respiratory failure. New tool to avoid endotracheal intubation?	Narrative review
Feltracco	Noninvasive ventilation in postoperative care of lung transplant recipients	Post-operative transplant patients
Feltracco	Noninvasive high-frequency percussive ventilation in the prone position after lung transplantation	Post-operative transplant patients
Feltracco	Non-invasive ventilation in prone position for refractory hypoxemia after bilateral lung transplantation	Post-operative transplant patients
Ghomari	Experience of the practice of prone position in patients with acute respiratory distress syndrome in intensive care (CHU Oran)	Intubated patients
Guerin	Prone positioning in severe acute respiratory distress syndrome	Intubated patients
Hasanin	Evaluation of fluid responsiveness during COVID-19 pandemic: what are the remaining choices?	Not related to prone positioning
Huang	Early and Critical Care in Severe Patients with COVID-19 in Jiangsu Province, China: A Descriptive Study	General descriptive paper, limited empirical data, wide ranging interventions
Karamouzos	High flow nasal cannula oxygen therapy in adults with COVID-19 respiratory failure. A case report	PP not part of intervention
Lee	Airway Pressure Release Ventilation Combined With Prone Positioning in Acute Respiratory Distress Syndrome: Old Tricks New Synergy: A Case Series	Intubated patients
Lin	Effect of body position on gas exchange in patients with idiopathic pulmonary alveolar proteinosis - No benefit of prone positioning	Patients with IPAP – chronic lung disease
Lindahl	Using the prone position could help to combat the development of fast hypoxia in some patients with COVID-19	Narrative mini-review – focus on physiological changes and mechanism of prone positioning
Longhini	Helmet Continuous Positive Airway Pressure and prone positioning: a proposal for an early management of COVID-19 patients	Suggested guideline
Ludwin	Cardiopulmonary Resuscitation in the prone position: a good option for patients with COVID-19	Guidance for CPR for patients in PP
Mędrzycka-Dąbrowska	Prone ventilation of critically ill adults with COVID-19: how to perform CPR in cardiac arrest?	Guidance for CPR for patients in PP
Qadir	Adjunctive Therapies in ARDS: The Disconnect Between Clinical Trials and Clinical Practice	Narrative piece
Sarma	Prone Positioning in Awake, Nonintubated Patients With COVID-19: Necessity Is the Mother of Invention	Review article
Scaravilli	Corrigendum to Reply to: Prone position in nonintubated hypoxemic respiratory failure. New tool to avoid endotracheal intubation? [J Crit Care 30/6 (2015) Page 1416]	Published correspondence
Sugimoto	Humidifier Use and Prone Positioning in a Patient with Severe COVID-19 Pneumonia and Endotracheal Tube Impaction Due to Highly Viscous Sputum	Intubated patient
Sun	Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province	Descriptive article – multi-faceted intervention
Telias	Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19?	Descriptive paper with focus on physiological changes and mechansism of PP
Vittorio	Reply to: Prone position in nonintubated hypoxemic respiratory failure. New tool to avoid endotracheal intubation?	Published correspondence
Winck	COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems	Narrative review

Supplementary Table 1. Summary of findings from included COVID-19 studies

Study Details	Study Design	Case numbers	Study Population	Intervention	Outcome Measure(s)	Summary of Findings	Study Limitations
Bastoni et al (2020), Italy	Case Series	10 patients	Non-intubated patients undergoing helmet CPAP for respiratory failure secondary to confirmed COVID-19 pneumonia	PP while continuing helmet CPAP plus low dose morphine infusion (to assist with compliance)	• PaO2/FiO2 one hour after commencing PP • Point-of-care lung US signs	• 4 patients were unable to tolerate PP • In 6 patients who were able to PP, median PaO2/FiO2 improved from 68+/-5 to 97+/-8 mmHg • Lung US showed no difference in B line quantity and distribution	• No comparator group • Small sample size • Limited documentation
