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Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE)

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ABSTRACT

OBJECTIVES

To assess the effectiveness of prone positioning to reduce the risk of death or respiratory failure in non-critically ill patients admitted to hospital with covid-19.

DESIGN

Multicentre pragmatic randomised clinical trial.

SETTING

15 hospitals in Canada and the United States from May 2020 until May 2021.

PARTICIPANTS

Eligible patients had a laboratory confirmed or a clinically highly suspected diagnosis of covid-19, needed supplemental oxygen (up to 50% fraction of inspired oxygen), and were able to independently lie prone with verbal instruction. Of the 570 patients who were assessed for eligibility, 257 were randomised and 248 were included in the analysis.

INTERVENTION

Patients were randomised 1:1 to prone positioning (that is, instructing a patient to lie on their stomach while they are in bed) or standard of care (that is, no instruction to adopt prone position).

MAIN OUTCOME MEASURES

The primary outcome was a composite of in-hospital death, mechanical ventilation, or worsening respiratory failure defined as needing at least 60% fraction of inspired oxygen for at least 24 hours. Secondary outcomes included the change in the

ratio of oxygen saturation to fraction of inspired oxygen.

RESULTS

The trial was stopped early on the basis of futility for the pre-specified primary outcome. The median time from hospital admission until randomisation was 1 day, the median age of patients was 56 (interquartile range 45-65) years, 89 (36%) patients were female, and 222 (90%) were receiving oxygen via nasal prongs at the time of randomisation. The median time spent prone in the first 72 hours was 6 (1.5-12.8) hours in total for the prone arm compared with 0 (0-2) hours in the control arm. The risk of the primary outcome was similar between the prone group (18 (14%) events) and the standard care group (17 (14%) events) (odds ratio 0.92, 95% confidence interval 0.44 to 1.92). The change in the ratio of oxygen saturation to fraction of inspired oxygen after 72 hours was similar for patients randomised to prone positioning and standard of care.

CONCLUSION

Among non-critically ill patients with hypoxaemia who were admitted to hospital with covid-19, a multifaceted intervention to increase prone positioning did not improve outcomes. However, wide confidence intervals preclude definitively ruling out benefit or harm. Adherence to prone positioning was poor, despite multiple efforts to increase it. Subsequent trials of prone positioning should aim to develop strategies to improve adherence to awake prone positioning.

STUDY REGISTRATION

ClinicalTrials.gov NCT04383613.

Introduction

As of December 2021, more than five million people worldwide had died from covid-19. The strongest risk factors for death are older age, comorbid disease, and severity of presenting illness, most commonly the presence of hypoxaemia.¹⁻³ Patients who present to hospital with severe hypoxaemia are typically cared for in an intensive care unit with mechanical ventilation. Patients without severe hypoxaemia are commonly cared for on a hospital ward with supplemental oxygen via nasal prongs or a face mask. However, approximately 20% of such patients progress to respiratory failure requiring mechanical ventilation.^{1,3}

In February 2020, reports emerged that prone positioning of patients with covid-19 and severe

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prone positioning is considered standard of care for mechanically ventilated patients who have severe acute respiratory distress syndrome

Recent data suggest that prone positioning is beneficial for patients with covid-19 who need high flow oxygen

Whether prone positioning is beneficial for patients not on high flow oxygen is unknown

WHAT THIS STUDY ADDS

Prone positioning is generally not well tolerated, and innovative approaches are needed to improve adherence

Clinical and physiological outcomes were similar with prone positioning and standard care among non-critically ill patients with hypoxaemia who were in hospital with covid-19

hypoxaemia may reduce the risk of respiratory failure and death.^{4,5} Prone positioning has been part of clinical practice since the 1970s and is considered standard of care for mechanically ventilated patients who have severe acute respiratory distress syndrome.^{6,7} Prone positioning can improve oxygenation for multiple physiological reasons, including decreased forces on the lungs from the heart and gastrointestinal organs that allow for improved lung expansion and decreased ventilation and perfusion mismatch.⁶ Early uncontrolled studies suggested that prone positioning might also be beneficial for patients with covid-19 who were not yet intubated, preventing the need for intubation.^{4,8} Because these findings occurred at a time when some intensive care units were overwhelmed and no effective treatments for covid-19 were available, they were shared widely on social media and in the lay press, leading to substantial adoption in practice.

