EVIDENCE SUMMARY

RESEARCH QUESTION: **Among severe to critical COVID-19 patients, should side lying position be used?**

Update by: Jhon Ryan Enriquez, MD, Christopher G. Manalo, MD, MSc (cand), Vaneza Leah A. Espino, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc
Initial Review by: Adrian Ronald A. Espino, MD, Vaneza Leah A. Espino, MD, Christopher G. Manalo, MD

RESEARCH QUESTION: **Among non-intubated severe COVID-19 patients, should self-proning be used?**

Latest Update by: Jhon Ryan Enriquez, MD, Christopher G. Manalo, MD, MSc (cand), Vaneza Leah A. Espino, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc
Previous Update by: Adrian Ronald A. Espino, MD, Vaneza Leah A. Espino, MD
Initial Review by: Myzelle Anne J. Infantado, PTRP, MSc (cand), Dan Louie Renz P. Tating, RN, MS (cand)

RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest awake prone positioning or self-proning in non-intubated adult patients with severe and critical COVID-19.	Very Low	Weak
We suggest prone positioning among intubated adult patients with critical COVID-19 in ARDS.	Very Low	Weak
We suggest the use of side lying in non-intubated adult patients with severe and critical COVID-19 who cannot tolerate proning.	Very Low	Weak

Consensus Issues

A weak recommendation was given on the use of awake prone positioning among non-mechanically ventilated adult patients with severe and critical COVID-19 on the basis of observed benefit in the reduction for the need of mechanical ventilation and absence of serious adverse events (harms of proning), low cost and resources required for the intervention, and equity. The panel further highlighted to consider the contraindications to prone positioning which include: pregnancy, patients with fractures, hemodynamic instability, patients who are unable to perform proning (e.g., obesity, recent abdominal/thoracic surgery), among others. Across the studies reviewed, the duration of the intervention varied from two hours to as long as tolerated with regular monitoring.

Similarly, among mechanically ventilated patients, prone positioning should be done as indicated (in ARDS patients which was reflective of the population in the reviewed studies) and in hemodynamically stable patients. Proper technique, however, should be performed and personnel training should likewise be considered.

The panel also weakly recommended implementing side lying or lateral positioning for patients who cannot tolerate prone positing (evidence was based on only one study who performed side lying after prone positioning). No study was available on side lying alone.

KEY FINDINGS

- Among non-intubated severe patients with COVID-19, pooled results of nine randomized controlled trials showed a statistically significant difference favoring proning in terms of need for intubation. There is also a trend towards benefit for proning in terms of mortality, need for intensive care, length of hospital stay in days, and length of ICU stay in days. Pooled estimates from six RCTs which reported data on adverse events (IV-line dislodgement, pain or discomfort, nausea/vomiting, pressure ulcers, coughing, dizziness, and shortness of breath) and serious adverse events (cardiac arrest, hypotension, desaturation, aspiration pneumonia, and venous thromboembolism) during proning only showed a trend towards harm.

- Two small observational studies of 20 subjects combined with COVID-19 patients associated acute respiratory distress syndrome under mechanical ventilation showed that side lying provided a statistically significant benefit by decreasing the incidence of overdistension and lung collapse, increase in lung compliance, a decrease in driving pressure and transpulmonary driving pressure, and improvement in oxygenation. One prospective cohort study of 52 subject with severe, non-intubated COVID-19 patients showed that positioning intervention (prone or lateral) did not show significant statistical difference in terms of rate of intubation and length of hospitalization. The same study showed a statistically significant increase comparing P/F ratio and ROX index before and after doing positional intervention (prone or lateral).

- Proning for critical, mechanically-ventilated COVID-19 patients showed a statistically significant benefit in in-hospital mortality based on one retrospective cohort study with 261 subjects. The same study showed significant statistical improvement comparing oxygenation-saturation index (OSI), oxygenation-index (OI) and arterial oxygen partial pressure to fractional inspired oxygen (PaO_2: FiO_2) before and after doing proning intervention. Four observational single arm studies among critical, mechanically-ventilated COVID-19 patients also showed a significant statistical improvement in P/F ratios before and after doing proning interventions. There were no adverse events reported.

- The certainty of evidence for both side lying and proning are very low due to serious risk of bias, substantial heterogeneity, and imprecision.

WHAT'S NEW IN THIS VERSION?

As of November 10, 2022, five new randomized controlled trials (RCTs) for proning in awake, non-intubated COVID-19 patients and one retrospective cohort study and 4 single arm observational studies for proning in critical, mechanically-ventilated COVID-19 were identified. One prospective observational cohort study and one prospective single arm observational study for side-lying in COVID-19 patients were likewise included in this review to evaluate the effects of proning and side-lying in COVID-19 patients.

PREVIOUS RECOMMENDATIONS
As of 26 October 2021

We suggest self-proning position in non-intubated patients with severe and critical COVID-19.
(Very low certainty of evidence; Weak recommendation)

Consensus Issues
Self-proning in non-intubated patients with severe and critical COVID-19 was suggested despite the lack of significant benefit in terms of mortality, need for endotracheal intubation, and need for intensive care unit stay on the basis that self-proning may still offer some benefit on improving oxygenation citing theoretical effect and personal experience, and taking into consideration the existing recommendations made by various international guidelines as well.

There is insufficient evidence to recommend the use of side lying in non-intubated patients with severe and critical COVID-19.
(Very low certainty of evidence)

Consensus Issues
There was very limited evidence to recommend side lying for the same subset of patients, although it was recognized that there may be some benefit. This intervention will depend on the physician's prerogative in situations where self-proning is not possible. Potential harm such as patient discomfort and risk of accidental removal of peripheral lines and endotracheal tubes and the need for additional healthcare workers to perform proning in sedated and mechanically ventilated patients should be considered for both patient and health care worker in attempting this intervention.

INTRODUCTION

Positioning maneuvers such as proning and side lying have been proven to provide benefit in patients with acute respiratory distress syndrome [1]. However, whether these benefits extend to patients with severe to critical COVID-19 is still under clinical investigation. Proning position results in improvement in ventilation-perfusion mismatching in patients with acute respiratory distress syndrome. Considering the potentially similar physiological mechanism, awake prone positioning has been broadly applied for non-intubated patients with COVID-19 since the early pandemic. However, despite the wide adoption of this maneuver, there is scarce evidence regarding early predictors of success and sufficient monitoring of clinical response after initiation of awake prone positioning. Such data might help select the patients who will benefit the most, and early identify those with inadequate response, avoiding unnecessary delay in escalation of care.

REVIEW METHODS

A comprehensive literature search was done on 10 November 2022 for the three clinical questions using Pubmed, Cochrane Library, MedRxiv and clinicaltrials.gov with the following keywords: “lateral positioning”, “side lying” “lateral decubitus”, “proning”, “prone positioning” “prone position”, “awake”, “non-intubated”, “severe”, “critical”, “Intubated”, “mechanical ventilation” and “COVID-19” “SARS-COV2”, “Corona virus 2019”.

All studies that resulted from the search were reviewed and appraised. Randomized controlled trials on proning and available observational studies relating to side lying were included. Outcomes of interest included mortality, ICU admission, Initiation of anti-inflammatory treatment, need for mechanical ventilation, length of hospital stay, lung collapse, overdistension, change in PaO_2/FiO_2, change in PaO_2, change in SpO_2 and change in ROX index. No limits were placed on age and subgrouping by duration of positioning was planned.

RESULTS

A. Awake proning or self-proning in severe and non-intubated critical COVID-19

A total of 41 RCTs were screened and evaluated at the time of the search. Of these, four RCTS were already included from the previous review [2, 3-5]. Five new studies [6-10] were added in our meta-analysis. Patients included in the studies were adults 18 years old and above, diagnosed with COVID-19 via RT-PCR, admitted in the ICU and medical wards, with oxygen saturation of at least 90% with an oxygen requirement of at least 1Lpm via nasal cannula to as high as 15Lpm via non-rebreather mask, high flow nasal cannula or non-invasive ventilation providing up to 0.50 FiO_2 or a P/F ratio of less than 300mmHg. Exclusion criteria were similar between studies which included pregnant women, patients who were unable to perform proning (e.g., obesity, recent abdominal surgery), patient who previously did self-proning, those with hemodynamic instability and those who needed immediate intubation or were previously intubated. Different protocols on proning were used in the included studies and ranged from 6 hours to as long as tolerated. All nine studies were instructed and encouraged by the medical team to perform self-proning. Two studies [2,10] provided illustration and flyers to strengthen adherence to the protocol. Three studies [3-5] encouraged proning for at least six to 48 hours. Three studies advised proning for as long as tolerated. [6,7,9] One study [8] advised 8-10 hours per day of proning while another study [10] advised 4 session per day of at least 2 hours per session. All studies had assigned teams of nurses and physicians for evaluation and monitoring of patients except for one study [10] where in hours of proning was self-monitored and reported by the subject.

Mortality (8 RCTs, n=2,835, Moderate certainty of evidence)
Eight randomized controlled trials evaluated mortality as an outcome [2,4-10]. Overall, awake proning or self-proning showed inconclusive effect in terms of mortality (RR 0.94, 95% CI 0.82-1.08; I^2=0%; Moderate certainty). Inconclusive effect on mortality reduction persisted on subgroup analysis with patients who did self-proning for 6 hours or more (RR 1.09; 95% CI 0.52-2.29; I^2=42%; Moderate certainty) and self-proning for 6 hours or less (RR 0.94; 95% CI 0.80-1.11; I^2=0%; Moderate certainty).

Need for intubation (8 RCTs, n=2,875, Moderate certainty of evidence)
Eight randomized controlled trials evaluated the need for intubation as an outcome [2,4-10]. Overall, need for intubation was significantly reduced (RR 0.81, 95% CI 0.73-0.91; I^2=0%; Moderate certainty) with awake proning or self-proning. Subgroup analysis was done based on duration of proning, which showed no difference between patients who underwent self-proning for 6 hours or more (RR 0.73, 95% CI 0.55-0.98; I^2=14%; Moderate certainty) and those who underwent self-proning for less than 6 hours (RR 0.84, 95% CI 0.74-0.95; I^2=0%; Moderate certainty*).*

Need for Intensive Care (4 RCTs, n=582, Very low certainty of evidence)
Four randomized controlled trials evaluated the effect of proning and the need for intensive care [2,3,5,6]. Two studies [2,6] who had proning for more than 6 hours and two studies who underwent proning for less than 6 hours [3,5]. The pooled effect of awake proning or self-proning showed a trend towards benefit, although not statistically significant in terms of need for intensive care (RR 0.91; 95% CI 0.72-1.16; I^2=0%; Very low certainty). In subgroup analysis, no significant difference was found with proning for more than 6 hours (RR 0.92; 95% CI 0.72-1.18; I^2=36%; Very low certainty) and for less than 6 hours (RR 0.83; 95% CI 0.33-2.13; I^2=28%; Very low certainty).

Length of hospital stay in days (2 RCTs, n=822, Moderate certainty of evidence)
Two randomized controlled trials evaluated length of hospital stay as an outcome in patients who underwent awake proning or self-proning [7,9]. The pooled results showed a total of 822 subjects on the prone group and 800 subjects on the supine group. The pooled effect of awake proning or self-proning showed a trend towards benefit, although not statistically significant (MD -0.32 days; 95% CI -1.34 to 0.71; I^2=0%; Moderate certainty).

Length of ICU stay in days (2 RCTs, n=1,622, Low certainty of evidence)
Two randomized controlled trials evaluated length of ICU stay as an outcome in patients who underwent awake proning [4,7]. The pooled results showed a total of 288 subjects on the prone group and 273 subjects on the supine group. The pooled effect of the two RCTs in awake proning or self-proning showed a trend towards benefit, although not statistically significant in terms of length of ICU stay (MD -0.38 days; 95% CI -2.01 to 1.26; I^2=0%; Low certainty).

Serious Adverse Events (5 RCTs, n=2,274, Very low certainty of evidence)
A total of five RCTs evaluated the occurrence of serious adverse events during awake proning [2,6,8-10]. Serious adverse events reported in the studies are cardiac arrest, hypotension, desaturation, aspiration pneumonia, and venous thromboembolism. The pooled effect of the RCTs in awake proning showed a trend towards harm (RR 2.74; 95% CI 0.49-15.36; I^2=29%; Very low certainty).

Adverse Events (6 RCTs, n=2,666, Very low certainty of evidence)
A total of six RCTs evaluated the occurrence of adverse events during awake proning [2,4-6,8,9]. Adverse events reported in the studies were IV access dislodgement, pain or discomfort, nausea and vomiting, pressure ulcers, coughing, dizziness, and shortness of breath. Occurrence of any adverse event was inconclusive between prone and supine groups (RR 1.08; 95% CI 0.54-2.14; I^2=48.5%; Very low certainty). On subgroup analysis, there were no significant differences in the occurrence of adverse events for patients who did self-proning for 6 hours or more (RR 0.69; 95% CI 0.31-1.254; I^2=47%; Low certainty) and self-proning for 6 hours or less (RR 5.04; 95% CI 0.34-74.13; I^2=79%; Very low certainty).

B. Proning in intubated critical COVID-19 patients

A total of five observational studies were included in this review [11-15]. There were no published or pre-print RCTs available during the time of our search.

In-hospital mortality (1 Cohort study, n=61, Very low certainty of evidence)
One retrospective cohort study [11] included patients from 41-80 years of age and placed on prone position for 16 hours a day. Results showed significant reduction of 30-day mortality with prone positioning (HR 0.46; 95% CI 0.46-0.80; Very low certainty).

Improvement in PaO_2/FiO_2 Ratio (4 Cohort studies, n=221, Very low certainty)
Four observational single arm studies [12-15] measured the change in PaO_2/FiO_2 ratio before and during proning among mechanically ventilated COVID-19 patients. Patients were maintained on prone position for at least 16 hours. Pooled analysis showed a significant improvement in in PaO_2/FiO_2 ratio at prone position (MD 69.01; 95% CI 32.45-105.58; I^2=86%; Very low certainty).

C. Side Lying

A total of three studies were included for review the evidence of side lying in COVID-19 [16-18]. Of the three studies, one study [16] was already included in the previous review.

Lung Overdistension and Collapse
Two small observational studies [16,17] evaluated the effect of side lying in COVID-19 patients who are mechanically ventilated. The studies included adults aged 44 to 85 years of age. One study [16] evaluated lung overdistention and collapse using electrical impedance tomography. Results showed a statistically significant reduction in overdistension accompanied with PEEP titration in the right lung ($p<0.0005$) when in side-lying and prevention of lung collapse in the left lung at PEEP 14 (p=0.034), PEEP 10 (p=0.028), PEEP 8 (p=0.019), and PEEP 6cmH_2O (p=0.007).

Respiratory Compliance, PaO_2/FiO_2 Ratio, Driving Pressure

Another study [17] reported respiratory mechanics and oxygenation after five sequentially applied positions for 30 minutes each: supine (baseline), lateral (first side), supine (second), lateral (second side), and supine (final). No significant difference in terms of respiratory compliance (MD -3.00 mL/cmH_2O; 95% CI -9.09 to 3.09), PaO_2/FiO_2 (MD -26.00; 95% CI -55.56 to 3.56), and driving pressure (MD 2.00; 95% CI 0.57-3.43) were noted.

One study [18] valuated the effects of positional change (proning or side-lying) in severe, non-intubated COVID-19 patients. Subjects included adults 50 to 74 years old. A total of 35 patients were included on the standard of care and 17 patients on the positional group where in 11 are place in prone and 7 on side-lying. The study noted an increase in cumulative P/F ratio (adjusted MD 409; 95% CI 86-733) and increase in cumulative ROX index (adjusted MD 26.95%, 95% CI 9-43; Very low certainty) during the first 7 days. The same study also showed no statistical difference in terms of mortality (OR 1.52 95% CI 0.06-39.2; Very low certainty) and length of hospital stay (MD -3.25 days; 95% CI -13.50 to 7.00; Very low certainty).

RECOMMENDATIONS FROM OTHER GROUPS

Four updated guidelines on the management of COVID-19 were identified. Their recommendations for proning are summarized in the table below. Currently, no recommendations for side-lying/lateral positioning for COVID-19 were noted.