Burton-Papp al (2020), England	Retrospective, single centre, Observational Cohort Study	33	Non-intubated patients who were COVID-19 positive and who required additional respiratory support beyond oxygen therapy (P/F ratio <200)	NIV (either CPAP or BiPAP) + encouragement to PP depending on tolerability	• Intubation • PaO2/FiO2 ratio • RR • HR • ICU Length of Stay (LOS) • Hospital LOS • Mortality	• 7/20 patients required intubation • Mean PaO2/FiO2 ratio improved by 28.7mmHg • Patients who were subsequently intubated demonstrated lower tolerance of PP and significantly poorer response to PP in terms of oxygenation • RR and HR were unchanged • For those who avoided intubation, ICU LOS was 5 days and Hospital LOS was 11 days • All patients survived to hospital discharge	• No comparator group • Small sample size • Retrospective • Non-representative population (ie most patients aged <60)
Caputo, et al (2020), USA	Prospective observational cohort study (convenience sample)	50	Non-intubated patients with suspected COVID-19 with hypoxia on arrival at the Emergency Department despite supplemental O2	PP without change in FiO2 / O2 delivery device	• Change in SpO2 before and 5 minutes after PP • Requirement for intubation within 24 hours	• Median SpO2 - at triage: 80% - after application of supplemental O2: 84% - after 5 minutes of PP: 94% • 13 patients (24%) failed to improve or maintain SpO2 and required intubation within 24 hours	• No comparator group • Questionable clinical relevance of SpO2 at 5 minutes after PP
Cohen et al, (2020), Israel	Case series	2	Non-intubated patients with Type 1 Respiratory failure secondary to COVID-19 pneumonia	PP	• Oxygenation (SpO2) • RR	• Both patients demonstrated marked improvement in SpO2 within 10-30 minutes after commencing PP • One of the patients exhibited a significant reduction in RR with PP	• No comparator group • Small sample size • Marked variation in PP protocols
Coppo et al (2020), Italy	Prospective Cohort study (convenience sample)	47	Non-intubated patients Age 18-75 COVID-19 positive	PP for at least 3 hours. O2 not changed if possible • Helmet CPAP 44 • Reservoir mask 9 • Venturi mask 3	• PaO2/FiO2 ratio - prior to PP - 10min after PP commenced - 1hour after moved back to supine • PaCO2 change • Intubation rate • Comfort	• Oxygenation improved by >50% 10min after PP • Oxygenation improvement not statistically significant once supine position resumed • No difference in accessory muscle use, dyspnea or PaCO2 • Responders to treatment had PP initiated earlier in their hospital stay • Higher CRP and LDH levels correlated to lower PF ratios • No difference in intubation rate between those who responded to PP and those who did not respond	• No comparator group • Significant selection bias to data provided • Exclusion criteria broad and subjective (eg NYHA class<2, BNP > double normal, had contraindication as decided by the attending physician) • 610 eligible patients did not participate • Adverse events not recorded • Excluded 9 patients based on poor tolerance • Excluded a patient based on age after intervention was performed

Damarla et al (2020), USA	Case series	10	Non-intubated adult patients who were COVID-19 positive with rapidly increasing O2 requirements or increased work of breathing (WOB) Admission to ICU Either on HFNP or NP alone	Patients asked to alternate between prone and supine 2 hourly during the day and sleep in prone position as tolerated	• Change in SpO2and RR 1 hour after initial PP compared to pre prone. • Incidence of intubation within two weeks of first PP • 28 day follow up	• Oxygenation improved following PP. Median SpO2 at 1 hour increased from 94% to 98%. • WOB improved with median RR reduced from 31 to 22. • No adverse events recorded. • 8/10 patients did not require intubation • 7/10 did not require escalation of respiratory care • All patients had been discharged home at 28 day follow up	• No comparator group • Small sample size • Measures of patient dyspnea and comfort not collected • Data on patient adherence to PP not collected after 1st episode • One patient also enrolled in trial remdesivir v placebo
