Clinical Outcomes of Routine Awake Prone Positioning in COVID-19 Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Received March 15, 2022; Accepted August 2, 2022.

Key words: COVID-19 – Awake prone positioning – Prone positioning – Proning – Meta-analysis

Abstract: Before coronavirus disease 2019 (COVID-19) emerged, proning had been demonstrated to improve oxygenation in those with acute hypoxic respiratory failure and be performed in non-intensive care settings. This benefit was further exemplified by the COVID-19 pandemic, leading to awake prone positioning (APP). We assessed the efficacy of routine APP versus standard care in preventing death and invasive mechanical ventilation (IMV) in non-intubated hypoxic COVID-19 patients. PubMed, Cochrane Library, Scopus, and medRxiv databases were used from January 1st, 2020, to January 15th, 2022, to identify randomized controlled trials (RCTs). Routine APP group were encouraged to be self-prone, whereas the standard care group received care according to local clinical practice and allowed APP crossover as rescue therapy. We included eight COVID-19 RCTs assessing 809 APP vs. 822 standard care patients. APP group had less IMV requirement (26.5% vs. 30.9%; OR – odds ratio 0.77; P=0.03) than the standard care group, with subgroup analysis showing greater benefit (32.5% vs. 39.1%; OR 0.75; P=0.02) for those mainly requiring oxygen support of non-invasive mechanical ventilation (NIMV) and high-flow nasal cannula (HFNC). The time to IMV initiation was similar (mean 8.3 vs. 10.0 days; P=0.66) for patients requiring NIMV and HFNC. Patients mainly

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https://doi.org/10.14712/23362936.2022.14

receiving supplemental oxygen and non-rebreather masks had improved oxygenation parameters, although not statistically significant. Other outcomes involving all-cause hospital mortality, hospital and ICU (intensive care unit) length of stay, and adverse events were comparable. APP appeared to be an important modality for reducing IMV requirements, especially in those requiring NIMV and HFNC.

Introduction

Before coronavirus disease 2019 (COVID-19), prone positioning was widely adopted as a standard practice due to improvements in oxygenation and reduction in mortality among invasive mechanical ventilation (IMV) patients with moderate to severe acute respiratory distress syndrome (ARDS). These benefits continued to be exemplified when combined with neuromuscular blockade and low-tidal volume ventilation (Guérin et al., 2013; Munshi et al., 2017). Similarly, among awake (non-ventilated) ARDS patients, prone positioning was shown to avert IMV requirements and was particularly useful in settings where intensive care resources were scarce (Ding et al., 2020). During the COVID-19 pandemic, many critically ill COVID-19 patients would develop hypoxic respiratory failure, resulting in IMV (Grasselli et al., 2020; COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators, 2021). The significant morbidity and mortality observed among critically ill COVID-19 patients requiring non-invasive mechanical ventilation (NIMV), high-flow nasal cannula (HFNC), and IMV lead to the implementation of prone positioning protocols across various medical institutions (Bentley et al., 2020; Ng et al., 2020; Venus et al., 2020; Touchon et al., 2021). Prone positioning has been demonstrated to improve oxygenation parameters involving partial pressure of arterial oxygen (PaO_2), partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio, and peripheral blood oxygen saturation to FiO_2 (SpO_2/FiO_2) ratio in critically ill COVID-19 patients requiring IMV (Sud et al., 2010; Beitler et al., 2014; Lee et al., 2014; Bloomfield et al., 2015; Park et al., 2015; Munshi et al., 2017; Shelhamer et al., 2021). The mechanisms by which prone positioning improves oxygenation in non-ventilated COVID-19 patients were thought to be similar to those requiring IMV. Our meta-analysis aimed to assess the clinical outcomes of routine awake prone positioning (APP) versus standard care in COVID-19 patients by analysing the current evidence from randomized controlled trials (RCTs).

Methods

This systematic review was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical approval and informed consent were not required for this study as it was a systematic review of previously published studies. The protocol for this review was registered and published in the International Prospective Register of Systematic Reviews (PROSPERO) under reference number CRD42022304024.

Search criteria and selection

A literature search was performed through PubMed, Cochrane Library, Scopus, and medRxiv databases for articles published from January 1st, 2020, to January 15th, 2022, using the keywords, title/abstracts, and Medical Subjects Headings (MeSH) terms: ("coronavirus disease 2019" OR "coronavirus 2019" OR "COVID-19") AND ("prone position" OR "awake prone positioning" OR "awake prone"). Moreover, to detect additional studies, any cited references were reviewed to identify relevant literature that met our inclusion criteria.