Multiple observational studies have examined the effectiveness of prone positioning in non-intubated patients with covid-19.⁶ The results have been conflicting, with some studies showing a modest improvement in oxygenation and others showing no improvement.⁶ One randomised trial of 30 non-intubated patients with covid-19 identified no improvement in oxygenation, but the trial was stopped early owing to a lack of adherence to the intervention.⁹ A recently published meta-trial of patients needing high flow nasal cannulas identified a lower risk of treatment failure (that is, a composite of intubation or death) for patients randomised to prone positioning.¹⁰ Whether prone positioning is effective in managing patients with milder forms of hypoxaemia remains unclear. Because prone positioning has potential risks to patients (for example, aspiration and patient discomfort) and healthcare providers (requires more personnel time spent in the room with an infectious patient) and may be difficult for patients to tolerate, randomised trials are needed to evaluate the risks and benefits. We conducted a multicentre pragmatic randomised clinical trial to assess the effectiveness of prone positioning to reduce the risk of death or respiratory failure in non-critically ill patients admitted to hospital with covid-19 (NCT04383613).

Methods

Trial design

We conducted an unblinded pragmatic randomised clinical trial of prone positioning of patients admitted to hospital with confirmed or suspected covid-19 in 15 hospitals in Canada and the United States from May 2020 until May 2021. Our study included a mix of academic teaching hospitals (62%) and community hospitals (38%). All patients were on a ward at the time of randomisation, most hospitals (69%) had more than 120 inpatient ward beds, the patient to physician ratio was typically 15 to one, and the patient to nurse ratio was typically four to one. Patients were eligible for inclusion if they had a laboratory confirmed or clinically highly suspected diagnosis of covid-19, needed supplemental oxygen

(up to 50% fraction of inspired oxygen), and were able to independently adopt a prone position with verbal instruction. Randomisation took place within 48 hours of admission to hospital, and patients were excluded if prone positioning was contraindicated (for example, owing to recent abdominal surgery), impractical (for example, owing to dementia or severe delirium), or mechanical intubation was indicated at the time of randomisation as per the patient's treating physician (see study protocol). Co-enrolment in other clinical trials was allowed.

The trial protocol was approved by the institutional review board at each site (or by a centralised institutional review board as applicable) and was overseen by the trial's steering committee (NCT04383613). An independent data monitoring committee was established and reviewed the interim analysis results so that the trial investigators were blinded. Each patient gave informed consent. Patients were not involved in the design or planning of this study.

Data collection

We collected the following baseline data for each patient: demographics, comorbid conditions, vital signs, laboratory values, and imaging reports. We also recorded oxygenation and fraction of inspired oxygen data up to five times a day for the first 72 hours after randomisation. Given the pragmatic nature of this trial, these data were abstracted from the patient's chart on the basis of routine vital signs documentation.

We assessed self-reported time spent in the prone position from the time of randomisation to 72 hours, and from 72 hours until day 7. The duration of the hospital admission, occurrence of adverse events, receipt of mechanical ventilation, and vital status at hospital discharge were also recorded.

Randomisation and trial procedures

Patients were randomly assigned in a one to one ratio, stratified by site, to either prone positioning or standard of care (that is, no instruction to adopt prone position), using a web based system with concealment of allocation. We followed patients until the first of death, discharge from hospital, or 30 days. Patients randomised to prone positioning were recommended to adopt a prone position four times a day (up to two hours for each session) and encouraged to sleep in prone position overnight. These practices were recommended for up to seven days in hospital, until hospital discharge, or until the patient no longer needed supplemental oxygen (whichever came first). Multiple strategies were implemented to encourage prone positioning. Firstly, on enrolment, a member of our research team instructed participants in the prone position group to adopt and maintain prone positioning. Secondly, participants received a phone call from the research team to encourage them to adopt a prone position on day 3 and day 7. Our data from the feasibility analysis indicated that additional strategies were needed to improve adherence, so

we implemented additional strategies. Specifically, after reviewing the data from the first 30 patients randomised, we identified that the time spent prone for patients randomised to prone positioning was lower than anticipated (median time of seven hours over the first 72 hours). We decided to continue with the trial and implement additional strategies to increase prone positioning. The decision was also informed by the urgent need for high quality trial evidence on this question during the worsening state of the pandemic in North America.