Despres et al (2020), France	Case series	6	Non-intubated patients who were COVID-19 positive with rapidly worsening dyspnea and oxygenation (SpO2 ≤92% despite O2 ≥ 5L/min)	PP with either HFNC or conventional O2 therapy (COT) Duration >1 hour and was maintained depending on tolerance and repeated as necessary	• PaO2/FiO2 ratio • Need for intubation • Subjective dyspnea	• 9 sessions total assessed of PP in 6 patients • 4/9 were with HFNC • 5/9 were with COT • PaO2/FiO2 ratio improved after 4 sessions (3 HFNP, 1 COT) • 3/6 patients intubated • All patients described subjective enhancement of dyspnea with PP	• No comparator group • Small sample size
Dong, et al (2020), China	Retrospective cohort study	25	Non-intubated COVID-19 patients with PaO2/FiO2 <300, RR≥30 or SpO2≤93% *Included patients receiving O2 via nasal prongs, O2 masks, HFNC, NIV masks *Of 48 patients identified in cross-sectional survey, 23 were excluded for reasons including inter-hospital transfer, intolerance of treatment protocol or rapid improvement resulting in exit from treatment protocol at <5days	PP *Duration determined by severity: a) PaO2/FiO2 <200 and bilateral chest infiltrates on CT: 10h/day b) All other patients: 4h/day *For patients not tolerating PP for prescribed length of time, Lateral Position was prescribed	• Mortality • Need for intubation	• All 25 patients survived • None required intubation	• No comparator group • Small sample size • Retrospective • Missing data • Not peer reviewed • Selection bias
Elharrar, et al (2020), France	Prospective, single centre, observational cohort study	24	Non-intubated patients with acute respiratory failure secondary to COVID-19	PP without change in O2 delivery device	• Patient tolerance ≥1h, ≥3h • Proportion of "Responders" (PaO2 increase ≥ 20% before vs during PP) • Variation PaO2 or PaCO2 before vs during PP • Proportion of "persistent responders" (PaO2 increase ≥20% before PP vs 6-12h after supination) • Complications • 10 day follow up	• Patient tolerance: - 4 did not tolerate for ≥1hour - 5 tolerated for 1-3 hours - 15 tolerated for ≥3 hours • Responders: 6 patients (25% of total, 40% of those who tolerated ≥3hours) • Persistent Responders: 3 patients • Complications: - 10 patients reported back pain during PP - No major complications • 10 day follow-up: - 5 patients required intubation and mechanical ventilation	• No comparator group • Small sample size • Outcome measures of questionable clinical significance

Elkattawy, et al (2020), USA	Case Report	1	Non-intubated patient with acute respiratory failure secondary to COVID-19	PP with O2 via nasal cannulae	• Tolerance • Oxygenation	• PP was well tolerated for 12 hours • Patient exhibited significant improvement in oxygenation and secretion clearance	• No comparator group • Small sample size
Froelich et al (2020), France	3 case reports	3	Non-intubated patients with Confirmed COVID-19	Various position: semi-sitting in bed sitting in chair, supine, left and right lateral, PP and PP ergonomically supported Oxygen: Mask 15L/min + NP 6L/min	• Vital signs • Dyspnoea	• Placing the most affected part of the lung on top had the best result • 2/3 tolerated prone positions with significant increases in SpO2 in the ergonomically supported PP (1 patient tolerated <30min)	• No comparator group • Small sample size • Poor tolerance with only 1 >30min • Limited measurements of useful data • No comparator group
Gallardo et al (2020), Italy	Case Series	13	Patients with moderate to severe ARDS secondary to COVID-19 (PaO2:FiO2 ratio <150) who were undergoing Helmet CPAP	PP initiated when PaO2:FiO2 <150 and maintained as long as tolerated (range 2-3.5 hours)	• PaO2:FiO2 ratio • Complications	• 12/13 patients exhibited a significant improvement in PaO2:FiO2 ratio • No complications were recorded	• No comparator group • Small sample size • Retrospective