Group / Society / Network	Year	Recommendation	Level of Evidence / Strength of Recommendation
World Health Organization [19]	2022	We suggest awake prone positioning of severely ill patents hospitalized with COVID-19 requiring supplemental oxygen (includes high flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence)	Conditional Recommendation
		In adult patients with severe ARDS (PaO_2/FiO_2 <150) prone ventilation for 12–16 hours per day is recommended	
National Institutes of Health [20]	2022	For adults with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the panel recommends a trial of awake prone positioning	BIIa
European Respiratory Society [21]	2021	Prone positioning may improve oxygenation in non-intubated patient with acute hypoxemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.	Very Low Conditional Recommendation
		The panel recommends against the use of awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation	AIII
		For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation	BIIa
Rapid Practice Guidelines Panel from Acta-Anaesthesiologica scandinavica [22]	2023	The panel made a strong recommendation for a trial of awake proning in adult patients with COVID-19 related hypoxemic acute respiratory failure who are not invasively ventilated	Full article not available

ONGOING STUDIES AND RESEARCH GAPS

There is still limited data on the use of proning in the management especially with critical COVID-19 patients. Development of randomized controlled trials in the use of side-lying position as adjuvant measure for COVID-19 patients will help a lot in the management especially for those who cannot tolerate proning (e.g., morbidly obese, pregnancy, etc.). As of now, RCTs on proning and side-lying are in the process of recruitment and data collection and may further contribute to provide evidence not only for its effectiveness but also to bring the light to its possible adverse effects.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST, PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There is still scarce data on the use of proning and side lying in the management of severe to critical COVID-19 patients. RCTs and observational studies on this topic is still unclear especially in terms of the critical COVID-19 population and the possible related adverse events. However, due to its availability of use as adjunctive therapy, its equity, its possible advantages and very unclear relationship to and adverse or serious adverse effects. Proning and side-lying, in the absence of contraindication, is still being use for COVID-19 patients.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7/10)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)				Yes, COVID-19 still affects a substantial number of the population and strong evidence with regards to use of positioning during illness as adjunctive treatment is still lacking.
Benefits	Large	Moderate (5)	Small (2)	Uncertain	Trivial	**Awake Proning in Severe COVID** Significant **benefit in terms of need for intubation** (RR 0.80; 95% CI 0.72-0.90; I^2=0%; moderate certainty). **Benefit in terms of mortality for both intubated and non-intubated** **Side lying in Severe to critical COVID-19** Significant benefit in terms of: • **Lung Collapse and overdistension** – less lung collapse in left lung in targeted lateral (P=0.014); and less overdistension along the PEEP titration was found within the right lung in targeted lateral (P=0.005) (very low certainty) • **Respiratory mechanics and gas exchange** • **Change in SpO_2/FiO_2** - increased cumulative adjusted mean difference of SpO_2/FiO_2 (409, 95% CI 86-733) during the first 7 days (very low certainty) • **Change in ROX index** - increased cumulative adjusted mean difference of ROX index (26, 95% CI 9-43) during the first 7 days (very low certainty)
Harm	Large	Moderate (3)	Small (2)	Varies / Uncertain (2)		**Awake proning in severe COVID-19**: No significant harm in terms of Adverse events Serious adverse events No data for proning in critical COVID-19 and side-lying on COVID-19
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low (2)		**Awake prone positioning in severe COVID-19:** MODERATE **Side lying in severe to critical COVID-19:** VERY LOW

							Proning in critical, mechanically ventilated COVID-19: VERY LOW
Balance of effects	Favors intervention (3)	Probably favors intervention (4)	Does not favor intervention	Probably favors no intervention	Favors no intervention	Varies	The balance between benefits and harm **favors treatment**
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain / Varies (1)	Large cost (1)	Moderate cost	Negligible cost (6)	Moderate savings	Large savings (1)	**Negligible cost or savings** Awake proning can be done by the patient with the help of proper instructions Proning and side-lying in the mechanically ventilated patient can be done by the critical care team without additional cost
Certainty of evidence of required resources	No included studies (5)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies	Probably / Favors the comparison	Probably favors the intervention (5)	Favors the intervention (2)	Varies		
Equity	Varies / Reduced (2)	Probably reduced (3)	Probably no impact (1)	Probably increased (1)	Increased (2)		
Acceptability	Varies	No	Probably no	Yes (3)	Probably yes (4)		**<u>For the use: 7 (5 weak)</u>** **<u>Against the use:</u>**
Feasibility	Varies	No	Probably no	Yes (3)	Probably yes (4)		

Appendix 2: Search Strategy

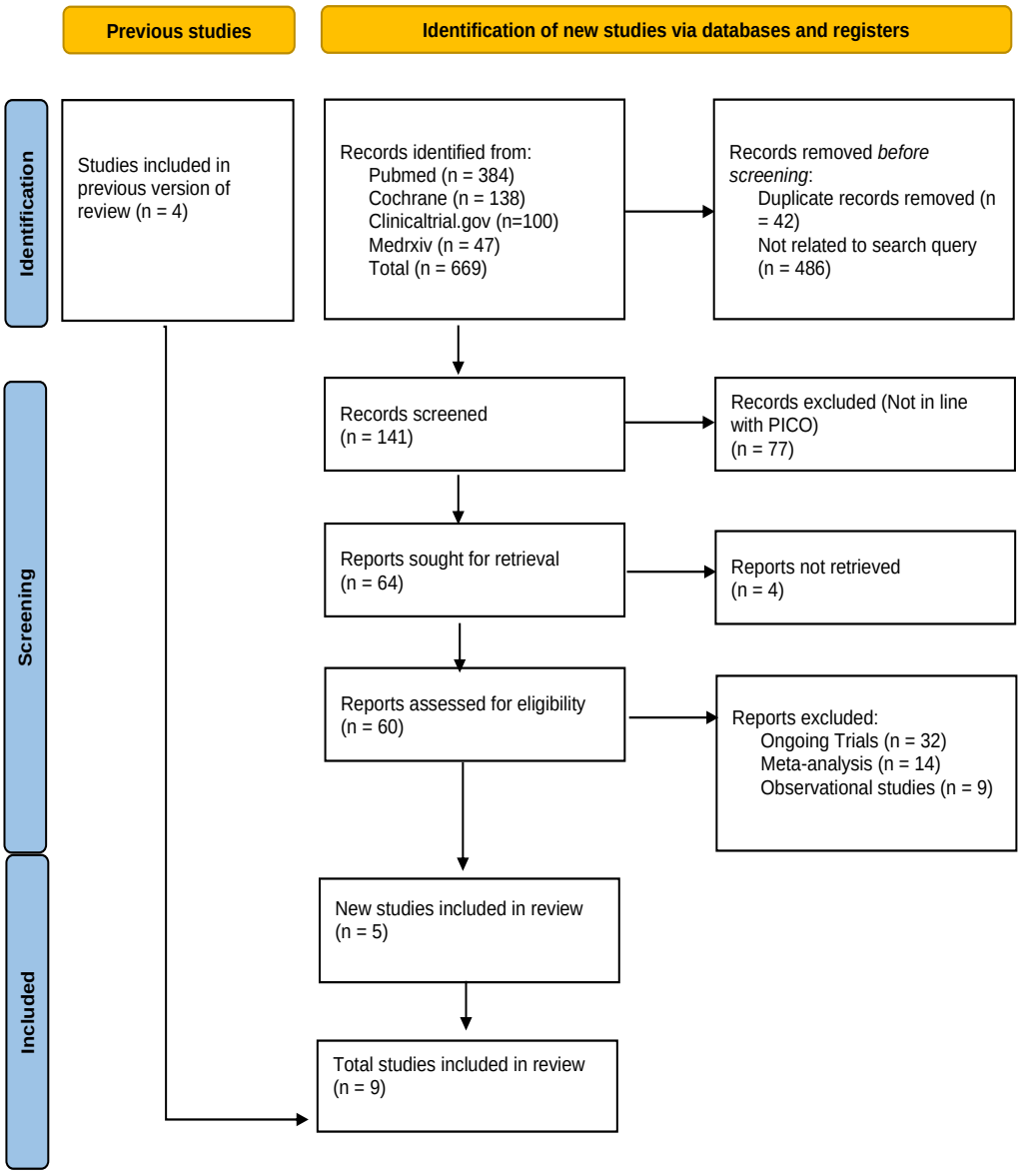

Figure 1. PRISMA flow diagram for awake prone positioning

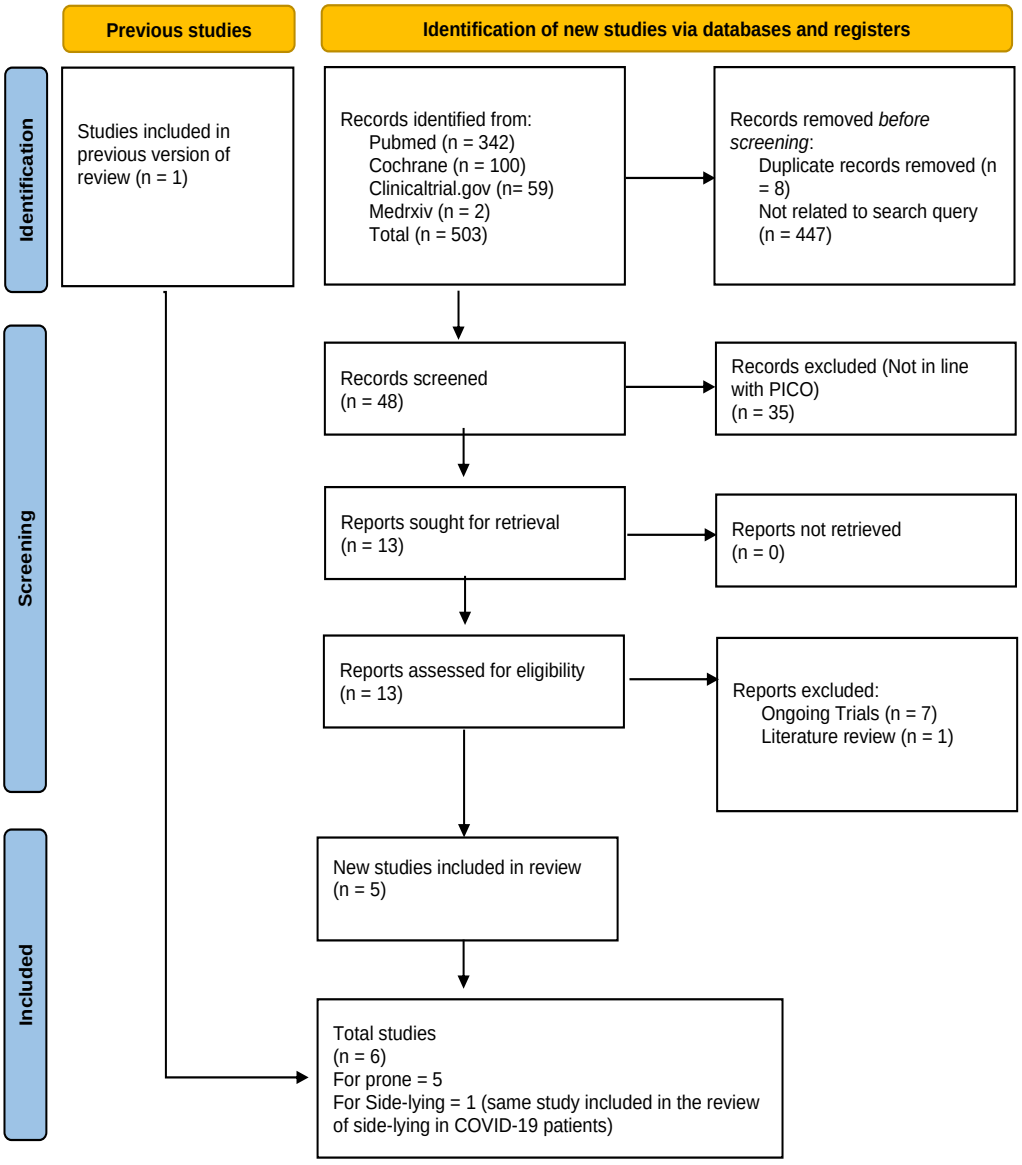

Figure 2. PRISMA flow diagram for prone positioning in critical COVID-19

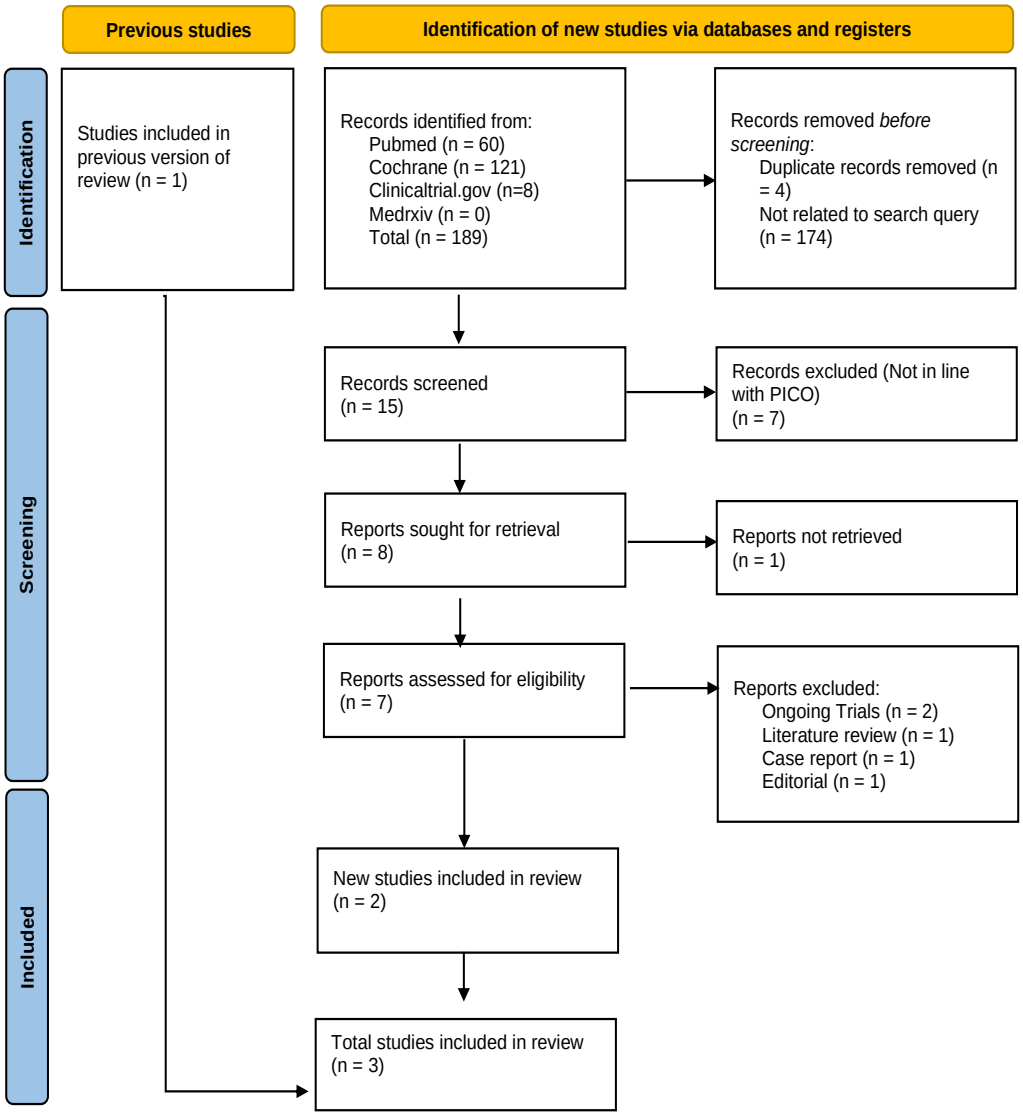

Figure 3. PRISMA flow diagram for side lying

Table 2. Detailed search strategy for awake proning

#	Query	Results
	Pubmed	
1	**prone OR prone position OR prone positioning OR proning**	94,029
2	**COVID-19 OR SARS-COV 2 OR 2019 NCOV**	312,730
3	**awake OR Severe OR non-intubated**	1,718,267
4	**#1 AND #2**	2,383
5	**#1 AND #2 and #3**	726
6	**Add Filter: Clinical Study, Clinical Trial, Meta-Analysis, Observational Study, Randomized Controlled Trial, Review, Systematic Review**	384
	COCHRANE	
1	**prone OR prone position OR prone positioning OR proning**	5691
2	**COVID-19 OR SARS-COV 2 OR 2019 NCOV**	12,977
3	**awake OR Severe OR non-intubated**	268,054
4	**#1 AND #2 AND #3**	138 (3 cochrane reviews, 135 trial)
	Clinical trials.gov	
1	**Prone position OR Prone OR prone positioning | COVID-19 AND awake OR non-intubated OR severe**	100
	Medrxiv	
1	**All in title: COVID-19 AND Severe OR awake AND Prone OR prone positioning AND observational OR clinical study OR controlled trial**	50

Table 3. Detailed search strategy for lateral positioning

#	Query	Results
	Pubmed	
1	**(lateral positioning) OR (lateral decubitus positioning)) OR (side lying)**	42,273
2	**COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019**	313,615
3	**#1 AND #2**	60
	COCHRANE	
1	**(lateral positioning) OR (lateral decubitus positioning)) OR (side lying)**	13,264
2	**COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019**	13,045
3	**Randomized controlled trial OR controlled trial OR observational study OR cohort study OR systematic review OR meta-analysis**	947, 437
4	**#1 AND #2 AND #3**	121 (5 cochrane reviews, 116 trial)
	Clinical trials.gov	
1	**(COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019) AND (lateral positioning OR side-lying) AND Trial**	8
	Medrxiv	
1	**All in title: COVID-19 OR Corona virus 2019 OR SARS-COV 2 AND side lying OR lateral positioning AND observational study OR clinical study OR controlled trial**	0