Our additional, and now third, mechanism to improve adherence included a member of the research team visiting the patients in hospital to encourage them to adopt prone positioning. Fourthly, the nurses caring for the patients were requested to remind the patients to lie prone. Fifthly, at sites where this was possible, an electronic order indicating that the patient should adopt prone positioning was placed in the patient's electronic medical record. Sixthly, additional pillows were provided to patients randomised to prone positioning. Seventhly, one common reason for difficulty maintaining a prone position was arthritis and a history of lower back pain, so we incorporated this information into the exclusion criteria as an additional reason why patients should be excluded because of an inability to maintain prone position. Finally, we created a chart insert for sites with paper charts, indicating the arm to which the patient was randomised to serve as a reminder to the healthcare team.

Outcome measures

The primary outcome was a composite of in-hospital death, mechanical ventilation (that is, intubation or bilevel positive airway pressure), or worsening respiratory failure defined as needing at least 60% fraction of inspired oxygen for more than 24 hours. We included the last of these in our composite outcome because of the inclusion of patients who had a pre-specified do-not-intubate order. Secondary outcomes included the components of the composite analysed individually, time spent in prone position, change in the ratio of oxygen saturation to fraction of inspired oxygen, time to discharge from hospital, and the rate of serious adverse events.

Statistical analysis

Our trial was planned before effective treatments were available for patients with covid-19. We planned for 80% power and a two sided α of 0.05, and we assumed that the risk of our composite outcome would be 45%.¹¹ With the goal of detecting a 15% reduction in the primary outcome, our total estimated sample size was 340 and allowed for one interim analysis at 50% patient recruitment (n=170).

The primary analysis was based on an intention-to-treat approach. We analysed our primary outcome by using a multivariable logistic regression model, controlling for age and sex. Relative risk was estimated from the odds ratio. We planned a priori the following

subgroup analyses of the primary outcome: severity of hypoxaemia at randomisation based on arterial blood gas, age, chest radiograph findings, and amount of supplemental oxygen at baseline before randomisation (see supplementary methods).

We analysed our secondary analysis of time to hospital discharge by using a Cox proportional hazards model that adjusted for age and sex. We analysed the change in the ratio of oxygen saturation to fraction of inspired oxygen over the first 72 hours by using an analysis of covariance model that adjusted for the baseline ratio as well as age and sex. We also did a post hoc analysis to identify whether longer time spent prone was associated with improved outcomes (supplementary methods).

The data monitoring committee reviewed the results from the interim analysis on 4 May 2021 while the trial investigators were blinded to the results. On reviewing results from the first 170 patients, the independent data monitoring committee requested to review results for all available patients after enrolment reached 230 patients. On 10 May 2021 they recommended stopping the clinical trial owing to futility. Patients who were in the study at that time continued in the arm to which they were randomised.

Patient and public involvement

Although there was no direct patient or public involvement in the study, the research question and the intervention were informed by our direct clinical interactions with patients and our own anecdotal observations that oxygen saturation improved for some patients in prone position. We also asked two members of the public who had no involvement in our study to read our manuscript and provide feedback after submission.

Results

Of the 570 patients who were assessed for eligibility, 257 were randomised and 248 were included in the intention-to-treat analysis (fig 1). The median time from hospital admission until randomisation was one day, 98% of patients had a diagnosis of covid-19 confirmed by laboratory polymerase chain reaction, the median age of patients was 56 (interquartile range 45-65) years, 36% were female, 40% had hypertension, 27% had diabetes, and 11% had a diagnosis of chronic obstructive pulmonary disease or asthma. Patients randomised to prone positioning were slightly older and more likely to have a diagnosis of hypertension, whereas patients randomised to the control arm were more likely to be a current smoker or have a diagnosis of asthma or chronic obstructive pulmonary disease at baseline (table 1). The most common oxygen delivery method was nasal prongs (90%), the median oxygen saturation was 94% (93-96), and the median fraction of inspired oxygen was 32% (28-36). At baseline before randomisation, 95% of patients received dexamethasone, 42% received remdesivir, and 1% received tocilizumab. We retrospectively polled sites to estimate the number of patients included who did not