Jena et al (2020), India	Case Report	1	Non-intubated patient with type I respiratory failure secondary to COVID-19	O2 therapy continuing via NRBM combined with PP for 30min every 2 hours during the day and continuously overnight *Total: 12 hours/day	• Oxygenation	• Patient demonstrated a progressive improvement in mean oxygenation over 2 days after commencing the PP protocol	• No comparator group • Small sample size
Lawton et al (2020), UK	Retrospective observational cohort study	559	Consecutive patients with COVID-19 admitted to Bradford Royal Infirmary, UK prior to 21 May 2020	Treatment algorithm utilising escalating O2 therapy *PP for 30 minutes 2x/day was encouraged in conjunction with the commencement of mask CPAP on the ward	• ICU admission • Intubation • Hospital Mortality • ICU Mortality *Comparisons were made against ISARIC database	• 40 patients were admitted to ICU and 27 patients were intubated (*Based on ISARIC data, expected numbers were 92 requiring ICU admission and 55 requiring intubation) • Hospital Mortality was 33.3% (compared to 38.6% for ISARIC) • ICU Mortality was 54.5% (ISARIC: 53.7%)	• No true comparator group • Retrospective • PP played a relatively minor role in the treatment algorithm and was not reported in detail in the findings • Early commencement of CPAP was the main intervention • Study population not representative of general UK (though likely skewed towards more severe disease due to higher comorbidities and low socio-economic status)
Ng et al (2020), Singapore	Case series	10	Non-intubated patients who were COVID-19 positive and requiring O2 in ward setting. *Excluded if FiO2 ≥50%	PP 1 hr per session, 5 sessions/day, spaced 3 hours apart during awake hours	• Haemodynamics and SpO2 at 0, 30 and 60 mins from start of each session	• 3 patients required increased oxygen support in ICU • 1 patient intubated and subsequently died • All able to tolerate PP protocol	• No comparator group • Small sample size • Rates of intubation compared a retrospective group of patients but no data provided • 8 patients initiated on other therapies (eg lopinavir/ritonavir)

Paul et al (2020), USA	Case Series	2	Non-intubated patients with Type I respiratory failure secondary to COVID-19 *Patient 2 deteriorated post extubation	PP accompanied by low dose alprazolam to manage anxiety and enhance tolerance	• Oxygenation	• Both patients exhibited marked improvement in oxygenation and decrease in O2 requirements within hours of pronation • Neither patient required subsequent intubation • Both were subsequently discharged from the ICU	• No comparator group • Small sample size
Retucci et al, (2020), Italy	Prospective, Pilot Observational Study	26	Consecutive patients with Type I respiratory failure secondary to COVID-19 who were already undergoing Helmet CPAP	Trial of PP (if lung impairment was bilateral) or Lateral Positioning (if lung impairment was unilateral - good lung down)	• A-a Gradient • RR • Dyspnoea • SBP • Patient comfort *Measured: - Prior to PP/LP - 1 hour after commencing PP/LP - 45 minutes after resuming semi-recumbent position *Each trial was designated as "success" or "fail" according to pre-designated criteria for the above measures	• Total of 39 trials (12 PP, 27 LP) were conducted • 6 trials were designated "successful" • 15 trials were designated "failed" • 2 patients were unable to tolerate PP/LP • 7 patients were intubated • 2 patients died	• No comparator group • Small sample size • Arbitrary designation of success/fail criteria (eg decrease in A-a Gradient >20%)
Xu, et al (2020), China	Case Series	10	Non-intubated patients with acute respiratory failure secondary to COVID-19 (PaO2/FiO2<300 mmHg)	Management bundle including: • HFNC • PP>16h/d • Antiviral drug • Negative volume balance • Corticosteroid	• Respiratory parameters measured each day for 3 days, before and after PP - PaO2/FiO2 ratio - PaCO2 • Intubation	• After PP: - Slight increase in median PaCO2 - Significant increase in PaO2/FiO2 • None of the patients progressed to critical illness / required intubation	• No comparator group • Small sample size • Retrospective