Inclusion criteria

We included studies: 1) containing non-intubated hospitalized COVID-19 adults (age > 18 years) patients with acute hypoxic respiratory failure requiring oxygen therapy; 2) RCTs containing comparative data describing the clinical outcomes of patients receiving routine APP versus standard care; 3) suspected or proven COVID-19 pneumonia (infiltrate on chest imaging) in which the diagnosis of COVID-19 was made by reverse transcriptase-polymerase chain reaction (RT-PCR) in all cases from respiratory tract that included nasopharyngeal swabs or lower respiratory tract specimens (sputum, endotracheal aspirate – ETA, and bronchoalveolar lavage – BAL); and 4) published in peer-reviewed and non-peer-reviewed journals. Patients randomized in the routine APP group were encouraged to be self-prone for as long as possible at the beginning of the trial before returning to the supine position as necessary. In contrast, patients in the standard care group received care according to clinical practice at respective hospitals and were allowed to crossover to prone positioning (neither encouraged nor disallowed) as a form of rescue therapy for acute hypoxic respiratory failure at the treating clinician's discretion.

Exclusion criteria

We excluded: 1) systematic reviews, literature reviews, editorials, conference abstracts, opinion articles, meta-analyses, observational studies, case reports, or series; 2) non-adult (< 18 years of age), non-consentable, and pregnant patients; 3) patients with contraindications for awake proning or require the immediate need for IMV before randomization; and 4) studies published in languages other than English if no translated version of the manuscript was available. Contraindications for awake proning were recent abdominal or thoracic surgery/trauma, facial/pelvic/spinal fractures, pneumothorax, brain injury without intracranial pressure monitoring, Glasgow Coma Scale (GCS) less than 15, and life-threatening cardiac arrhythmias.

Data collection and synthesis

Two researchers (W.H.C. and B.K.S.) independently screened the titles and abstracts, and reviewed the full texts of articles to identify RCTs that compare the clinical outcomes of COVID-19 patients receiving routine APP versus standard care. Any disagreements were resolved by discussion with a third researcher (C.K.T.).

The extracted data from full texts of included studies was added into a standardized Excel (Microsoft Corporation) form. The following information was summarized in Tables 1 and 2 for each group of patients receiving routine APP and standard care and reported as means and standard deviations (SDs) for continuous variables. When continuous variables were described by the median and interquartile range (IQR) instead of mean and SD, the following formula was used for approximations: mean = (median + IQR)/3 and SD = IQR/1.35 (Wan et al., 2014). For studies that reported PaO_2/FiO_2 ratio without a corresponding SpO_2/FiO_2, we derived a conversion based on $SpO_2/FiO_2 = 64 + 0.84 \times (PaO_2/FiO_2)$ (Rice et al., 2007). Mortality was defined as all-cause in-hospital mortality. If in-hospital mortality was not described among the included studies, but ICU (intensive care unit) mortality was, we accepted the ICU mortality rate as the most suitable replacement. We used the lengthiest interval of mortality to determine the in-hospital mortality rate for studies that comprehensively described mortality at different intervals of 28-day, 30-day, 60-day, 90-day, or 180-day.

Outcomes

The primary outcomes assessed were all-cause in-hospital mortality and IMV requirement in COVID-19 patients receiving routine awake prone positioning versus standard care. The secondary outcomes were changes in SpO_2/FiO_2 ratio, time to IMV initiation, hospital and ICU LOS (length of stay), and adverse events. Adverse events were defined as skin breakdown or pressure sore/ulcer, vomiting, and invasive line dislodgement involving an arterial or central venous catheter.

Quality assessment

Two researchers (W.H.C. and B.K.S.) performed quality assessments and the risk of bias for each RCTs using the Cochrane Collaboration's Risk of Bias Tool in Table 3 (Higgins et al., 2021). The Cochrane Collaboration's Risk of Bias Tool determines the quality of RCTs based on the assessment for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We considered a study's overall risk of bias to be high if any domain was judged to be at high risk of bias, except blinding of the participants and personnel, and blinding of outcome assessment. By the design and intervention of all RCTs, it was not possible for blinding between the APP (intervention) and standard care (control) groups to occur. Therefore, we accepted standardization of care according to clinical practice at respective hospitals to mitigate performance and detection bias.

Statistical analysis

A meta-analysis was performed for the primary and secondary outcomes using the Review Manager (RevMan) software, Version 5.4, The Cochrane Collaboration, 2020. Using DerSimonian and Laird's random-effects model, pooled odds ratios

Table 1 – Clinical characteristics of eight RCTs comparing routine APP versus standard care