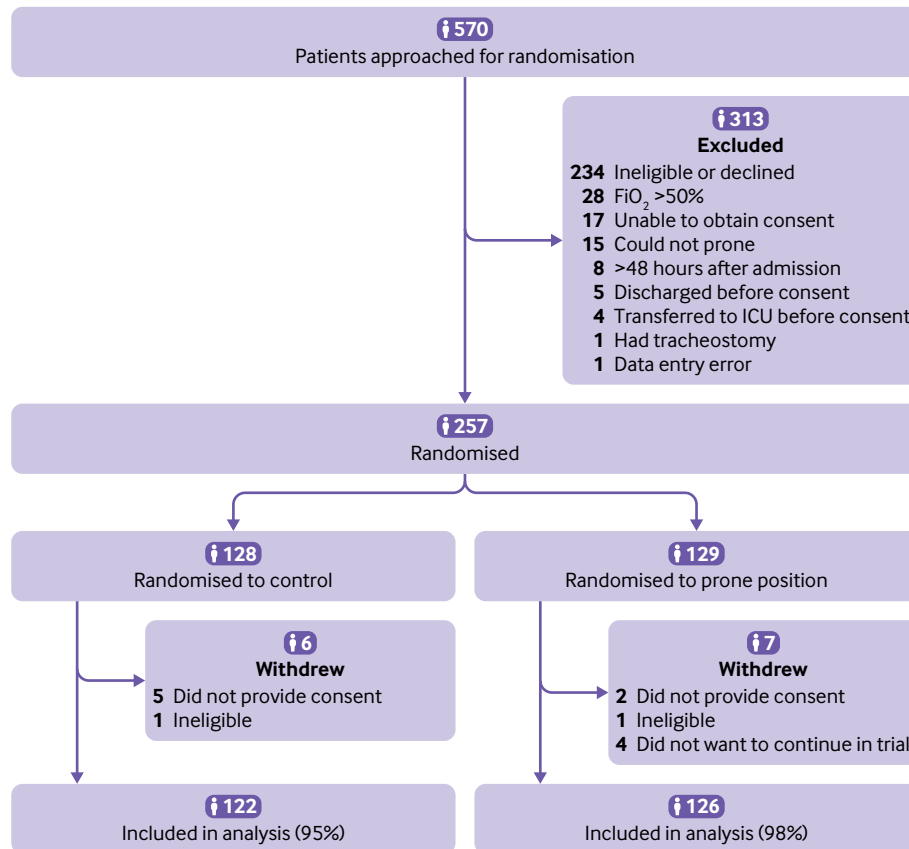


Fig 1 | Enrolment and randomisation of participants. Among patients who withdrew owing to lack of consent, this occurred because trial allowed for deferred consent. Among patients who withdrew because they were ineligible, that was because one patient was on room air at time of randomisation and one patient was on >50% fraction of inspired oxygen (FiO₂) at time of randomisation. Data for four patients who withdrew in prone arm were analysed up until withdrawal. Data from three patients who did not consent or were ineligible were not analysed. ICU=intensive care unit

speak English. One site reported that 0% of patients did not speak English, five sites reported 1-10%, five sites reported 11-20%, one site reported 21-30%, and one site reported >30%.

The median total time spent in prone position up to the first 72 hours was 6 (1.5-12.8) hours in patients randomised to prone positioning and 0 (0-2) hours in the control arm. After we accounted for hospital discharge or outcomes occurring within the first 72 hours, on a per day basis this equated to approximately 2.5 hours per day in the prone arm compared with 0 hours per day in the control arm in the first 72 hours.

The median time from randomisation until the primary outcome was one day. The rate of the primary outcome was similar between the prone group (18 (14%) events) and the standard of care group (17 (14%) events) (odds ratio 0.92, 95% confidence interval 0.44 to 1.92). In the subgroup analysis stratified by baseline hypoxaemia, the odds ratio for the primary outcome for patients randomised to prone compared with standard of care was 1.77 (0.69 to 4.80) for patients on more than 30% fraction of inspired oxygen and 0.26 (0.05 to 0.96) for those on up to 30% fraction of inspired oxygen (P for interaction=0.02). In the subgroup analysis stratified by age, the odds ratio for the primary outcome for patients randomised

to prone compared with standard of care was 1.52 (0.43 to 5.55) for patients 55 years and younger and 0.74 (0.30 to 1.81) for those older than 55 years (P for interaction=0.42). In our post hoc analysis stratified by adherence, the odds ratio of the primary outcome was 0.98 (0.26 to 3.73) for patients at hospitals with higher adherence and 0.96 (0.38 to 2.37) for patients at hospitals with lower adherence. The time spent prone at the high adherence sites in the prone group was four hours a day compared with one hour a day at the sites with lower adherence.