Table 4. Detailed search strategy for Critical COVID and Positioning

#	Query	Results
	Pubmed	
1	**COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019**	314,294
2	**Critical OR intubated OR Mechanically ventilated OR mechanical ventilation NOT awake**	462,363
3	**Side lying OR Lateral positioning OR prone OR prone positioning OR position**	188,586
4	**#1 AND #2 AND #3**	1364
5	**#4 with (clinical study[Filter] OR clinical trial[Filter] OR meta-analysis[Filter] OR observational study[Filter] OR randomized controlled trial[Filter] OR review[Filter] OR systematic review[Filter]))**	342
	COCHRANE	
1	**Critical OR Intubated OR Mechanically ventilated OR mechanical ventilation NOT awake**	84,544
2	**COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019**	13,042
3	**Side lying OR Lateral positioning OR prone OR prone positioning OR position**	192,602
4	**#1 AND #2 AND #3**	100 (Trial)
	Clinical trials.gov	
1	**All in title Critical OR Mechanically ventilated OR mechanical ventilation NOT awake | COVID-19 OR SARS-COV 2 OR 2019 NCOV OR Corona virus 2019 | Side lying OR Lateral positioning OR prone OR prone positioning OR position**	59
	Medrxiv	
1	**All in title: COVID-19 OR Sars COV 2 AND lateral position OR side-lying OR Prone OR prone position" (match all words) and abstract or title "Critical OR mechanical ventilation OR intubated OR mechanically ventilated**	2

Appendix 3: Characteristics of Included Studies

Table 5. Characteristics of Included Studies on awake proning (n=9)

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial Rosen et.al 2021	Prospective multicenter, open-label, parallel arm, randomized clinical superiority trial	Sweden	75	Adults ≥ 18 years old - SARS-CoV-2 reverse transcription polymerase chain reaction tests on naso- or oropharyngeal swabs - hypoxemic respiratory failure, -HFNO or NIV for respiratory support - PaO2/FiO2-ratio ≤ 20 kPa or corresponding values of SpO2 and FiO2	at least 16h Awake Prone Positioning (APP) per day Prone and semi-prone positioning was allowed During in-hospital transportation, oxygenation by face mask and positioning appropriate for adequate monitoring and safety was allowed	APP was not encouraged but could be prescribed by the attending clinician at his/her discretion.	• Primary outcome ○ Intubation within 30 days after enrollment • Secondary outcome ○ Duration of APP ○ Use of NIV ○ Time of NIV for patients included with HFNO ○ use of vasopressors/inotropes ○ CRRT,ECMO ○ Ventilator-free days ○ Days free of NIV/HFNO for patients not intubation ○ Hospital and ICU length of stay ○ 30 day mortality ○ WHO ordinal scale for clinical improvement at day 7, 30 ○ Adverse events
Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomized controlled trial Kharat et. Al 2021	Single-centre cluster randomized controlled trial	Geneva, Switzerland	27	patients aged ⩾18 years on low-flow oxygen therapy (defined as 1–6 L·min−1) through nasal cannulas to obtain a SpO2 level of 90–92%.	self-proning for 12 h per day as an addition to usual care for 24 h	Usual care consisted of 1) oxygen titration with nasal cannula according to our institutional recommendations to target SpO2 values between 90% and 94%.	The pre-specified **primary outcome** was oxygen needs assessed by nasal cannula oxygen flow at 24 h. **Secondary outcomes** were the SpO2/FiO2 ratio (defined as SpO2 percentage divided by the FiO2) at 24 h; respiratory and • heart rate at 24 h; patient trajectory (transfer to critical care unit); potential intervention-related adverse effects as

							defined by neck pain, position-related discomfort and gastroesophageal reflux
Standard Care Versus Awake Prone Position in Adult Nonintubated Patients with Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection—A Multicenter Feasibility Randomized Controlled Trial Jayakumar et.al, 2021	Multicenter feasibility randomized controlled trial	India	60	18 years of age and requiring 4 or more liters per minute (LPM) of supplemental oxygen to maintainSpO2 92% PaO2/FiO2 ratio between 100 and 300 mmHg (mild to moderate ARDS) with PaCO2 <45mmHg Patients with AHRF and Hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine were also considered for inclusion.	lie prone for a minimum of 6 hours in a day (cumulative)	Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed.	Primary outcome measure proportion of patients adhering to the protocol in each group Secondary outcomes • proportion of patients requiring escalation of respiratory support in either group; number of hours prone and maximum hours of continuous prone positioning in a day; length of stay in the ICU; ICU mortality; adverse events; reasons for not lying prone
Awake prone positioning strategy for non-intubated Hypoxic Patients with COVID-19: A pilot trial with embedded implementation evaluation Taylor, et. al 2021	Pragmatic, two-arm parallel cluster RCT and a qualitative study	North Carolina, USA	40	positive for SARS-CoV-2 within 7 days or were suspected to have COVID-19 pneumonia, room air oxygen saturation,93% or oxygen requirement of 3 liters per minute or greater without the need for mechanical ventilation.	Awake Prone Positioning Strategy (APPS) Patients were encouraged to sustain the prone position as long as possible but were allowed to return to the supine position as necessary	Usual Care	primary outcome • Establish outcomes relative to successful implementation of a future definitive RCT. • Specific research outcomes • nadir oxygen saturation to fraction of inspired oxygen (S/F) ratio • Time spent with S/F ratio less than 315 • Receipt of intensive care, greater than 6 L/min • Oxygen support • Intubation • Hospital length of stay • Hospital mortality
Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxemic respiratory failure: analysis of a randomized controlled trial	multicenter randomized controlled trial	Western Mexico	430	Patients aged ≥ 18 years RT-PCR confirmed COVID-19 SpO2 < 90% despite receiving oxygen at 15 L/min through a non-rebreather mask	Awake prone positioning as tolerated	standard care group where awake prone positioning was discouraged If Awake prone positioning was performed for ≥ 1 h, patients were excluded	**Primary outcome** • Intubation within 28 days **Secondary outcome** • Treatment success defined as being alive

Ibarra-Estrada, et al 2022				Requirement of a fraction of inspired oxygen (FIO2) ≥ 0.3 through HFNC at the maximum tolerated flow to maintain a SpO2 ≥ 90% Exclusion criteria Severe respiratory failure requiring immediate intubation do-not-intubate/resuscitate orders laparotomy within 2 weeks pregnancy vasopressor requirement to maintain median arterial pressure > 65 mmHg refusal to participate			without intubation at day 28 • mortality at 28 days • HFNC duration • Use of NIV • Time to intubation • Days of invasive ventilation Hospital length of stay • Physiological response to the first APP session • Adverse events **Exploratory Outcomes** • Predictors for treatment success in the overall population and in the APP group • Association between treatment success and mean daily duration of APP • Difference in outcomes among patients with silent hypoxemia
Assessment of Awake Prone Positioning in Hospitalized Adults With COVID-19: A Nonrandomized Controlled Trial Qian Et al 2022	pragmatic nonrandomized controlled trial	Nashville, Tennessee Evanston, Illinois	501	Patients aged 18 years or older Hospitalized with acute hypoxemic respiratory failure (defined as the need for supplemental oxygen provided by standard low flow nasal cannula, high-flow nasal cannula (HFNC), or noninvasive positive-pressure ventilation to maintain an oxygen saturation of 89% or higher) COVID-19 infection (based on polymerase chain reaction testing) Had not received mechanical ventilation.	Awake prone positioning as often and as consistently as they are able, ideally 3 hours at a time 4x a day	Usual care without routine suggestion of prone positioning	**Primary outcome** • Highest level of oxygen support on day 5 after enrollment according to a modified WHO COVID-19 ordinal outcome scale **Secondary outcome** • most intensive level of respiratory support used for each patient on each day leading up to study day 5 **Exploratory outcomes** • length of stay, • ventilator-free days • need for invasive mechanical ventilation

				.			• maximum FiO2 levels on study days 1 through 5 • most severe outcome on the modified WHO ordinal scale on study days 14 and 28
Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial (COVI-PRONE) *Alhazzani et al 2022*	Pragmatic, unblinded randomized clinical trial	21 hospitals in Canada, Kuwait, Saudi Arabia, and the USA	400	Patients aged 18 years or older not intubated suspected or confirmed COVID-19 required at least 40% oxygen (via low- or high-flow oxygen devices) or noninvasive positive pressure ventilation being treated in an intensive care unit (ICU) or a monitored acute care unit. **Exclusion Criteria** 1. received invasive mechanical ventilation, 2. had contraindications to prone positioning 3. with risk of complications from prone positioning 4. had been self-prone positioning prior to enrollment	Awake prone positioning with a target duration of 8 h/d to 10 h/d with 2 to 3 breaks (1-2 hours each)	Usual Care with nurse instructions not to position in the prone position	**Primary outcome** • endotracheal intubation within 30 days of randomization **Secondary outcome** • mortality at 60 days • days free from invasive mechanical ventilation or noninvasive ventilation at 30 days • days free from the ICU or hospital at 60 days • adverse events and serious adverse events
Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial Ehrmann et al 2021	prospective,a priori set up and defined, collaborative meta-trial of six randomised controlled open-label superiority trials	Canada, France, Ireland, Mexico, USA, Spain	1126	adults (>18 years old) acute hypoxemic respiratory failure (defined as needing high-flow nasal cannula and a ratio of peripheral arterial oxygen saturation (SpO2) to the fraction of inspired oxygen (FiO2) [SpO2 :FiO2] of 315 or less (which is equivalent	prone position for as long and as frequently as possible each day	Standard care	**Primary outcome** • treatment failure within 28 days of enrolment, defined as intubation or death **Secondary outcomes (all censored at 28 days after enrolment**)

				to a ratio of partial pressure of arterial oxygen [PaO2] to FiO2 [PaO2 :FiO2] ≤300 mm Hg) proven (or highly clinically suspected, pending microbiological confirmation) COVID-19 pneumonia Exclusion criteria unable or refused to provide informed consent hemodynamically unstable severely obese(body-mass index higher than 40 kg/m²) pregnant contraindication to awake prone positioning			• use of noninvasive ventilation • length of hospital stay • time to high flow nasal cannula weaning in patients with treatment success (defined as the patient being alive and not having required intubation within 28 days of enrolment) • time to treatment failure • time to intubation • time to death • duration of invasive mechanical ventilation in intubated patients surviving to day 28 • mortality in invasively mechanically ventilated patients • predefined safety outcomes as prospectively recorded by investigators • physiological response to awake prone positioning, including the ratio of SpO2 :FiO2 to respiratory rate (ROX index)
Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE) Fralick et al 2022	Multicentre pragmatic randomised clinical trial	Canada and the United States	257	laboratory confirmed or a clinically highly suspected diagnosis of covid-19 needed supplemental oxygen (up to 50% fraction of inspired oxygen) able to independently lie prone with verbal instruction	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)	standard of care (no instruction to adopt prone position)	**Primary outcome** • 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** • time spent in prone position • change in the ratio of oxygen saturation to

							fraction of inspired oxygen • time to discharge from hospital • rate of serious adverse events

Table 6. Study Characteristics of Included Studies for Side Lying (n=3)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Targeted lateral positioning decreases lung collapse and overdistension in COVID-19-associated ARDS Micek 2021	Prospective observational study	Brazil	5	Patients with COVID-19 associated ARDS in the first days of mechanical ventilation ARDS by Berlin Criteria	Targeted lateral position defined by selecting the less aerated lung to be positioned up and the more aerated lung to be positioned down. During all the procedures, the patients were deeply sedated and under muscle paralysis		Regional overdistension and collapse

Sequential lateral positioning as a new lung recruitment maneuver: an exploratory study in early mechanically ventilated Covid-19 ARDS patients
 	
Roldan 2022
	single-center prospective observational study	Canada	15	Positive SARS-CoV-2 infection (confirmed by using real-time quantitative PCR on nasopharyngeal swabs)
				
				Moderate-to-severe ARDS as per the Berlin definition (PaO2/ FiO2 ≦200 mmHg)
				
				under mechanical ventilation
				
				Age ≧ 18 years old
				
				body mass index ≤35 kg/m
				
				Exclusion Criteria
				
				contraindications for EIT monitoring as
				
				• unstable spine or pelvic fractures
				• pacemaker, automatic implantable cardio-defibrillator
				• skin lesions between the 4th and 5th ribs where the EIT belt is positioned
				pregnancy
				
				mechanical ventilation > 1 week
					Patients were studied in five body positions in sequential order, each maintained during 30 min:
					
					• Supine-1 (S1), which served as the baseline condition
					• Lateral-1 (L1-the less ventilated lung evaluated by EIT was positioned up first)
					• Supine-2 (S2-after first lateral position)
					• Lateral-2 (L2-the contralateral lung was positioned up)
					• Supine-3 (S3-after second lateral position)
					
					Lateral positioning was done with an inclination of 30° using a custom-made support cushion lined with a special foam
							Primary outcome
							
							• Effects of a postural recruitment maneuvers on
							  ○ lung aeration
							  ○ distribution of ventilation
							  ○ gas exchange
							  ○ respiratory mechanics
							  ○ hemodynamic

				multi-organ failure hemodynamic instability defined as persistent mean arterial pressure lower than 60 mm Hg despite adequate fluid resuscitation and two vasopressors or increase of vasopressor dose by 30% in the previous 6 h COPD Pneumothorax increased intracranial pressure			
Efficacy of early prone or lateral positioning in patients with severe COVID-19: a single-center prospective cohort Zhong Ni 2020	prospective, observational cohort study	China	52	Diagnosis of COVID-19 was defined as the presence of severe acute respiratory syndrome coronavirus 2 before admission, determined by RT-PCR severe category of COVID-19(manifesting as dyspnea with respiratory rate (RR) ≥ 30 breaths/min, pulse oxygen saturation ≤ 93% at rest, or partial pressure of arterial oxygen (PaO2)to fraction of inspired oxygen(FiO2) ratio ≤ 300 mmHg14; with chest computerized tomographic (CT) images showing exudation or consolidation mainly in the bilateral peripheral and posterior parts of the lungs) Exclusion Patients were excluded if they were aged < 18 or > 80 years old Pregnant	prone positioning was superimposed on the standard care at the doctors' discretion without pre-defined selection criteria. Where prone positioning was not tolerated by a patient, lateral positioning was implemented as an alternative. Each patient was placed in position for at least 4 hours per day for 10 days.	standard care comprised supplemental oxygen and ventilation, antivirals antibiotics, anticoagulants, and glucocorticoids, as necessary, based on the clinical condition of the patients. In this group, no position intervention was introduced.	**primary outcome** • oxygenation improvement, determined by cumulative adjusted mean difference of SpO2/FiO2 (serving as oxygen saturation index), Respiratory rate-Oxygenation (ROX) index, and Borg scale between position intervention and standard care **Secondary outcome** • lung lesion absorption • NEWS2 • time to clinical improvement • rate of intubation avoidance • death • time to virus shredding • length of hospital stay • adverse events

				Critically ill (invasive mechanical ventilation, severe cardiac failure, or hemodynamically unstable)14 contraindicated to the prone or lateral position unable to cooperate.			