Sartini, et al (2020), Italy	Prospective observational study *Selected by cross-sectional survey	15	Non-intubated patients with acute respiratory failure secondary to COVID-19, limited response to NIV in supine position	PP+NIV *Duration and frequency was individualised	• Respiratory parameters *data collected: - before NIV+PP - during NIV+PP (1 hour after start) - 1 hour after NIV+PP ending • Patient comfort (numerical rating scale) • 14 day follow-up	• Respiratory rate: all patients had a reduction during and after pronation • SpO2 and PaO2/FiO2 ratio: - all patients had improvement during pronation - 12/15 patients had improvement after pronation • Comfort: - 11/15 patients reported improvement during pronation - 13/15 patients reported improvement after pronation - 2/15 reported no change • At 14 days: - 9 patients discharge home - 1 improved and ceased pronation - 3 continued pronation - 1 intubated - 1 died	• No comparator group • Small sample size • Intervention compares PP+NIV to supine position with no NIV - therefore does not isolate PP as a variable • Non-standardised protocol • Observation study only • Selection bias: didn't include those patients who failed NIV in PP or those that were intubated or died before selection date.
Sztajnbok, et al (2020), Brazil	Case Series	2	Non-intubated patients with acute respiratory failure secondary to COVID-19	PP without change in O2 delivery device (non-rebreather 10L)	• Oxygenation • Dyspnoea	• Both exhibited dramatic improvements in symptoms and oxygenation • Neither patient required intubation	• No comparator group • Small sample size

Thompson et al (2020), USA	Case series	29	Non-intubated patients who were COVID-19 positive with Severe respiratory failure • RR >30 • SpO2 <93% despite O2 (15L/min by Non-rebreather mask or 6L/min by NP)	PP as long as tolerated up to 24 hours/day. Minimum 1 hour	• Change in SpO2 before and 1 hour after initiation of PP	• 4 refused any PP attempt and were immediately intubated • Median improvement in SpO2 1 hour after PP was 7%. • 19/25 had improved SpO2 • 12/25 required intubation	• No comparator group • Small sample size
Tu et al (2020), China	Pilot study Case series	9	Non-intubated patients who were COVID-19 positive receiving O2 via HFNC *PaO2/FiO2 <150mmHg	Twice daily PP procedures	Pre and post PP measurements of: • PaO2 • PaCO • SaO2 • pH Intubation	• Median duration of PP was 2 hours. IQR 1-4hours • SaO2 and PaO2 increased post PP • 2 required intubation (1 extubated day 8, 1 ECMO	• No comparator group • Small sample size • No time points of when post PP measurements were taken
Whittemore et al (2020), UK	Case Report	1	Non-intubated 60 year old male with Type I respiratory failure secondary to COVID-19	Prolonged PP > 18 hours/ day	• Oxygenation	• Marked and rapid improvement in oxygenation occurred with each resumption of PP	• No comparator group • Small sample size

Supplementary Table 2. Summary of findings from included non-COVID-19 studies

Study Details	Study Design	Case numbers	Study Population	Intervention	Outcome Measure(s)	Summary of Findings	Study Limitations
Bellone, Basile (2018), Italy	Case Series	3	Non-intubated patients with acute respiratory failure secondary to bilateral pneumonia with no significant improvement after 48 hours of standard treatment	PP prescribed 6 hours/day + HFNC	• Daily PaO2/FiO2, RR and PaCO2	• Improvement in respiratory parameters throughout the course of 5 days - most significant improvement between day 2 and 3	• No comparator group • Small sample size • Limited documentation • Multiple potential confounders