The adjusted difference in the ratio of oxygen saturation to fraction of inspired oxygen from the time of randomisation until 72 hours was similar between the two groups (table 2; fig 2). The median time to hospital discharge was 5 (3-9) days for the prone arm and 4 (3-8) days for the control arm (supplementary figure). Serious adverse events were rare and affected five (4%) patients in the prone group and three (2%) patients in the standard of care group (table 2).

Discussion

In this multicentre pragmatic randomised clinical trial of encouraging prone positioning in patients admitted to hospital with covid-19 with hypoxaemia who were not critically ill, we did not observe improvements in the risk of the composite of death, mechanical

Table 1 | Baseline characteristics of included patients. Values are numbers (percentages) unless stated otherwise

Characteristics	Prone (n=126)	Control (n=122)
Median (IQR) age, years	59.5 (45-68)	54 (44-62)
Age group:		
<50 years	37 (29)	44 (36)
50-70 years	67 (53)	66 (54)
>70 years	22 (17)	12 (10)
Female sex	44 (35)	45 (37)
Comorbid conditions:		
Diabetes	36 (29)	31 (25)
Hypertension	56 (44)	42 (34)
Current smoker	0 (0)	7 (6)
COPD or asthma	12 (10)	15 (12)
Heart failure	4 (3)	2 (2)
Illness severity:		
Median (IQR) lymphocyte count, 10 ⁹ /L	0.8 (0.6-1.1)	0.9 (0.6-1.2)
Median (IQR) creatinine, µmol/L	79 (66-97)	78 (65-94)
Median (IQR) systolic BP, mm Hg	124 (116-135)	121 (112-130)
Median (IQR) oxygen saturation, %	94 (93-95)	94 (93-96)
Median (IQR) FiO ₂ , %	32 (28-36)	32 (28-36)
Median (IQR) S/F ratio	303 (261-336)	305 (267-339)
FiO ₂ delivery method:		
Nasal prong	110 (87)	112 (92)
High flow nasal cannula	5 (4)	2 (2)
Face mask	8 (6)	7 (6)
Drug treatment:		
Dexamethasone	117 (93)	119 (98)
Remdesivir	56 (44)	48 (39)
Tocilizumab	0 (0)	2 (2)
Code status:		
Full code	113 (90)	116 (95)
Do not resuscitate	5 (4)	0 (0)
Other	7 (6)	6 (5)

<2% missing data for included variables.

BP=blood pressure; COPD=chronic obstructive pulmonary disease; FiO₂=fraction of inspired oxygen; IQR=interquartile range; S/F ratio=ratio of saturation of oxygen to fraction of inspired oxygen

ventilation, or worsening respiratory failure. However, the wide confidence intervals preclude definitively ruling out benefit or harm. Additionally, although we also did not observe improvements in oxygenation, the overall time spent prone per day was lower than planned despite inclusion and exclusion criteria identifying patients most likely to be able to lie prone and interventions to encourage adherence.

Comparison with other studies

Initial reports suggested that prone positioning might be potentially lifesaving for patients admitted to hospital with covid-19.⁶ However, early data were based on anecdotal reports and small case series. In the largest available studies of patients on a medical ward, the duration of prone positioning was often not reported,¹² and when reported it was typically less than three hours a day.⁶ Most of these studies focused on oxygenation rather than clinical outcomes and identified improvements in oxygenation while the patient was prone, but improvements did not necessarily persist after prone positioning was stopped.⁶ The one available randomised trial for patients with mild hypoxaemia showed no improvement in oxygenation, but the trial was small and was stopped early because of poor adherence (that is, mean duration of 1.6 hours spent prone in the

first 72 hours).⁹ Our study found that patients did not adhere to a prolonged time spent prone, and we saw no sustained improvement in oxygenation related to prone positioning. Specifically, the change in the ratio of oxygen saturation to fraction of inspired oxygen was similar in the two groups over the first 72 hours. Furthermore, the rate of worsening respiratory failure, intubation, or death was similar in the two groups.