Table 7. Study Characteristics of Included Studies for Critical COVID and Positioning (n=5)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Prone Positioning in Moderate to Severe Acute Respiratory Distress Syndrome Due to COVID-19: A Cohort Study and Analysis of Physiology Shelhamer 2020	single center retrospective cohort study	New York	261	• adult patients (>17 years of • age) • intubated • not undergone prone positioning • met criteria for prone positioning • confirmed SARS-CoV-2 infection by real-time reverse transcription-polymerase chain nasal swab	primary exposure was positional maneuvers, defined as regular alternation between prone and supine positioning	Did not undergo positional changes (supine)	primary outcomes • in-hospital mortality • among exposed patients, differences in physiological parameters in prone vs supine position
Predicting Impact of Prone Position on Oxygenation in Mechanically Ventilated Patients with COVID-19 Bell 2022	retrospective observational study	Washington DC	125	• All consecutive patients from 3/1/2020 to 7/ 1/2021 • diagnosed with SARS-CoV2 • mechanically ventilated for hypoxemic respiratory failure • underwent prone positioning	Prone positioning	None (single arm)	Primary outcome • change in oxygenation, as measured by PaO2/FiO2
Evaluation of Oxygenation in 129 Proning Sessions in 34 Mechanically Ventilated COVID-19 Patients Berill 2020	Single center retrospective observational study	UK	34	• proned for >3 hours • mechanically ventilated and survived >24 hours from ICU admission	Prone positioning	None (single arm)	Primary outcome • Improvement in PF ratio • Decrease in Fio2
Prone positioning improves oxygenation and lung recruitment in patients with SARS-CoV-2 acute respiratory distress syndrome; a single centre cohort study of 20 consecutive patients Clarke 2021	prospective cohort study	Ireland	20	• patients > 18 years of • age • laboratory confirmed SARS-CoV-2 infection • invasively ventilated in the ICU • met the Berlin criteria for the diagnosis of ARDS • underwent prone positioning as part of their management	Prone positioning	None (single arm)	Primary outcome • gas exchange and respiratory mechanics • ICU free days and ventilator free days • 28-day mortality • ICU free days

Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study Weiss 2020	retrospective observational cohort study	USA	42	• Adult subjects admitted to any of the adult ICU • laboratory-confirmed COVID-19 infection • invasive mechanical ventilation • prone positioning	Intubated subjects diagnosed with ARDS were placed in the prone position by the team when a patient had a PaO2/FiO2 ratio of <20 kPa with PEEP set 10 cm H2O and FiO20.6. Prone positioning was maintained for at least 16 h, except if cardiopulmonary resuscitation was needed Prone positioning was terminated when PaO2/FiO2 ratio remained >20 kPa in the supine position or if extracorporeal membrane oxygenation (ECMO) or palliative care was needed		Primary outcome • oxygenation, assessed by PaO2/FiO2 ratio, before and after the initial prone positioning manoeuver. ○ A positive response was defined a priori as an increase in PaO2/FiO2 ratio 20% Secondary outcome • Serial PaO2/FiO2 ratios were assessed after repeated prone positioning, compared between subjects discharged to home or long-term care facility versus those who died or required ECMO • Haemodynamic (heart rate, arterial blood pressure) and ventilatory parameters (tidal volume, ventilatory frequency, PEEP, plateau pressure and ventilatory ratio) after repeated prone positioning

Appendix 4: Risk of Bias Assessment

Awake Proning

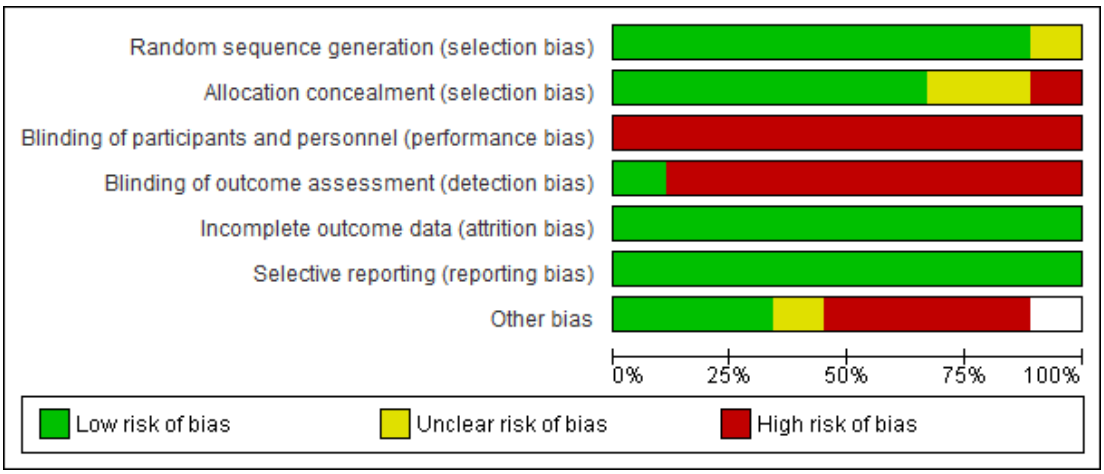

Figure 4. Risk of bias graph for awake prone positioning

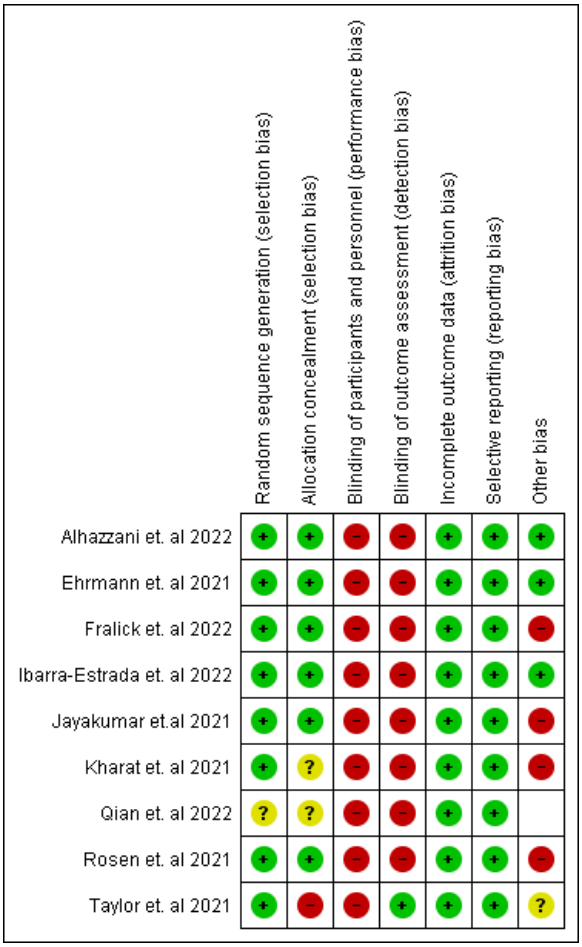

Figure 5. Risk of bias graph for awake prone positioning

Proning Critical COVID

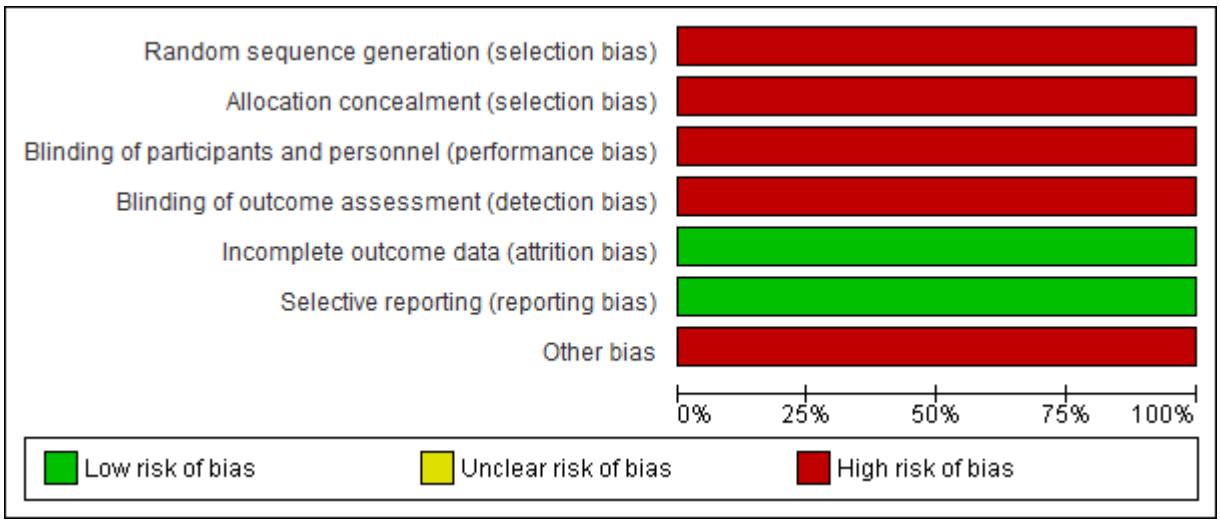

Figure 6. Risk of bias graph for prone positioning among intubated critical COVID-19

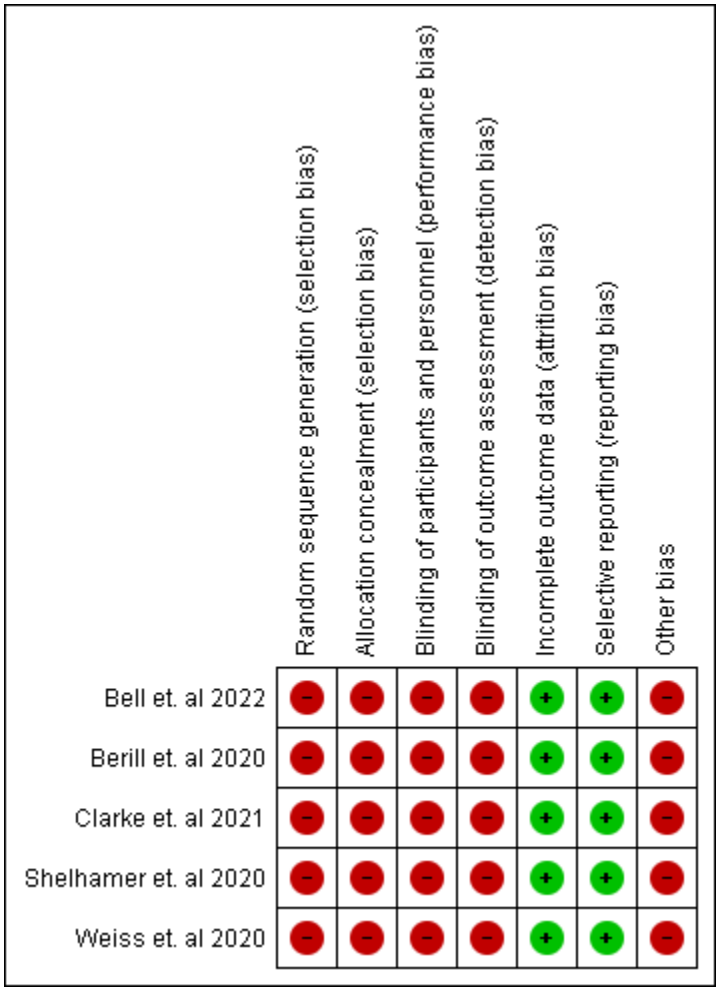

Figure 7. Risk of bias graph for prone positioning among intubated critical COVID-19

Side lying

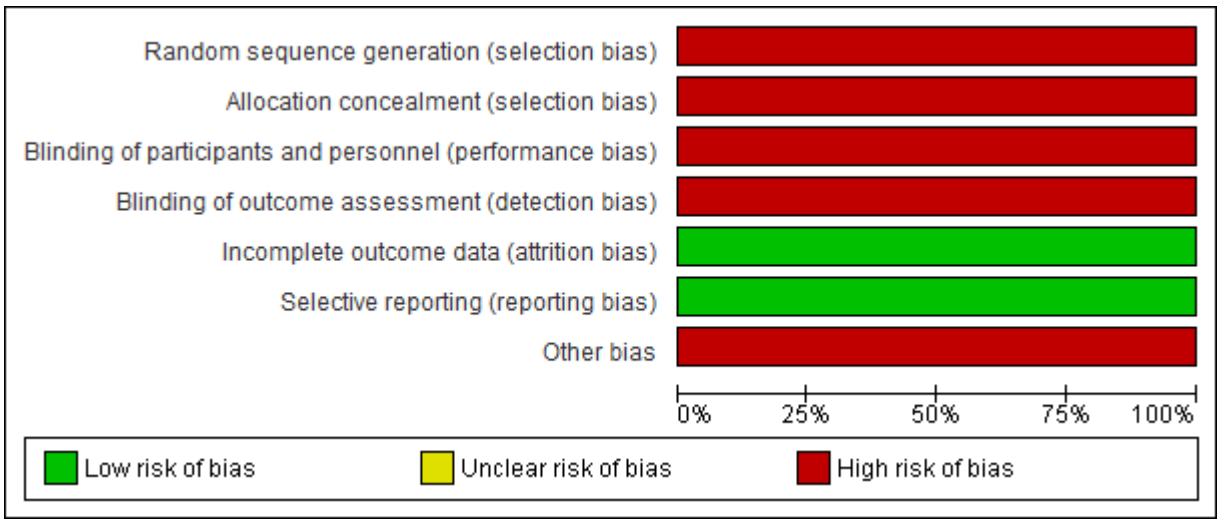

Figure 8. Risk of bias graph for side lying

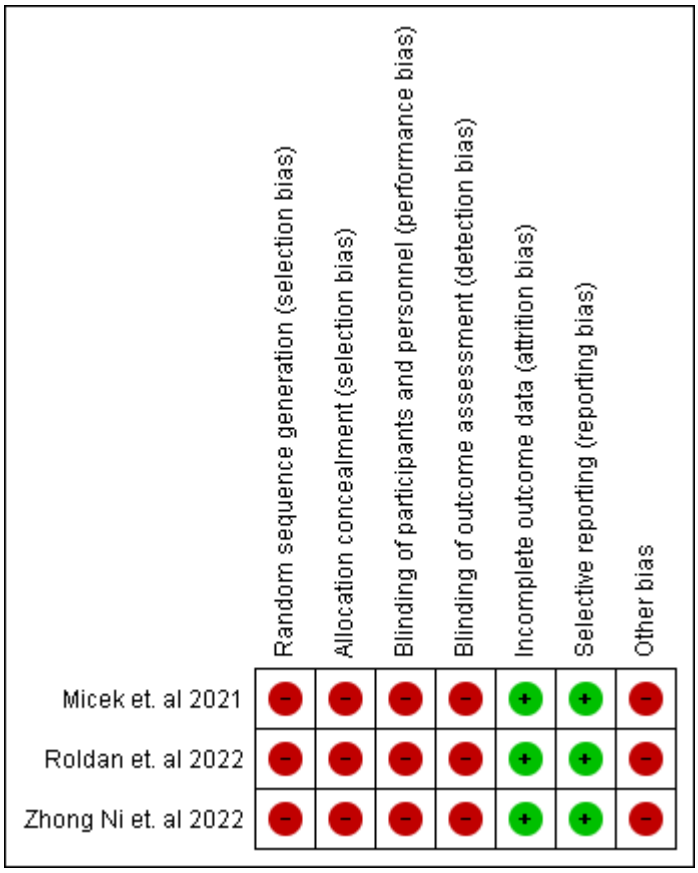

Figure 9. Risk of bias summary for side-lying

Appendix 5: GRADE Evidence Profile

Author(s): Jhon Ryan G. Enriquez
Question: Prone compared to Supine for Awake, Non-intubated, COVID-19 patients
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Supine	Relative (95% CI)	Absolute (95% CI)		
Need for intubation												
8	randomised trials	serious[a]	not serious	not serious	not serious	none	373/1448 (25.8%)	448/1427 (31.4%)	**RR 0.81** (0.73 to 0.91)	**60 fewer per 1,000** (from 85 fewer to 28 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (follow-up: mean 30 days)												
8	randomised trials	not serious[b]	not serious	not serious	serious[c]	none	300/1429 (21.0%)	310/1406 (22.0%)	**RR 0.94** (0.82 to 1.08)	**13 fewer per 1,000** (from 40 fewer to 18 more)	⨁⨁⨁◯ Moderate	CRITICAL
Need for intensive care												
4	randomised trials	serious[d]	serious[e]	not serious	serious[c]	none	75/275 (27.3%)	90/307 (29.3%)	**RR 0.91** (0.72 to 1.16)	**26 fewer per 1,000** (from 82 fewer to 47 more)	⨁◯◯◯ Very low	CRITICAL
Length of Hospital stay (Days)												
2	randomised trials	not serious[b]	not serious	not serious	serious[c]	none	822	800	-	MD **0.32 Days fewer** (1.34 fewer to 0.71 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Length of ICU stay (Days)												
2	randomised trials	not serious[b]	serious[e]	not serious	serious[c,f]	none	288	273	-	MD **0.38 Days lower** (2.01 lower to 1.26 higher)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Blinding of Participants and outcome assessors cannot be done, 3 of the included studies were under powered, 1 at risk of recall bias (fralick et. al) and 1 is at risk of bias due to clustering (kharat et. al)
b. Although blinding of participants and outcome assessors cannot be done, this will have minimal effect in terms of the outcome measure
c. CI of the meta-analytical effect crosses the line of no effect
d. Blinding of participants and outcome assessors cannot be done, 3 of the included studies are under powered, 1 at risk of bias due to clustering (kharat et. al)
e. Wide variances of point estimates
f. Wide confidence intervals

Author(s): Jhon Ryan G. Enriquez
Question: Prone compared to Supine for Awake, non-intubated COVID
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Supine	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
6	randomised trials	serious[a]	very serious[b,c]	not serious	very serious[d,e]	none	110/1064 (10.3%)	94/1062 (8.9%)	**RR 1.08** (0.54 to 2.14)	**7 more per 1,000** (from 41 fewer to 101 more)	⨁◯◯◯ Very low	IMPORTANT
Serious Adverse events												
5	randomised trials	serious[a]	not serious	not serious	very serious[d,e,f]	none	10/1147 (0.9%)	3/1127 (0.3%)	**RR 2.74** (0.49 to 15.36)	**5 more per 1,000** (from 1 fewer to 38 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Blinding of Participants and outcome assessors
b. Wide variances of point estimates
c. Substantial statistical heterogeneity
d. Wide confidence interval
e. Confidence interval of the meta analytical effect crosses the line of no effect
f. low event rates