Ding, et al (2020), China	Prospective observational cohort study	20	Non-intubated patients with moderate to severe ARDS due to pneumonia (influenza / other viruses)	Treatment algorithm utilising an escalating protocol of HFNC / HFNC+PP / NIV / NIV+PP as determined by severity and response *Average period of PP was 2h, 2x/day	• Rate of intubation • Improvement in PaO2/FiO2 ratio	• Intubation rate was 55% (11/20 patients) *The authors felt this compared favourably to the anticipated intubation rate for moderate to severe ARDS of 75% • Patients with more severe initial hypoxia were more likely to be intubated • PaO2/FiO2 showed a trend of increase in transitions from HFNC to HFNC+PP to NIV to NIV+PP	• No comparator group • Small sample size
Muralidhar (2015), India	Case Series	16	Non-intubated patients with severe ARDS and limited response to NIV in supine position	NIV (mask BiPAP) + PP	• Intubation • Oxygenation • Complications	• 14/16 patients "improved" and transitioned to supine NIV • 2/16 patients required intubation • No complications	• No comparator group • Small sample size • Retrospective • Limited documentation (published as a poster presentation abstract) • Not peer-reviewed
Perez-Nieto, et al (2020), Mexico	Case Series	6	Non-intubated patients with acute respiratory failure secondary to non-infective ARDS *Causes included: thoracic trauma with pulmonary contusions, lupus pneumonitis, bone marrow transplantation, atelectasis	PP prescribed 2-3h every 12h for 2 days + NIV or HFNC	• PaO2/FiO2 ratio and S/F ratio • Need for Intubation • Mortality	• All patients exhibited improved oxygenation with PP • 2/6 patients required intubation • 1 patient died	• No comparator group • Small sample size • Retrospective
Scaravilli, et al (2015), Italy	Case Series	15	Non-intubated ICU patients with acute respiratory failure (PiO2/FiO2 <300mmHg) + 1 episode of PP (?) *Causes included: - pneumonia (13) - fasciitis (1) - Sepsis of unknown origin (1)	PP (duration 2-8h) *Variable O2 delivery devices used	• Respiratory and haemodynamic parameters *data collected: - 1-2h prior to PP - during the last hour of PP - 6-8h post re-supination • Complications	• In total, 43 PP procedures were performed • 18 of these were performed with no change in respiratory support / O2 delivery device • Improvement in PaO2 occurred with PP relative to pre-PP and post-PP, though this did not reach statistical significance • No significant change was noted in respiratory rate or haemodynamic parameters • Complications: 2 PP procedures were interrupted due to patient intolerance	• No comparator group • Small sample size • Retrospective • Confounder: variation in O2 delivery device (Hudson mask/ HFNC / Helmet CPAP / NIV mask) and variation in FiO2/PEEP

Sorrenson, et al (2002), Denmark	Pilot study case series	4	Non-intubated patients with acute respiratory failure secondary to pneumonia	PP + O2 via nasal cannulae (duration 50-300min)	• PaO2/FiO2 • Intubation	• All patients exhibited significant improvements in oxygenation • None required intubation	• No comparator group • Small sample size • Conference abstract only
Tulleken, et al (1999), The Netherlands	Case Report	1	Non-intubated 16 year old male with acute respiratory failure secondary to near-drowning	PP + supplemental O2 via face mask 2 sessions of: • 3 hours • 20 hours	• PaO2	• Significant improvement in oxygenation within 1 hour • No ventilatory support required	• No comparator group • Small sample size
Valter, et al (2003), Denmark	Case series	4	Patients with acute respiratory failure in whom intubation was deemed indicated. *Causes included: bilateral pneumonia, infective exacerbation of COPD, bilateral pulmonary infiltrates with new myelodysplastic syndrome.	PP + supplemental O2 but no ventilatory support	• Intubation • Oxygenation • Death • Time to discharge	• All 4 patients exhibited significant improvement in symptoms and oxygenation within 1 hour • 1 pt was 1 day post extubation with deterioration at time of prone position which prevented re-intubation however died from a cerebral infarction 4 days later. • None subsequently required intubation • 3/4 patients had been trialled and failed on NIV prior to PP	• No comparator group • Small sample size