The time spent prone in our study can be characterised as “low intensity prone positioning.” We did not intend this a priori; rather, our study planned for two hour sessions of prone positioning four times a day and prone sleeping at night. However, despite inclusion and exclusion criteria aimed at identifying people able to prone independently and with reminders to patients by nurses, physicians, and study team members, this was not achieved. The most common reason for the lack of adherence that patients would anecdotally report to research coordinators was discomfort. This feedback, coupled with the results from our study, confirms that simply instructing patients to lie prone and providing them with reminders is insufficient for most patients to spend a prolonged period in the prone position.

Contrasting the low adherence to prone positioning in our study to prone positioning of patients who are in the intensive care unit is important. Time spent prone in the intensive care unit can be directly controlled by the healthcare team because patients who are receiving invasive mechanical ventilation are typically sedated and potentially also receiving neuromuscular blockade. In earlier trials of mechanically ventilated patients with acute respiratory distress syndrome without covid-19, a mortality benefit was observed only with longer durations of prone positioning, typically more than 12 hours or 16 hours.^{13 14} Benefits of prone positioning in patients in the intensive care unit with acute respiratory distress syndrome were not observed in earlier trials that had shorter durations of prone positioning (that is, less than 12 hours a day).¹³ In a meta-trial (n=6 individual trials) of prone positioning in patients with covid-19 on high flow nasal cannulas (median fraction of inspired oxygen at randomisation of 60%), the median duration of prone positioning per day was less than five hours, with the exception of study sites in Mexico where it was 8.6 hours per day.¹⁰ The overall meta-analysis identified a lower risk of the primary outcome for patients randomised to prone positioning; however, notably, only the trial in Mexico identified a lower relative risk of the primary outcome on its own. In addition to the measures we adopted, the trial in Mexico implemented three strategies that may explain the improved adherence to prone positioning. Firstly, study investigators typically corresponded with onsite healthcare providers three times a day to emphasise adherence to prone position. Secondly, they had a critical care physician available 24 hours a day who was committed to ensuring adherence to the protocol. Thirdly, they included labels on the head of the patient’s bed to provide a constant reminder to the patient and the healthcare team. Moreover, the patients

Table 2 | Primary and secondary study outcomes. Values are numbers (percentages) unless stated otherwise

	Prone (n=126)	Control (n=122)	Effect estimate (95% CI)
Primary outcome			
Composite of death, mechanical ventilation, and $\text{FiO}_2 > 60$	18 (14)	17 (14)	OR*: 0.92 (0.44 to 1.92)
Components of composite:			
Death	1 (1)	1 (1)	-
Mechanical ventilation	6 (5)	5 (4)	-
$\text{FiO}_2 > 60\%$	18 (14)	17 (14)	-
Secondary outcomes			
Median (IQR) S/F ratio after 72 hours	336 (216-438)	336 (232-443)	MD†: 8 (-18 to 35)
Median (IQR) change in S/F ratio in first 72 hours	14 (-52-94)	49 (-32-102)	MD†: 20 (-17 to 36)
Median (IQR) days to discharge	5 (3-9)	4 (3-8)	-
Discharged	115 (91)	118 (97)	HR: 0.83 (0.64 to 1.08)
Serious adverse events			
Serious adverse event composite	5 (4)	3 (2)	OR: 1.37 (0.32 to 6.96)
Components of composite:			
Aspiration pneumonia	2 (2)	1 (1)	OR: 1.38 (0.12 to 31.53)
Venous thromboembolism	3 (2)	2 (2)	OR: 1.35 (0.22 to 10.57)
Other	0 (0)	0 (0)	-
Hours spent prone			
Median (IQR) in first 72 hours	6 (1.5-12.8)	0 (0-2)	MD: 6.0 (4.0 to 7.9)
Missing first 72 hours	8 (6)	5 (4)	
Median (IQR) from 72 hours to 7 days	0 (0-12)	0 (0-0)	MD: 4.3 (1.7 to 6.9)
Missing 72 hours to 7 days	13 (10)	12 (10)	

For primary outcome, risk difference was -0.01 (95% CI -0.07 to 0.10) and risk ratio was 0.93 (0.48 to 1.70).