Author(s): Jhon Ryan G. Enriquez
Question: Proning compared to Supine in Critical COVID-19 patients
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proning	Supine	Relative (95% CI)	Absolute (95% CI)		
In-hospital Mortality												
1	observational studies	very serious[a,b]	not serious	not serious	not serious	none	48/62 (77.4%)	167/199 (83.9%)	HR 0.61 (0.46 to 0.80)	167 fewer per 1,000 (from 271 fewer to 71 fewer)	⨁◯◯◯ Very low	CRITICAL
Length of Hospital stay (in days, median, IQR)												
1	observational studies	very serious[a,b]	not serious	not serious	not serious	none	18.1	8	-	Median 9 days higher (5.4 higher to 14.3 higher)	⨁◯◯◯ Very low	IMPORTANT
Change in PaO2/FiO2 ratio												
4	observational studies	very serious[a,c]	not serious	not serious	not serious	none	Four observational single arm studies measured the change in PaO2/FiO2 ratio before and during proning among mechanically ventilated COVID-19 patients. Patients were maintained on prone position for at least 16 hours. Pooled analysis showed a significant improvement in in PaO2/FiO2 ratio at prone position (MD 69.01; 95% CI 32.45 to 105.58; I2=86%; Very low certainty)				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **HR:** hazard Ratio

Explanations

a. Non randomized study
b. Inadequate control of confounders
c. Lack of Comparator arm (single arm studies)

Author(s): Jhon Ryan G. Enriquez
Question: Side-lying compared to Supine in COVID-19 patients
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	side-lying	Supine	Relative (95% CI)	Absolute (95% CI)		
Lung Collapse and Over distention												
1	observational studies	serious[a]	very serious[b]	not serious	very serious[b]	none	Less collapse along the PEEP titration was found within the left lung in targeted lateral (P = 0.014); and less overdistension along the PEEP titration was found within the right lung in targeted lateral (P = 0.005). Regarding collapse within the right lung and overdistension within the left lung: no differences were found for position				⨁◯◯◯ Very low	IMPORTANT
Respiratory mechanics and gas exchange												
1	observational studies	serious[a]	very serious[c]	not serious	very serious[c]	none	Comparing supine baseline and final, respiratory compliance (29±9 vs 32±8 mL/cmH2O; p < 0.01) and PaO2/FIO2 ratio (138±36 vs 164±46 mmHg; p < 0.01) increased, while driving pressure (13±2 vs 11±2 cmH2O; p < 0.01) and lung ultrasound consolidation score decreased [5 (4–5) vs 2 (1–4); p < 0.01]				⨁◯◯◯ Very low	IMPORTANT
Change in SpO2/FiO2												
1	observational studies	serious[a]	serious[d]	very serious[e]	serious[d]	none	Noted increased cumulative adjusted mean difference of SpO2/FiO2 (MD 409, 95% CI 86 to 733) during the first 7 days				⨁◯◯◯ Very low	IMPORTANT
Change in ROX index												
1	observational studies	serious[a]	serious[d]	very serious[e]	serious[d]	none	Noted increased cumulative adjusted mean difference of ROX index (MD 26, 95% CI 9 to 43) during the first 7 days				⨁◯◯◯ Very low	IMPORTANT
Rate of Intubation												
1	observational studies	serious[a]	serious[d]	very serious[e]	serious[d]	none	0/17 (0.0%)	1/35 (2.9%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Length of Hospital stay												
1	observational studies	serious[a]	serious[d]	very serious[e]	serious[d]	none	No significant differences were observed in the length of hospital stay between the two groups (Days, median IQR - Position group - 35d (27–52) VS Standard group - 35d (28–42), p value = 0.914)				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. inadequate control of confounding factors
b. Single study with a population of 5
c. Single study with a population of 15
d. Single study with small sample size
e. Intervention arm is a mixture of Proning and Side lying without clear delineation of outcome between the two

Appendix 6: Forest Plots

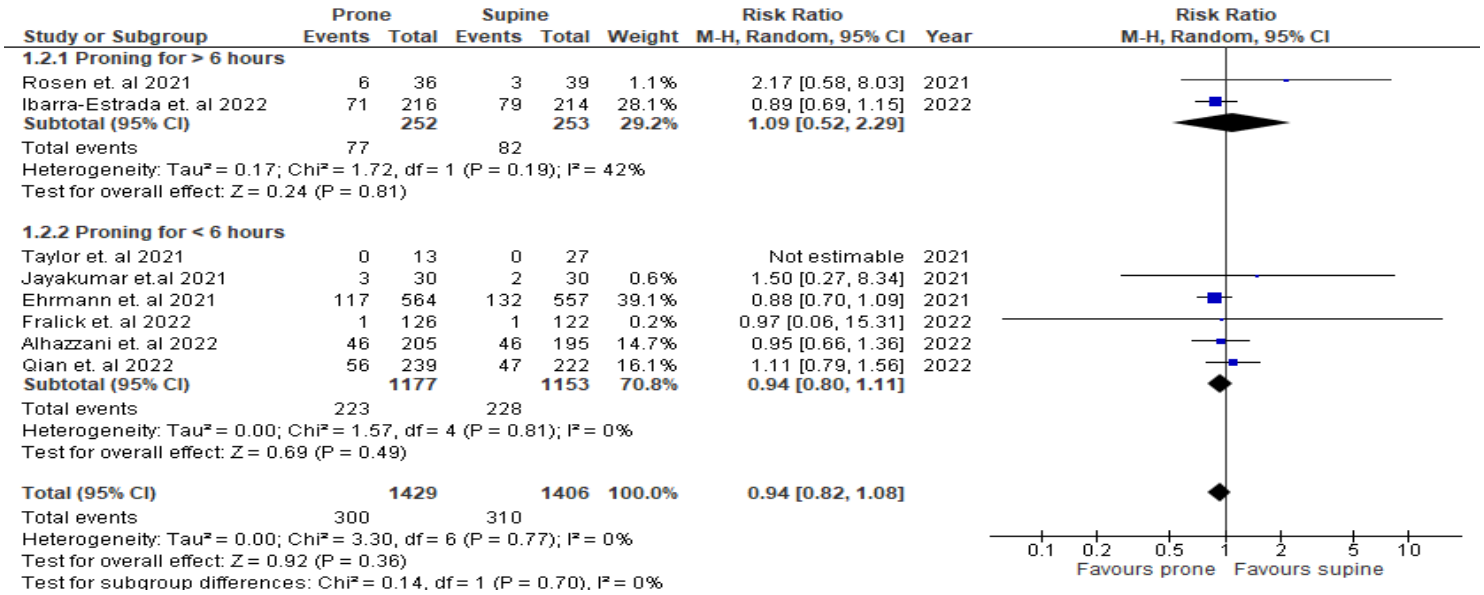

Figure 10. Forest plot for mortality for awake prone positioning

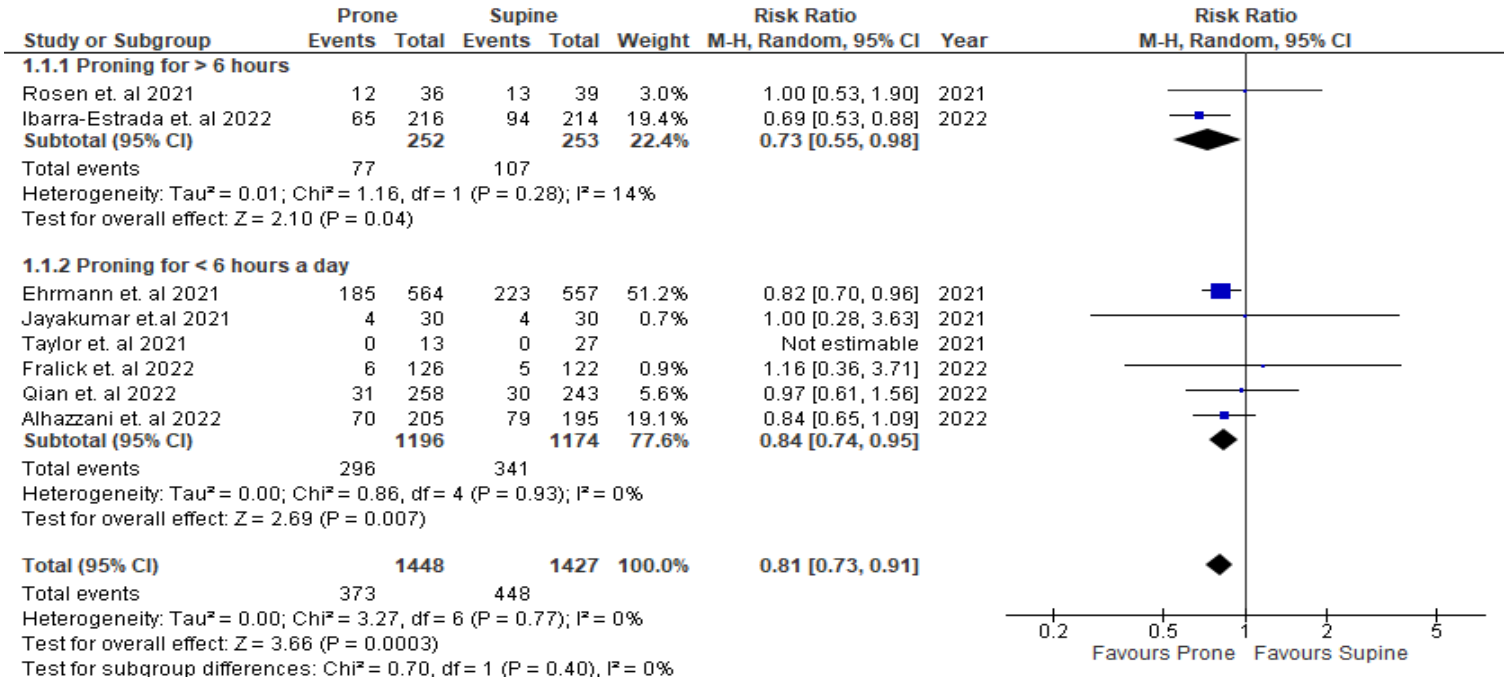

Figure 11. Forest plot for need for mechanical ventilation for awake prone positioning

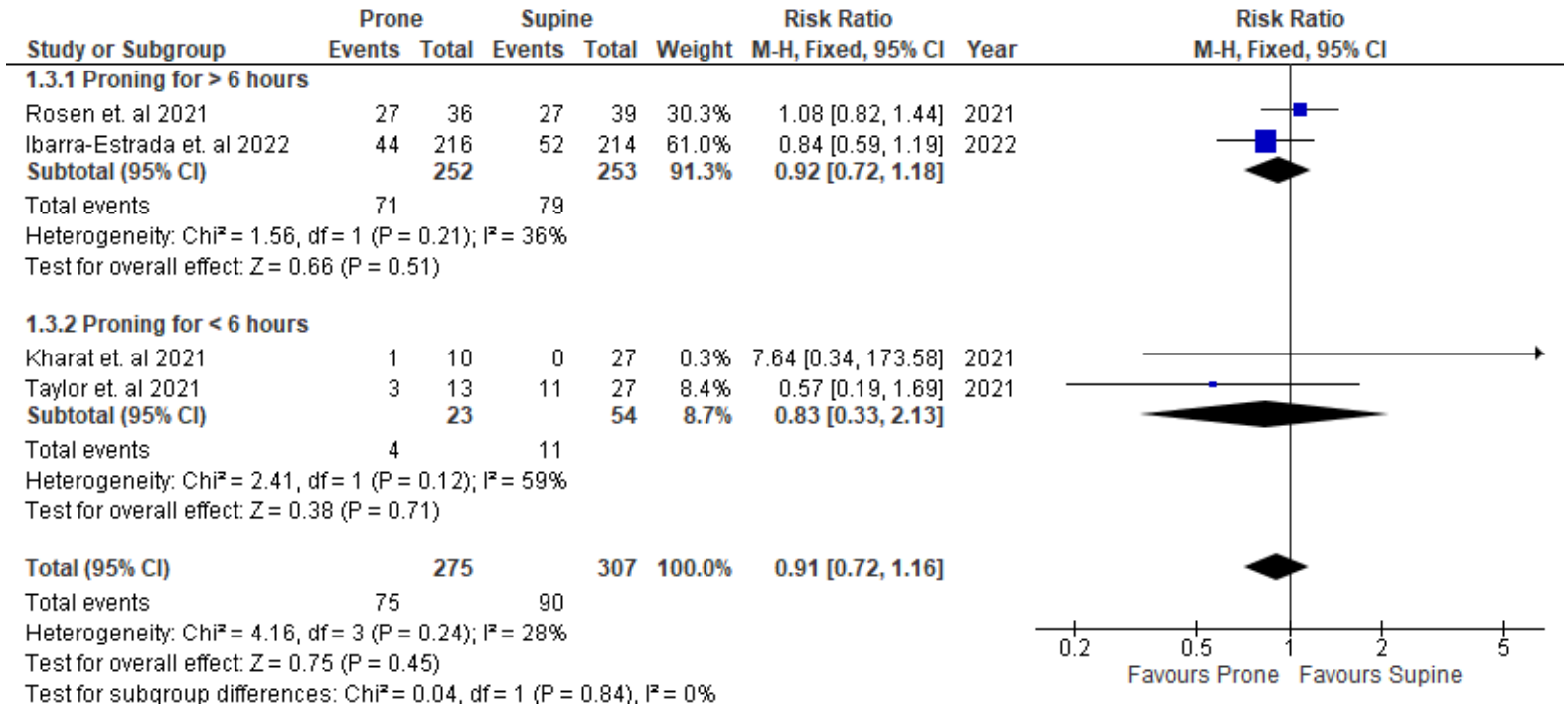

Figure 12. Forest plot for need for intensive care unit admission for awake prone positioning

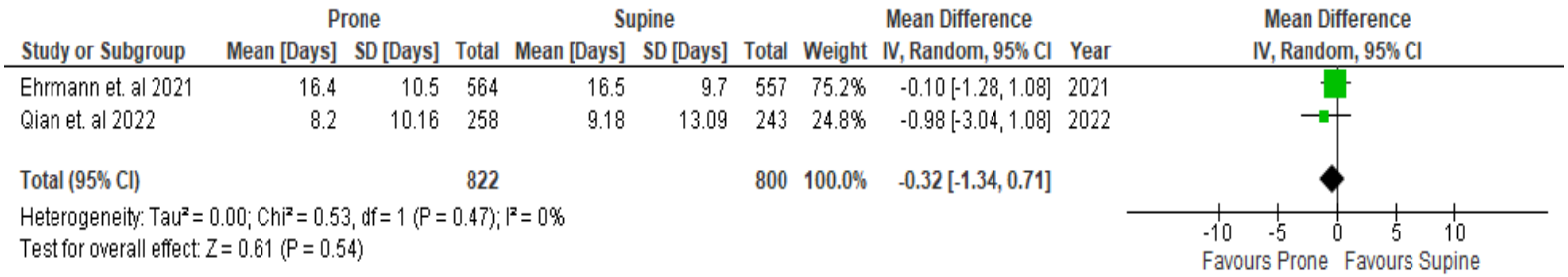

Figure 13. Forest plot for length of hospitalization (in days) for awake prone positioning

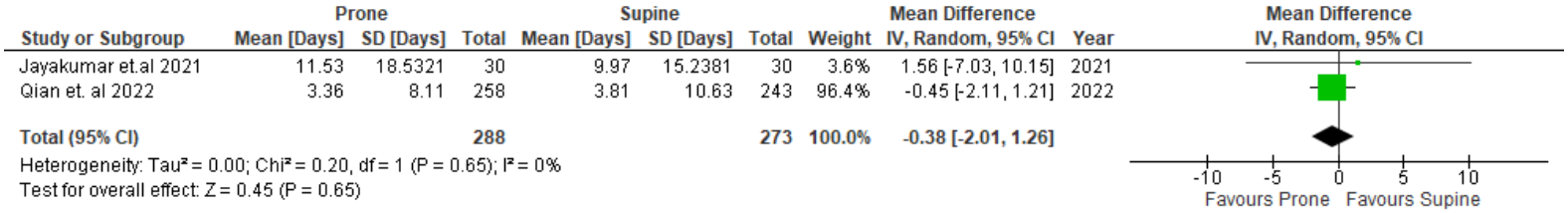

Figure 14. Forest plot for length of intensive care unit stay for awake prone positioning

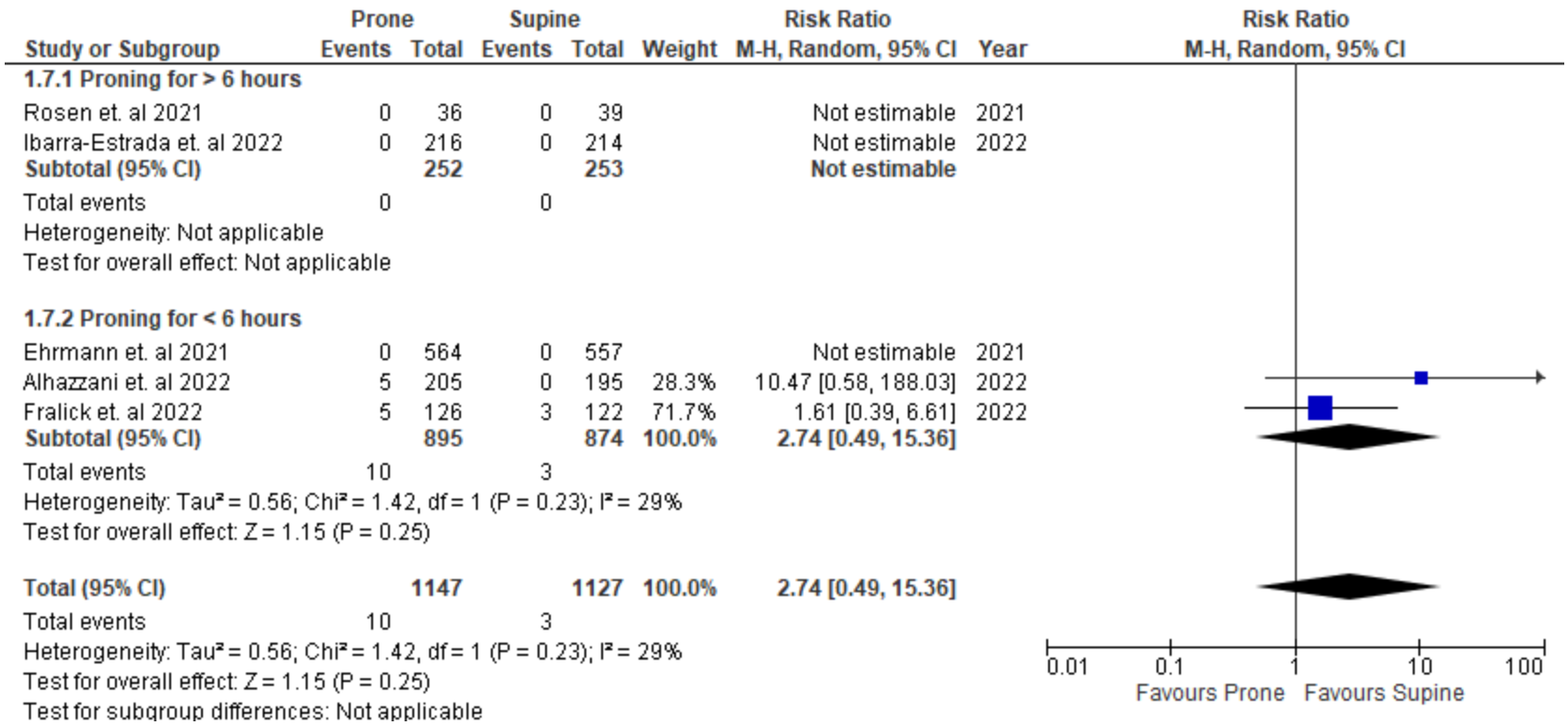

Figure 15. Forest plot for serious adverse events for awake prone positioning

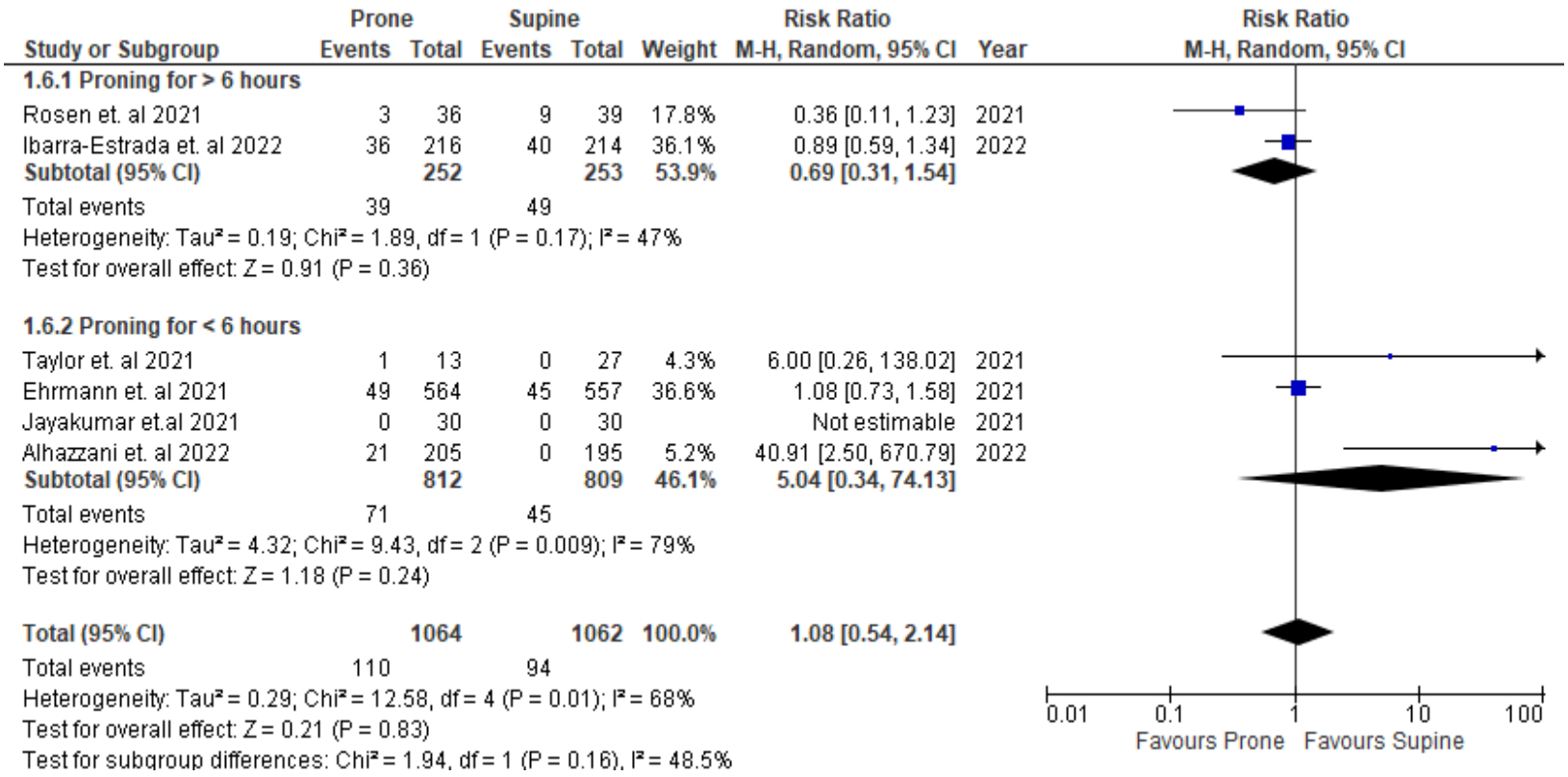

Figure 16. Forest plot for adverse events for awake prone positioning

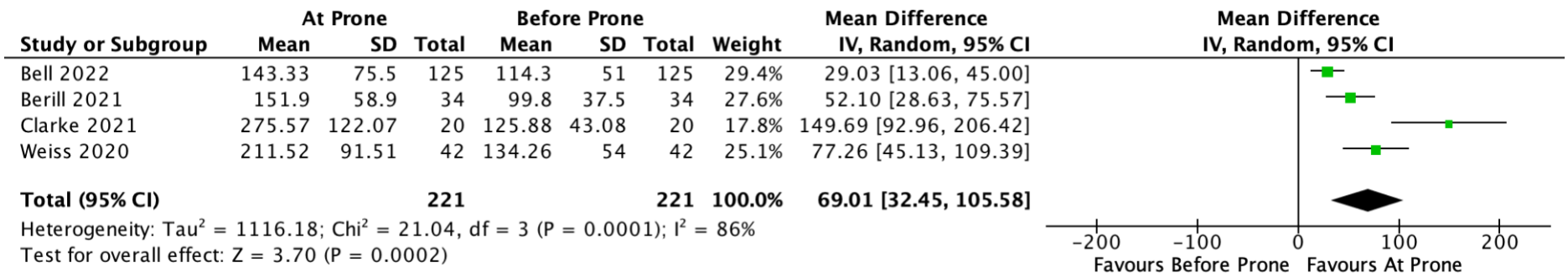

Figure 17. Forest plot for change in PaO_2/FiO_2 ratio for intubated critical COVID-19

Appendix 7: Ongoing Studies

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes

NCT05083130
 	
Evaluation of Awake Prone Positioning Effectiveness in Moderate to Severe COVID-19
 	
Estimated Study Completion Date: November 1, 2023
	prone position group will have a special intervention team who visits patients' rooms aiming for patients to maintain the prone position for at least 8 hours a day	Standard care will consist of routine clinical care, including any advice to lie in prone position as routinely recommended by participating sites	• 18 Years and older
			• Probable or confirmed COVID-19 infection according to WHO criteria
			• Moderate or severe COVID-19 respiratory infection according to Vietnamese guidelines
			• Requirement for supplemental oxygen therapy
				Primary Outcome
				Escalation of respiratory therapy within 28 days of randomization, defined as any of the following:
				
				• Escalation to next level respiratory support (with lowest level nasal cannula or face mask, escalating through HFNC to NIV or mechanical ventilation).
				• Intubation
				Secondary outcome
				• Fatal event [Time Frame: Up to 28 days after enrollment]
				  • all-cause of death within first 28 days will be compared between groups
				• Duration of hospital stay [Time Frame: Up to 2 months after enrollment]
				  • Days since admission to discharge
				• Improvement in oxygen related parameters [Time Frame: Up to 28 days after enrollment]
				  • SpO2, respiratory rate, heart rate, FiO2, ROX index will be documented before and at end of period of prone positioning every day. The improvement will be measured by resolution of them compared with baseline parameters
				• Number of adverse events [Time Frame: Up to 28 days after enrollment]
				  • An adverse event (AE) is defined as any unfavorable and

				unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. The severity of all AEs in this trial should be graded in line with the toxicity grading in Toxicity grading and management (CTCAE)
NCT04641182 Observational Study of Prone Position for Nonintubated Patients With COVID-19 and Hypoxemic Respiratory Failure Completed No Results	Prone position per institutional protocol and as indicated by the treating physician	The control group will not be in prone position	• 18 Years and older • Hospitalized patients with confirmed or suspected COVID-19 pneumonia requiring more than 3 liters per minute of supplemental oxygen or a Fraction of Inspired Oxygen (FIO2) over 35% to keep Pulse Oximetry Saturation (SpO2) over 90% • Treating physician indicated prone position as instructed by the institutional protocol • Patient capable of changing position with minimal help from the personnel	Primary Outcome • Therapeutic failure [Time Frame: At 14 days] • Defined by death or intubation or use of non-invasive ventilation • Mortality [Time Frame: At day 28] • Number of patients that die • Length of hospital stay [Time Frame: At 28 days] • Number of days spent by the patients at the hospital • Days requiring high flow nasal oxygen [Time Frame: At 28 days] • Number of days the patients require high flow nasal oxygen therapy • Days requiring supplemental oxygen [Time Frame: At 28 days] • Number of days the patients require supplementary oxygen

				• Displacement of invasive devices during position changes [Time Frame: At 28 days] • Unintentional displacement or removal of Invasive devices including : central and peripheric vascular catheters, urinary catheter and chest tubes • Occurrence of pressure ulcers on the anterior surface of the body [Time Frame: At 28 days] • Number of patients that developed pressure ulcers on the anterior surface of the body
NCT04344106 Prone Positioning in Spontaneously Breathing Nonintubated Covid-19 Patient: a Pilot Study (ProCov) Recruiting Current status: unknown	Participants are all turned to prone position for an optimal minimum duration of 3 hours	None	• 18 Years and older • Patient aged at least 18 years; • Hospitalized in a COVID unit or intensive care unit; • Spontaneously breathing and with oxygen therapy with nasal canula, mask or High Flow Oxygen Therapy; • Requiring oxygen therapy ≥ 1l for Sat ≥ 90%; • COVID 19 positive in RT-PCR or diagnosis on clinicals symptoms and highly evocative scannographics lesions in an epidemic period; • Chest scanner without injection within 72 hours prior to inclusion; • Bilateral scannographic lesions, including posterior condensations and/or posterior predominance of lesions; • Patient benefiting from French social security, under any regime	Primary outcome • Proportion of "responder" patients to prone position [Time Frame: 1 hour] ○ PaO2 improvement of more than 20% after one hour in prone position in spontaneously breathing non intubated COVID-19 patients Secondary outcome • proportion of "persistent responders" patients after prone position [Time Frame: 1 day] ○ PaO2 improvement of more than 20% at 6 to 12 hours from return to supine position. • Evolution of PaO2 [Time Frame: 1 day] ○ PaO2 at 1 hour from the start of prone position and at 6 to 12 hours after return to supine position.

				• Duration of prone positioning and PaO2 evolution [Time Frame: 2 days]
				  ○ Look for an association between the time spent in Prone position and persistent responder or not;
				• Evolution of Spo2 [Time Frame: 1 hour]
				  ○ proportion of patients improving their arterial saturation within 1 hour of Prone Position
				• EVA Dyspnea [Time Frame: 1 day]
				  ○ evolution of the EVA scores for dyspnea at 1 hour from the start of the Prone Position and at 6 hours after the end of the Prone Position
				• Intolerance to prone positioning [Time Frame: 1 day]
				  ○ proportion of patients intolerant to prone position (Prone Position <1h);
				• Tolerance to prone positioning [Time Frame: 1 day]
				  ○ proportion of patients who can maintain prone position for more than 3 h.

NCT04517123 Prone Position and Respiratory Outcomes in Non-Intubated	Prone Positioning	Usual Care	• Age ≥ 18 years • COVID-19 positive by nasopharyngeal swab or serostatus	Primary outcome • Occurrence of an escalation in respiratory related care (yes vs no) [Time Frame:

COVID-19 PatiEnts The "PRONE" Study
 	
Completed
No results
			• Use of supplemental oxygen OR respiratory rate ≥ 20	During hospitalization, up to 30 days]
				• Participants will be assessed for the occurrence of an escalation in respiratory related care (Yes or No). Escalation in respiratory related care is clinically defined as any of the following:
				  • intubation
				  • any increase in flow of supplemental oxygen
				  • transition to high flow nasal cannula
				  • increase in fraction of inspired oxygen
				  • transfer from a lower to a higher level acuity of care (e.g. medical floor to intermediate care unit (IMC) or intensive care unit (ICU); IMC to ICU)
				Secondary outcome
				• Oxygen Saturation [Time Frame: Over a consecutive 24-hour period after randomization]
				  • Oxygen Saturation measured in percent oxygen over a 24-hour period.
				• Respiratory Effort as assessed by Respiratory Rate [Time Frame: Over a consecutive 24-hour period after randomization]
				  • Respiratory effort will be assessed using the respiratory rate (in breaths per minute) over a 24-hour period.