CI=confidence interval; FiO_2 =fraction of inspired oxygen; HR=hazard ratio; IQR=interquartile range; MD=mean difference; OR=odds ratio; S/F ratio=ratio of saturation of oxygen to fraction of inspired oxygen.

*Adjusted for age and sex.

†Adjusted for baseline S/F ratio as well as age and sex.

in this meta-trial were all on high flow nasal cannulas and thus more likely to be in an intensive care unit and have a lower nurse-to-patient ratio. Additional trials of prone positioning of ward patients will help to identify alternative strategies to increase adherence to prone positioning in the non-intubated patient and determine whether a sustained physiological benefit exists across a certain subgroup that translates to improved clinical outcomes (for example, non-intubated patients with a higher severity of acute respiratory failure). On the basis of the adherence we observed in our trial, innovative, more directive strategies may be needed to encourage awake patients to adopt a prone position for more than a few hours each day.

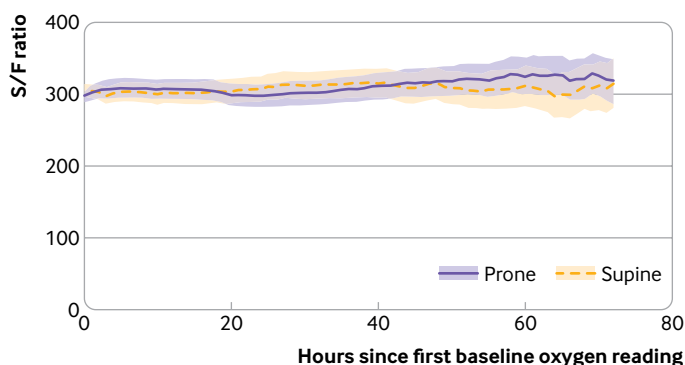


Fig 2 | Change in ratio of oxygen saturation to fraction of inspired oxygen (S/F ratio) over time. Creating this curve was a two step process. (1) Hourly linear interpolation of each patient's measurements. Median number of measurements per person within first 72 hours was 9 (interquartile range 6-12), and median time between first and last reading (within first 72 hours) was 55 (45- 65) hours. No extrapolation was used; patients with only one measurement were excluded. (2) Calculation of mean and confidence interval at each hour for each cohort

To understand how longer duration of time spent prone is associated with our primary outcome, we did a post hoc exploratory analysis and compared outcomes at the sites with the highest adherence to prone positioning compared with the sites with the lowest adherence. We found no difference in the primary outcome at the sites with the highest adherence; however, our null finding might be related to lack of statistical power because of the relatively low number of overall events or because the longer duration of prone positioning may still be insufficient for a clinically important benefit. We also did a pre-planned subgroup analysis to identify how baseline hypoxaemia may affect the efficacy of prone positioning. In that analysis, we identified a lower risk of the primary outcome for patients randomised to prone positioning who needed 30% fraction of inspired oxygen or lower at the time of randomisation. This should be considered hypothesis generating, however, because of the low overall number of events, which increases the possibility of chance alone underlying our observed findings. Future studies are needed to identify whether this finding is replicable and robust across other protocols.

Strengths and limitations of study

Our study has several strengths. Firstly, it was pragmatic and multicentred and included both academic and community hospitals. We anticipate that our results reflect the effectiveness of real world interventions to encourage prone positioning in similar healthcare settings. Secondly, we collected a physiological outcome (oxygenation) and clinically relevant outcomes (death or mechanical ventilation), and we included patients with a do-not-resuscitate

order to enhance generalisability and surrogates for healthcare utilisation (for example, need for more than 60% fraction of inspired oxygen and length of hospital stay). Thirdly, unlike most of the available published studies, our trial included data on the potential risks of prone positioning.