NCT04982341 Effectiveness of High-flow Nasal Cannula and Prone Positioning in Awake Patients With COVID-19 and Severe Acute Respiratory Failure	awake patients with COVID-19 and severe acute respiratory failure receiving HFNC in prone position	Not described	aged ≥18 years, admitted to the medical ICU for confirmed Covid-19 and acute hypoxemic respiratory failure	Primary outcome • Number of patients without intubation

Completed No results				
NCT04924816 Evaluation of the Response to the Awake Prone Position in Patients With COVID-19 Completed No results, not yet published	The prone position in awake patients consists of asking the patient to voluntarily change to prone position, in a swimmer's posture	None	Patients with a confirmed diagnosis of COVID-19, spontaneously ventilating, dependent on supplemental oxygen	Primary outcome • ICU admission rate [Time Frame: Patients were followed up for up to 15 days of hospitalization.] ○ The criteria defined for admission to the ICU included maintenance of SpO2 below 90% with oxygen flow at 15 L / min, RF greater than 30 incursions per minute, reduced level of consciousness, or clinical signs of persistent increase in respiratory work, such as paradoxical ventilatory pattern.
NCT04649658 Awake Prone Position in Critical and Severe COVID-19 Patients Undergoing Noninvasive Respiratory Support: a Retrospective Multicenter Cohort Study Completed No results, not yet published	Severe and critical COVID-19 patients undergoing non-invasive respiratory support subjected to prone position	Severe and critical COVID-19 patients undergoing non-invasive respiratory support subjected to standard care	• patients aged =18 and < 80 years old • acute respiratory failure	Primary outcome • Endotracheal intubation Secondary outcome • Mortality [Time Frame: 28 days] • Tracheostomy [Time Frame: 28 days] • Length of Respiratory Intensive Care Unit stay [Time Frame: 60 days] • Length of Hospital stay [Time Frame: 60 days]
NCT04853979 Awake Prone Positioning in COVID-19 Suspects With Hypoxemic Respiratory Failure Completed No results, not yet published	Any combination of prone or side position (defined as any part of the anterior chest wall being in contact with the bed) for at least 3 hours and up to 16 hours per day during wakefulness	Usual care (no Prone unless asleep and assumes this position spontaneously).	• 18 Years and older • suspected or confirmed COVID-19 • SPO2 less than 94% or Oxygen requirement of more than 5 liters. • Requiring oxygen therapy in Hospital< 24 hours	Primary outcome • Proportion of patients requiring escalation to NIV (CPAP or BIPAP) or IV in each group [Time Frame: 30 days] ○ To assess the potential for prone position to reduce the requirement for escalation of respiratory support

NCT05178212 Characteristics and Outcomes of Patients With COVID-19 Related Acute Respiratory Failure Treated With High-flow Nasal Oxygen and Awake-prone Position Recruiting Estimated Study Completion Date December 31, 2022	Prone Position	Not described	• Older than 17 years, admitted to the ICU • Confirmed diagnosis of COVID-19 (real-time PCR) • Receiving HFNO for at least 4 hours. Patients received HFNO when any of the following criteria were present: peripheral oxygen saturation (SpO2) < 92% with oxygen > 4 liters/minute; increased work of breathing with use of accessory respiratory muscles, and a respiratory rate > 30/min; PaO2/FiO2ratio < 200 mmHg	Primary outcome • ET intubation Secondary outcome • In-hospital mortality
NCT04402879 A Prospective Randomized Trial of Prone Positioning Versus Usual Care for Patients With Do-not-intubate Goals of Care and Hypoxemic Respiratory Failure During the Coronavirus SARS-CoV-2 (COVID-19) Pandemic Recruiting Status unknown	The intervention for this study is PP. Patients at participating sites allocated to the intervention arm of the study will be prompted by ward nurses and respiratory therapists to assume and maintain a prone position for varying durations, four times per day	The control group will consist of standard medical care with no instructions or prompts to change positioning to staff or patients	• 18 Years and older • Hospitalized patients with probable COVID-19. Probable is defined as Influenza like illness (ILI) symptoms OR confirmed COVID-19 exposure AND COVID-19 testing performed. ILI is defined as any one of the following symptoms including: fever, new or worsening cough, coryza, new or worsening dyspnea, or sore throat. • Goals of care are do-not-intubate (R3 or M1/M2 in Alberta). • Need for oxygen ≥2 L to maintain SpO2 ≥92%. If the patient is on long-term oxygen, the O2 requirements must be ≥2 L above their baseline. • Patient can be positioned to and from prone to supine with minimal assistance (maximum one person assistance)	Primary outcome • Hospital mortality or discharge to hospice [Time Frame: 60 days] ○ In-hospital mortality or discharge to hospice at Day 60 Secondary Outcome • Adverse Events and Serious Adverse Events ○ Results in death (primary outcome) ○ Is life threatening ○ Results in persistent of significant disability or incapacity ○ Requires in in-patient hospitalisation or prolongation of Hospitalisation • Change in SpO2 [Time Frame: 60 days] ○ Change in SpO2 during each PP session (SpO2 in prone position - SpO2 prior to prone positioning). Clinicians will be asked to record this change for the first proning session per shift (for 12 hour

				shifts this will result in 2 proning sessions being documented per 24 hour period, and for 8 hour shifts this will result in 3 proning sessions being documented per 24 hour period).
				• Hospital free days [Time Frame: 60 days]
				  ○ Number of hospital free days in the 60 days after enrolment.
				• Admission to ICU [Time Frame: 60 days]
				  ○ Admission to the Intensive Care Unit.
				• Intubation and mechanical ventilation [Time Frame: 60 days]
				  ○ Patient is intubated and requires mechanical ventilation.
				• Initiation of non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO). [Time Frame: 60 days]
				  ○ Patient requires non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO).
				• Oxygen-free days [Time Frame: 60 days]
				  ○ The number of oxygen-free days at Day 60 (censored at discharge).
				• In-hospital death (time) [Time Frame: 60 days]
				  ○ Time from admission to all-cause in-hospital death.
				• Death at 90 days [Time Frame: 90 days]

				○ Death at 90 days.
NCT04408222 Awake Proning in Patients With COVID-19-Induced Acute Hypoxemic Respiratory Failure Completed No results, not yet published	COVID-19 patients with hypoxemic respiratory failure with awake prone positioning, as tolerated, up to 24 hours daily.	Not described	• 18 Years and older • Laboratory confirmed COVID-19 infection with severe hypoxemic respiratory failure defined as respiratory rate ≥30 breaths/min and oxyhemoglobin saturation (SpO2) ≤93% while receiving supplemental oxygen 6 L/min via nasal cannula and 15 L/min via non-rebreather facemask	Primary outcome • Change in SpO2 Secondary outcome • Mean Risk Difference in Intubation Rates
NCT05130541 Proning Early in Awake COVID-19 Hypoxic Respiratory Failure (PREACHR) Study Completed No results, not yet published	Proning, rotating 90 degrees on long axis every 30 minutes - 2 hours	Usual Care	• Age >18 • Presenting to the ED with symptoms suggestive of COVID-19 • Assessed by ED attending physician to not require emergent intubation • Normal mental status and ability to communicate symptoms/distress • Able to follow instructions independently	Primary outcome • All-cause mortality [Time Frame: Within 30 days of discharge from hospital] • Need for intubation [Time Frame: At any time during first hospitalization for hypoxia from COVID-19 up to 2 months] Secondary outcome • Number of repeat visits for same complaint
NCT05150847 The Effect of Prone Positioning on Oxygenation and Respiratory Mechanics in Patients With COVID-19 Pneumonia Recruiting Results submitted but not yet posted Not yet published	Prone positioning will be performed over periods of 16 hours when PaO2/FiO2 was persistently lower than 150 mm Hg	None	• 18 Years and older • Adult patients with laboratory-confirmed COVID-19 admitted to the ICU • The patients receive invasive mechanical ventilation and meet the criteria for ARDS	Primary outcome • Oxygenation Secondary outcome • Static compliance • Recruitability
NCT05405335 Effect of Prone Positioning on the Severity of COVID-19 Pneumonia and Acute Respiratory Distress Syndrome. A Randomized Clinical Trial Completed No results, not yet published	Intermittent prone positioning for a total of eight hours per day for seven days. Each cycle of prone positioning should not be less than 30 minutes and note more than 3 hours at one time.	Treatment as per institutional protocols- the protocols does not involve prone positioning of the patients	• Child and adult • Confirmed covid pneumonia/ acute respiratory distress syndrome cases	Primary Outcome • percentage of patients dying COVID-19 pneumonia/ ARDS in both groups Secondary outcome • Respiratory physiology- mean PaO2 and Mean respiratory rate of both groups at first, seventh and fourteenth day of admission
IRCT20210724051970N1 Evaluation of prone positioning in improving the oxygenation of	Covid-19 patients referred to Ali Ibn Abitaleb Hospital in Rafsanjan, with a change in posture, lie on the	particular intervention will not be done	• 18-70 years of age • confirmed diagnosis of COVID-19	Primary outcome • Improve oxygenation

patients with non-intubated & awake with lung involvement due to COVID-19 pneumonia Recruiting	abdomen at least two to three times a day (morning, noon and night, at least one hour after a meal for three consecutive days		• requiring non-invasive supplemental oxygen • awake and able to do prone positioning	
RBR-2k66ft Randomized, open, controlled study to evaluate early prone position in awake patients on spontaneous ventilation with mild to moderate respiratory distress syndrome secondary to COVID-19 - APC Trial : APC Trial - Awake Proning on COVID-19 Trial Not yet recruiting	Prone position in awake patients for 3h up to 3 times a day. Positioning will be performed with the assistance and under the supervision of a physical therapist. Putting the patient in a prone position means placing him/her in a prone position for up to 3 hours.	No change in position	Patients with COVID-19 confirmed by RT-PCR or strong suspicion, defined as both typical clinical picture and typical chest CT scan. Presence of bilateral infiltrate on chest tomography and one of the following two: Patient with SpO2 below 94% in room air or Need for O2 by nasal catheter above 4L per min to maintain SpO2 above 94%	Primary outcome • intubation rate in the group undergoing prone positioning in 14 days • Mortality Secondary outcome • ROX index • Time of intubation • Factors of orotracheal intubation
CTRI/2021/05/033869 Can awake prone positioning strategies spark a revolution in management of oxygen dependent Covid-19 patients Open to recruitment	awake prone positioning method employed in oxygen dependent COVID-19 patients for a maximum of 3 hrs in the morning and 3 hrs maximum in the evening , if the patient is not comfortable for aduration of 3 hrs then as much time as possible and comfortable to the patient will be suggested and recorded accordingly	not applicable as it is a single arm trial	• Onset within 1 week of covid 19 • new onset or worsening respiratory symptoms • hypoxia (Spo2 < 94% on RA) • Diagnosed covid with RTPCR nasal / nasopharyngeal / oropharyngeal swab	Primary outcome • Duration of weaning from oxygen support Secondary outcome • assess the tolerance to awake prone positioning therapy • Occurrence of any adverse events • To assess / evaluate the proportion of patients requiring intubation and mortality rate
IRCT20120215009014N425 Effect of prone and orthopnea positions versus supine position on comfort, dyspnea and arterial blood oxygen saturation in patients with Covid-19: a randomized clinical trial Recruiting	Laying the patient in the prone position for 30 minutes Laying the patient in the orthopedic position for 30 minutes	Laying the patient in the supine position for 30 minutes	Age 18 to 60 years Covid-19 infection Conscious Mild to moderate arterial oxygen saturation (80% to 90%)	Primary outcome • Arterial blood oxygen • Feeling comfortable • Dyspnea
NCT05008380 Open-label, Controlled, Randomized Clinical Trial on the Efficacy of Early Prone-positioning in Patients With Mild Pneumonia Due to SARS-CoV-2 Completed	Prone-positioning cycles as the following: 3-6 hours of prone-positioning twice a day.	Standard of care	• 18 years • positive PCR for Sars-Cov-2 Rna on any respiratory samples within 7 days from enrollment • imaging positive for pulmonary involvement or clinical evidence of respiratory involvement (new onset of hypoxemia with	Primary outcome • death, start of high flow oxygen therapy, CPAP, mechanical ventilation, P/F <200 • Secondary outcome • time of recovery [Time Frame: 0-28 days]

No results, not yet published			02 <80mmHg or SpO2 < 94% in air or need for oxygen therapy in oreder to maintained SpO2 > 93%. • need of hospitalization	• time of weaning from oxygen [Time Frame: 0-28 days] • variation of the clinical condition [Time Frame: 0-28 days] • mortality [Time Frame: 0-28 days] • number of adverse event [Time Frame: 0-28 days] • number and duration of prone positioning cycles [Time Frame: 0-28 days]
NCT04424797 Prone Positioning on Admission for Hospitalized COVID-19 Pneumonia Protocol Recruiting Last update April 25, 2022	The Prone Experimental Group will position patient in approximately 15-degree reverse Trendelenburg and prone using pillows for comfort. The participant will be asked to rotate to prone positioning every 2 hours while awake and encourage to sleep prone overnight as possible with a goal of 10-12 hours daily.	The Standard Supine Control Group will utilize standard oxygen (O2) device in supine position at approximately 30-60 degrees to target peripheral capillary oxygen saturation (SpO2) >90% and the participant or nurse will document time in non-supine position.	• Patients >18 years old and above • Patients admitted to the hospital floor with primary diagnosis of confirmed COVID-19 pneumonia and respiratory failure requiring greater than or equal to 2 Liters(L) Nasal Cannula (NC) to maintain SpO2>90% • Ability to independently change positions in bed • Able to tolerate prone positioning	Primary Outcome • Incidence of intubation Secondary Outcome • Maximum oxygen o Measure of maximum oxygen requirements • Length of Stay o Measured in days of hospitalization • Ventilator-free days o Measured in days not on a ventilator • Treatment failure of prone positioning due to worsening SpO2 status while prone o Whether or not the participant met treatment failure descriptions • Mortality Whether or not the participant died while hospitalized
ACTRN12620000740998 A Randomised Controlled Trial of Early Prone Positioning to Improve Oxygenation in Non-Intubated Adults Admitted to Intensive Care with COVID-19 Estimated completion date: no data Not yet recruiting	lying prone for up to 12 hours a day in a prone position no minimum time been period of proning and no restriction on participants positioning outside of the 'intervention' periods. If this duration is not tolerated for an individual patient, staff will trial a variety of comfort measures		• Adults, over the age of 18 • COVID-19 Diagnosis Confirmed – either by PCR or as per any unit policy changes that may be applied during the enrolment period • Admitted to Intensive Care • Any severity of disease (As defined by National COVID 19 Clinical Evidence Taskforce "Australian Guidelines for the clinical care of people with COVID-19" assessable at https://covid19evidence.net.au).	Primary Outcome • Oxygen Saturations in the blood o Difference in average gradient of the PaO2:FiO2 (PF ratio) in the prone and control groups over the trial period (72 hours). o Calculated by pulse oximetry recordings and oxygen delivery method Secondary Outcome(s)

	The intervention will continue for 72 hours (a maximum of 36 hours prone). If a participant is unable to tolerate a 12h/day prone position as above Step 1 - Trial 3 x 3hr sessions/9 hours a day Step 2 - If needing longer breaks not prone - Trial 2 x 4hr sessions/8 hours a day Step 3 - Trial 2 x 3hr sessions/6 hours a day Step 4 - 3 x 2 hour sessions/6 hours a day Step 5 - 2 x 2 hours sessions/4 hours a day Step 6 - Abandon proning, document in EMR why proning was abandoned		• For patients with severe disease, the treating intensivist must be consulted prior to randomisation (see exclusion criterion #2) • Willing and able to tolerate prone positioning (A pre-enrollment screening test to ensure they can tolerate the position and can maneuver into & out of the prone position with minimal assistance from their usual care staff only.) • Prior informed consent has been obtained from the patient	• Median number of hours spent prone per day during trial period in the intervention group o Number of adverse events in the prone group compared to control, as collected by staff survey, and any other incidence of adverse events brought to the attention of investigators.
CTRI/2020/06/025804 Effectiveness of awake self proning strategy in COVID-19: An open-labelled randomized controlled trial Not yet recruiting	:The COVID-19 patient will be asked to be in prone position and its effect on improvement of their blood oxygenation will be seen using a finger saturation probe.	The COVID-19 patient will be lying supine or sitting and its effect on improvement of blood oxygenation will be seen using a finger saturation probe	• >18 years of age • Diagnosed as COVID-19 positive by RT- PCR • Oxygen saturation < 94% as assessed by pulse oximeter or requiring oxygen support • Can communicate and self-prone	Primary outcomes (Phase 1 study): • Oxygen saturation measured using by pulse oximeter at 0, 10, 20, 30, 40 minutes Primary Outcomes (Phase 2 study): • Need for endotracheal intubation and mechanical ventilation measured at discharge or death • Mortality up to 30 days after enrolment • Oxygen saturation measured using by pulse oximeter at 0, 10, 20, 30, 40 minutes Primary Outcomes (Phase 2 study): • Need for endotracheal intubation and mechanical ventilation measured at discharge or death • Mortality up to 30 days after enrolment

				Secondary Outcome (For phase 2 study): • Time to endotracheal intubation/ventilation measured using hospital record at discharge. • Duration of requirement of oxygen support measured using clinical proforma at patient discharge Duration of hospital stay measured using hospital record at discharge
NCT04547283 Awake-Prone Positioning Strategy for Hypoxic Patients With COVID-19: A Pilot Randomized Controlled Trial COMPLETED Not yet published No results	Clinical team guidance on prone positioning of patients	No clinical team recommendation, patients will remain in their natural choice of position	18 Years old and above hospitalized patients with positive COVID testing during hospitalization or 7 days prior OR Hospitalized with suspected COVID pneumonia room air oxygen saturation <93% or oxygen requirement > or equal to 3 Liters per minute	Primary Outcome Measures: • Average S/F ratio • Average oxygen saturation to fraction of inspired oxygen ratio • Time spent with S/F ratio < 315 • Time spent with oxygenation saturation to fraction of inspired oxygen ratio less than 315 Secondary Outcome Measures • Highest oxygen support • Highest level of supplemental oxygen required • Number of patients requiring ICU admission during study • Number of patients requiring ICU admission during study period • Number of patients requiring ICU admission during hospitalization • Number of patients requiring ICU admission during hospitalization • Number of patients experiencing who die prior to discharge • Number of patients who die prior to hospital discharge • Number of patients requiring intubation • Number of patients requiring intubation • Hospital length of stay Number of days from hospital admission to discharge

NCT04359797 Pragmatic Trial Exploring Impact of Patient Positioning in the Management of Patients Infected With COVID-19: Supine vs. Prone COMPLETED Not yet published	prone position for as much time as is tolerable during hospitalization.	remain in their natural choice of position, which is anticipated to favor a supine, semi-recumbent position.	18 years old and above patients admitted to VUMC who test positive for COVID-19 and require supplemental oxygen, but are not yet mechanically ventilated.	Primary Outcome Measures: • Modified WHO Ordinal Scale • The highest level of support on the 5th day after enrollment according to the following scale adjusted for patient status at enrollment according to the same scale and ranked by mean FIO2 within each category, as appropriate. • Death • ECMO • Mechanical ventilation (ranked by mean FIO2) • Non-invasive ventilation such as BiPAP (ranked by mean FIO2) • High flow nasal cannula, • Standard nasal cannula (titrated by L/min up to 15 L/min) or face mask (ranked by mean FIO2) • Room air Secondary Outcome Measures • FIO2
CTRI/2020/07/026532 Awake Prone Position Versus Repeated Position Change in Moderate to Severe COVID-19 patients: A Pilot Randomized Controlled Trial Not yet recruiting	Repeated Position Change: One hour right lateral, two hours prone and one hour left lateral	Awake Prone Positioning for 4h in patients presented with shortness of breath	Adult patients (aged between 18 and 75y) with laboratory confirmed diagnosis of COVID-19 pneumonia,	Primary Outcome • repeated positioning with 4h continuous prone positioning in terms of self-reported dyspnea in a 10- point visual analogue scale Secondary Outcome • oxygenation status (room air oxyhemoglobin saturation or PaO2/FiO2 ratio in arterial blood gas) • requirement of rescue therapy (high flow nasal oxygen) in both the groups. • hemodynamic variables in both the groups. • requirement of mechanical ventilation within 24h in both the groups. change in respiratory rate in both the groups.

NCT04363463 Impact of Prone Position in Patients Under Spontaneous Breathing on Intubation or Non-invasive Ventilation or Death Incidence During COVID-19 Acute Respiratory Distress Recruiting Estimated Completion Date: August 28 2022	Two sessions minimum of prone position over the day. With a total objective of at least 2h30 of cumulated duration over the day. The objective is to spend as much time as possible in prone position if the patient tolerates it well.	semi-seated in bed or seated in a chair during the day. The prone position is not allowed during the day (it is allowed at night if it is the natural sleeping position).	Patients aged from 18 to 85 years old with COVID-19 documentation Undergoing oxygen therapy (nasal cannula, medium or high concentration mask or high flow nasal oxygen therapy) Able to move to PP by him/herself or with minimal assistance Written consent Hospitalized in COVID medical department for less than 72 hours	Primary Outcome Measures: • Percentage of patients who will have endotracheal intubation or non-invasive ventilation at two pressure levels and/or die, in each of the 2 randomization groups. • Endotracheal intubation or non-invasive ventilation (NIV) with two pressure levels • And/or death Secondary Outcome Measures: • Duration in days for the change of 2 points on the WHO ordinal scale • Rate (%) of intubation and invasive ventilation in the 2 randomization groups. • Rate (%) of non-invasive ventilation at two pressure levels in the 2 randomization groups • Duration of oxygen therapy in the 2 randomization groups. • Duration of hospitalization in the 2 randomization groups. • Hospital mortality and mortality at D28 in the 2 randomization groups • Rate (%) of need for transfer to intensive care unit • Rate (%) of use of non-invasive ventilation at two pressure levels, intubation throughout the entire stay when the stay is longer than 28 days. Compare the impact of the use of non-invasive ventilation and intubation on the entire hospital stay when the hospital stay is longer than 28 days between the two groups.
NCT04366856 PROne Positioning in coVID-19 Oxygeno-dependent Patients in Spontaneous Ventilation (PROVID Study)	the interventional group will be suggested to spend at least 6 hours a day in prone position	the control group will get no instruction regarding positioning	Laboratory-confirmed SARS-CoV-2 infection as determined by PCR and/or CT scan showing typical radiological findings (ground glass abnormalities)	Primary Outcome Measures: • Proportion of patients who meet one or both following criteria: need for intubation (for mechanical ventilation), occurrence of death during hospital stay.

Completed No results, not yet published			Need for O2 3L/min to get an SpO2 higher or equal to 95%. Patient able to understand and to get in prone position themself No therapeutic limitation	Secondary Outcome Measures: • Proportion of patients admitted to ICU (for patients included out of ICU) • Days alive and free from non-invasive ventilation (NIV) or high flow nasal canula oxygen delivery (HFNC) (for those neither under NIV or HFNC at the time of study inclusion) • Days alive and out of ICU Maximum oxygenotherapy rate during hospital stay
NCT04667286 Awake Pronation for Covid-19 Treatment Recruiting	Oxygen via a Venturi mask in order to keep an oxygen saturation between 92 and 96% plus PP for a minimum of 10 hrs a day	Oxygen via a Venturi mask in order to keep an oxygen saturation between 92 and 96%	confirmed COVID-19 infection using PCR Acute Respiratory Failure (200 <PaO2/FiO2 <300) and respiratory rate < 30 atti/min O2 therapy initiated <72 hrs informed consent	Primary Outcome Measures: • number of day free of ventilatory support Secondary Outcome Measures: • changes in respiratory pattern • daily changes in the ratio SaO2/FiO2 • dyspnea • comfort during PP Other Outcome Measures: number of hours on PP
NCT04589936 Prone Position to Improve Oxygenation in COVID-19 Patients Outside Critical Care (PRONE-COVID) Recruiting Status unknown	Patient will first lay supine for a given time period, followed by lateral position on either side, then prone position, lastly return to supine position. Participants are anticipated to stay in prone position for a minimum of 30min to a maximum of 2 hours depending on tolerability.	Patient will first lay supine for a given time period, followed by lateral position on either side, then prone position, lastly return to supine position. Participants are anticipated to stay in prone position for a minimum of 30min to a maximum of 2 hours depending on tolerability. Participants will be guided in how to independently position themselves and rotate through the cycle of positions.	Have confirmed or suspected COVID-19 or non-COVID pneumonia (confirmed with radiological changes) FiO2 ≥24% or requiring basic respiratory support (supplementary oxygen via face mask, nasal cannula, venturi, non-rebreathe bag) to achieve clinical target SpO2 (e.g. SpO2 92-96%), ensuring patient is on appropriately titrated oxygen to be within this range. Be able to provide informed consent Communicate and cooperate with the procedure Rotate and adjust position independently No anticipated airway issues	Primary Outcome Measures • Peripheral Oxygen saturation (FiO2) Secondary Outcome Measures: • PaO2 :FiO2 ratio calculated from formulae • Respiratory rate measured with Masimo device • Heart rate measured with Masimo device • Blood pressure measured with Masimo device • Patient reported severity of breathlessness on a continuous linear scale of 0 to 10cm (10cm being the most severe) • Patient tolerability of prone position on a continuous linear scale of 0 to 10cm (10cm being the most unacceptable)

				• Investigator experience of delivering prone positioning To assess patient's peripheral oxygen saturation
NCT04427969 Early Prone Position on Coronavirus Disease 2019 Pneumonia (Prone Position)	Behavioral: prone position to lay in prone position at least 12 hour in a day at ICU	patient who only get conventional oxygen therapy as respiratory supply	Patients who developed acute respiratory failure due to coronavirus disease 2019 pneumonia received conventional oxygen therapy with reservoir mask oxygen at the stage of admission to the intensive care unit older than 18 years old	Primary Outcome Measure: • intensive care unit stay • short term mortality Secondary Outcome Measure • blood gases
NCT04344587 Awake Prone Position for Early Hypoxemia in COVID-19 (APPEX-19) Completed No results, not yet published	Self-proning A recommendation to "prone" while lying in bed (4 times for 1-2 hours each during the day and at night every 24 hours). A reminder to keep track of the time spent in 1) prone position, 2) lying flat on back, 3) lying on side, 4) sitting up, and 5) standing or walking	Usual Care	Assigned to or admitted to a COVID-19 ward team at a participating site (these teams only admit patients who are under investigation for COVID-19 or who have confirmed COVID-19 infection) via the emergency department (ED) within the last 24 hours Have access to their own functioning smartphone in the hospital room English or Spanish-speaking Ability to read simple instructions and answer simple written questions	• Change in respiratory status • Length of time in each position • Reports of dyspnea, discomfort • Length of hospital stay • Invasive mechanical ventilation • ARDS diagnosis • Loss of IV access as a consequence of turning Hospital mortality
KCT0005258 The effect of prone positioning on non-intubated patients with postoperative acute respiratory failure Recruiting	Prone positioning at least 12 hours in prone positioning group position change q 2hr(within 45 degree of Lt or Rt decubitus position change). dexmedetomidine continuous infusion if RASS > +1, target : light sedation	supine positioning and keep going management of respiratory failure	adult patients (18 years and older) with acute respiratory failure - 30 minutes after applying High flow nasal cannula(FiO2 0.5, flow 50L) - > PaO_2< 150㎜Hg, $PaCO_2$< 50㎜Hg	• Intubation rate within 7 days • Lung ultrasound reaeration score • PaO_2/FiO_2 ratio • Mechanical ventilation (MV) duration • ventilator-free days • tracheostomy rate • ICU, 30 days, 90 days mortality • Complication related to prone positioning 1. sedative

Table 8. Study Characteristics of Ongoing studies for side lying (n=2)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
Immediate effect of prone and side lying position on oxygen saturation in patients with COVID 19- A Randomised Controlled Trial Main ID: CTRI/2021/03/031939 NOT YET RECRUITING	Prone position after doing Diaphragmatic breathing exercises, thoracic expansion exercise Lateral Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise patients will adopt the position (supine) after breathing exercises for 1 hour. Frequency - 1 session per day The patient's face could be placed on either side and patients were allowed to adjust their position for comfort.	Supine Position after doing Diaphragmatic breathing exercises, thoracic expansion exercise and patients will adopt the position (supine) after breathing exercises for 1 hour. Frequency - 1 session per day	Patients who required additional oxygen supplementation (HFNC) Age group of >30 years both male and female	Spo2Timepoint: 1 hour
Awake Prone Position Versus Repeated Position Change in Moderate to Severe COVID-19 patients: A Pilot Randomized Controlled Trial Main ID: CTRI/2020/07/026532 NOT YET RECRUITING	Repeated Position Change: One hour right lateral, two hours prone and one hour left lateral	Awake Prone Positioning: Awake Prone Positioning for 4h in patients presented with shortness of breath	Adult patients (aged between 18 and 75y) with laboratory confirmed diagnosis of COVID-19 pneumonia, self-reported symptom of shortness of breath patients,	Primary Outcome • compare repeated positioning with 4h continuous prone positioning in terms of self-reported dyspnea in a 10- point visual analogue scale Time point: 4hour since randomization Secondary Outcome • oxygenation status (room air oxyhemoglobin saturation or PaO2/FiO2 ratio in arterial blood gas) • requirement of rescue therapy (high flow nasal oxygen) in both the groups. • hemodynamic variables in both the groups. • requirement of mechanical ventilation within 24h in both the groups. • the change in respiratory rate in both the groups. • Timepoint: 4 hour since randomization • Secondary ID(s)

Table 9. Study Characteristics of Ongoing studies for Critical COVID and Positioning (n=7)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
NCT04359407 The Effect of Prone Positioning on Lung Aeration and Ventilation-perfusion Matching in Mechanically Ventilated Patients With Coronavirus Disease Related Acute Respiratory Distress Syndrome Completed No results, not yet published	Change the positioning of the COVID patients who are intubated and mechanically ventilated from supine to prone	Not described	• 18 Years to 80 Years • Mechanically ventilated • Fit the Berlin Definition for moderate or severe acute respiratory distress syndrome (arterial oxygen partial pressure over inspiratory fraction of oxygen less than 200 mmHg) • Infection with coronavirus confirmed • Scheduled to undergo prone positioning	Primary outcome • Tidal electrical Impedance Secondary outcome • Intrapulmonary shunt • Volumetric capnography
NCT05092737 Physiological Response to Prone Position in Intubated Adults With COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): a Retrospective Study Completed No results, Not yet published	Prone position during invasive mechanical ventilation	Not described	• 18 Years and older • COVID-19 associated moderate to severe ARDS • Invasive mechanical ventilation • Prone positioning • admitted to ICU	Primary outcome • PaO2/FiO2 Secondary outcome • Alveolo-arterial oxygen gradient • Ventilatory Ratio • Mortality or Extracorporeal membrane oxygenation (ECMO) support
NCT04692129 Short-term Effects of Prone Positioning on Tissue Oxygen Saturation, Measured by Near-infrared Spectroscopy, in COVID-19 Patients With Acute Respiratory Distress Syndrome Recruiting Estimated Study Completion Date: October 31, 2022	Prone positioning		• COVID-19 patients admitted in the ICU receiving invasive mechanical ventilation and requiring prone positioning for severe hypoxemia management, as decided by the medical team • 18 Years and older	Primary outcome • Change in tissue oxygenation Secondary outcome • Change in local hemoglobin content
NCT05209477 Effects of Body Position and Recruiting Maneuver on Lung Aeration Assessed Through Ultrasound in Patients Intubated for Acute Respiratory Failure Related to Novel Coronavirus 19 Disease	In patients undergoing invasive mechanical ventilation with an arterial oxygen tension on inspired oxygen fraction ratio < 200 mmHg requiring recruitment maneuver and prone positioning as a rescue therapy, lung aeration will be evaluated at: • baseline, in supine position under protective ventilation • after two minute of recruitment maneuver in pressure controlled ventilation		• 18 Years and older • Patients intubated for COVID-19 hARF	Primary outcome • lung ultrasound score • lung ultrasound score recruitment • lung ultrasound score prone positioning

Recruiting	• at 1 hour following prone positioning application			
NCT05150847 The Effect of Prone Positioning on Oxygenation and Respiratory Mechanics in Patients With COVID-19 Pneumonia Recruiting Results submitted but not posted Not yet published	Prone Positioning Patients will be ventilated in volume-controlled mode with Vt at 6 ml/kg of predicted body weight. Prone positioning will be performed over periods of 16 hours when PaO2/FiO2 was persistently lower than 150 mm Hg. Flow, volume, and airway pressure will be measured by ventilators. Measurements of oxygenation and respiratory mechanics were performed at 5 and 15 cmH20 PEEP levels and will be repeated every season as before first period of prone positioning, before supine positioning, and again before second period of prone positioning. Total PEEP and plateau pressure will be measured by a short end-expiratory and an end-inspiratory occlusion respectively. Complete airway closure will be assessed by performing a low-flow (4 L/min) inflation(PV tool). The potential for lung recruitment will be assessed by means of the R/I ratio		• 18 Years and older • Adult patients with laboratory-confirmed COVID-19 admitted to the ICU • patients receive invasive mechanical ventilation and meet the criteria for ARDS	Primary outcome • Oxygenation Secondary outcome Secondary outcome • Static compliance • Recruitability
NCT04818164 Prone Position Improves End-Expiratory Lung Volumes in COVID-19 Associated Acute Respiratory Distress Syndrome: An Observational Study Completed No results, not yet published	prone position for at least 16 hours	Not described	• 18 Years and older • Patients were considered eligible if they met the Berlin definition criteria for ARDS and intubated due to increased work of breathing and/or worsening hypoxemia. All patients had a positive Covid-19 real time Polymerase Chain Reaction test	Primary outcome • Partial Pressure of Oxygen/ Fraction of Inspired Oxygen Secondary outcome • End Expiratory Lung Volume
NCT05012267 OptiMal pronE Position LEngTh in Patients With acuTE Respiratory Distress Syndrome Due to COVID-19 (OMELLETTE study) Completed No results yet, not yet published	Anytime from 16 hours when PaO2/FiO2 ≥ 150 mmHg with a FiO2 < 60%	48 hours of PP	• 18 Years and older • Patient above 18 year-old. • Diagnosis of severe ARDS due to COVID-19 under invasive mechanical ventilation, • Meet criteria for PP: PaO2/FiO2 < 150 millimeters of mercury column (mmHg), PEEP ≥ 5 Centimeters of Water (cmH2O), FiO2 ≥ 60	Primary outcome • Ventilator-free days at 28 days • Ventilator-free days at 60 days Secondary outcome • Survival • ICU and Hospital stay • Evolution of respiratory parameters • PP complications Others • Enteral nutrition administration