The most important limitation of our study was poor adherence to time spent prone. As described, this probably reflects the real world challenges of lying in a prone position when sick with a respiratory and multisystem viral illness and without high nurse-to-patient ratios. Future studies are needed to determine whether a greater amount of time spent in the prone position is associated with clinical benefit, including whether specific devices or interventions (for example, smartphone apps, pillows/padding, prone positioning teams) can increase time spent prone. Furthermore, the time spent prone was self-reported and thus at risk of recall bias, which may have resulted in overestimates or underestimates of the time spent prone. Secondly, our expected event rate was lower than anticipated because our study was planned before effective treatments became available. These treatments (for example, dexamethasone, remdesivir, tocilizumab), at least in part, resulted in a lower event rate than we anticipated, so larger randomised trials would be needed to identify a smaller absolute risk reduction. Thirdly, we lacked data on use of personal protective equipment and the number of times a healthcare provider had to enter the room to help to reposition a patient to aid with prone positioning. Both are important to evaluate when considering the potential drawbacks of prone positioning. Fourthly, fraction of inspired oxygen for non-intubated patients depends on multiple physiological factors and needs to be estimated for certain devices (for example, a non-rebreather mask) on the basis of the flow rate of oxygen delivered.

Conclusions

In our multicentre pragmatic randomised clinical trial of encouraging prone positioning in patients admitted to hospital with covid-19 who were hypoxaemic but not critically ill, we did not observe improvements in the risk of the composite of death, mechanical ventilation, or worsening respiratory failure. However, the wide confidence intervals preclude definitively ruling out benefit or harm. The trial was stopped early on the basis of the futility of finding the pre-specified effect size. Ongoing studies are evaluating whether prone positioning might be beneficial for non-intubated patients with more severe forms of hypoxaemia. The poor adherence to prone positioning that we observed highlights that it is generally not well tolerated and innovative approaches are needed to improve adherence.

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Ethical approval: The trial protocol was approved by the institutional review board at each site (or by a centralised institutional review board as applicable) and was overseen by the trial's steering committee (NCT04383613)

Data sharing: No additional data available.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to share our results with clinicians through professional societies and quality improvement networks and with a general audience through social media (eg, Twitter), the Rounds Table podcast (<https://healthydebate.ca/special-series/podcasts/>), and our patient facing website (<https://www.covid19ask.com/>).

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- 1 Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966. 10.1136/bmj.m1966
- 2 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430-6. 10.1038/s41586-020-2521-4
- 3 Verma AA, Hora T, Jung HY, et al. Characteristics and outcomes of hospital admissions for COVID-19 and influenza in the Toronto area. *CMAJ* 2021;193:E410-8. 10.1503/cmaj.202795
- 4 Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care* 2020;10:33. 10.1186/s13613-020-00650-2
- 5 Elharrar X, Trigui Y, Dols A-M, et al. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. *JAMA* 2020;323:2336-8. 10.1001/jama.2020.8255
- 6 Venus K, Munshi L, Fralick M. Prone positioning for patients with hypoxic respiratory failure related to COVID-19. *CMAJ* 2020;192:E1532-7. 10.1503/cmaj.201201
- 7 Fan E, Del Sorbo L, Goligher EC, et al. American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63. 10.1164/rccm.201703-0548ST
- 8 Caputo ND, Strayer RJ, Levitan R. Early Self-Prone in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Acad Emerg Med* 2020;27:375-8. 10.1111/acem.13994
- 9 Johnson SA, Horton DJ, Fuller MJ, et al. Patient-directed Prone Positioning in Awake Patients with COVID-19 Requiring Hospitalization (PAPR). *Ann Am Thorac Soc* 2021;18:1424-6. 10.1513/AnnalsATS.202011-1466RL
- 10 Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake Prone Positioning Meta-Trial Group. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021;9:1387-95. 10.1016/S2213-2600(21)00356-8
- 11 Liu Y, Li J, Liu D, et al. Clinical features and outcomes of 2019 novel coronavirus-infected patients with cardiac injury. *medRxiv* 2020;2020.03.11.20030957. 10.1101/2020.03.11.20030957
- 12 Perez-Nieto OR, Escarraman-Martinez D, Guerrero-Gutierrez MA, et al. APRONOX group. Awake prone positioning and oxygen therapy in patients with COVID-19: The APRONOX study. *Eur Respir J* 2021;2100265. 10.1183/13993003.00265-2021
- 13 Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S280-8. 10.1513/AnnalsATS.201704-3430T
- 14 Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. *Cochrane Database Syst Rev* 2015;(11):CD008095.

Web appendix: Supplementary materials

Web appendix: Study protocol