Author	Ehrmann et al. (2021)	Fralick et al. (2022)	Gad (2021)	Jayakumar et al. (2021)	Johnson et al. (2021)	Kharat et al. (2021)	Rosén et al. (2021)	Taylor et al. (2021)
Study design	Multi-center, RCT	Multi-center, RCT	Single-center, RCT	Multi-center, RCT	Single-center, RCT	Multi-center, RCT	Multi-center, RCT	Single-center, RCT
Country	Canada, France, Ireland, Mexico, USA, Spain	Canada, USA	Egypt	India	USA	Switzerland	Sweden	USA
Recruitment date	April 2, 2020 – January 26, 2021	May 2020 – May 2021	June 2020 – September 2020	N/A	April 29, 2020 – August 6, 2020	April 6, 2020 – April 25, 2020	October 7, 2020 – February 7, 2021	June 1, 2020 – August 31, 2020
Inclusion criteria	1) Adults proven or suspected COVID-19 pneumonia 2) HFNC and SpO_2:FiO2 < 315 or PaO_2:FiO_2 < 300 mm Hg	1) Adults proven or suspected COVID-19 pneumonia 2) Supplemental oxygen up to 50% FiO_2 3) Within 48 hours of hospitalization	1) Adults proven or suspected COVID-19 pneumonia 2) Supplemental oxygen 5–10 LPM and SpO_2 < 90%, RR > 24 bpm	1) Adults proven or suspected COVID-19 pneumonia 2) Supplemental oxygen > 4 LPM and SpO_2 > 92% or PaO_2/FiO_2 100–300 mm Hg and $PaCO_2$ < 45 mm Hg 3) < 0.1 mcg/kg/min of norepinephrine	1) Adults proven or suspected COVID-19 pneumonia	1) Adults proven or suspected COVID-19 pneumonia 2) Supplemental oxygen 1–6 LPM and SpO_2 90–92%	1) Adults proven or suspected COVID-19 pneumonia 2) HFNC and NIMV	1) Adults proven or suspected COVID-19 pneumonia 2) SpO_2 < 93% in room air or supplemental oxygen > 3 LPM 3) Within 7 days of illness onset
Exclusion criteria	Pregnant, BMI > 40 kg/m^2, hemodynamically unstable, IMV, or awake proning contraindication	IMV, awake proning contraindication, dementia, delirium	IMV, RR > 40 bpm, SBP < 100 mm Hg, awake proning and NIMV contraindication	Pregnant, GCS < 15, IMV, awake proning contraindication	Pregnant, IMV, unable to change position without assistance or provide consent, incarcerated	Pregnant, unable to prone, terminally ill, recovered ARDS	Pregnant, IMV or previous IMV, hemodynamic instability, non-consentable, do-not-intubate	Awake proning contraindication

Author	**Ehrmann et al. (2021)**	**Fralick et al. (2022)**	**Gad (2021)**	**Jayakumar et al. (2021)**	**Johnson et al. (2021)**	**Kharat et al. (2021)**	**Rosén et al. (2021)**	**Taylor et al. (2021)**
Awake proning (N)	564	126	15	30	15	10	36	13
Proning duration/daily, mean ± SD (H)	5.6 ± 4.4	6.8 ± 8.4	N/A	2.0 ± 0.7	1.6 ± 2.2	4.9 ± 3.6	8.0 ± 4.6	N/A
Clinical characteristics								
Age, mean ± SD (Y)	61.5 ± 13.3	57.5 ± 17.0	49.6 ± 17.8	54.8 ± 11.1	52.3 ± 18.5	54.0 ± 14.0	64.3 ± 15.6	50.6 ± 8.9
Male gender, N (%)	380 (67.3)	82 (65.1)	9 (60.0)	25 (83.3)	8 (53.3)	6 (60.0)	23 (63.8)	7 (53.8)
BMI, mean ± SD (kg/m^2)	29.7 ± 6.6	N/A	N/A	28.2 ± 5.7	33.3 ± 8.8	29.7 ± 5.3	27.6 ± 3.7	33.0 ± 11.1
SpO_2:FiO_2 admission, mean ± SD	147.9 ± 43.9	300.0 ± 55.6	170.8 ± 111.3	233.3 ± 163.8	N/A	314.3 ± 42.2	152.0 ± 31.9	N/A
Initial O_2 support								
Supplemental oxygen or NRM, N (%)	0 (0)	118 (93.7)	15 (100)	26 (86.6)	5 (33.3)	17 (100)	0 (0)	13 (100)
NIMV, N (%)	0 (0)	0 (0)	0 (0)	2 (6.7)	0 (0)	0 (0)	5 (13.9)	0 (0)
HFNC, N (%)	564 (100)	5 (3.9)	0 (0)	1 (3.3)	0 (0)	0 (0)	31 (86.1)	0 (0)
Standard care, (N)	557	122	15	30	15	17	39	27
Proning duration/daily, mean ± SD (H)	0.3 ± 1.2	0.7 ± 1.5	N/A	1.0 ± 1.5	0	0.1 ± 0.5	4.5 ± 4.9	N/A

Author	Ehrmann et al. (2021)	Fralick et al. (2022)	Gad (2021)	Jayakumar et al. (2021)	Johnson et al. (2021)	Kharat et al. (2021)	Rosén et al. (2021)	Taylor et al. (2021)
Clinical characteristics								
Age, mean ± SD (Y)	60.7 ± 14.0	53.3 ± 13.3	43.3 ± 13.3	57.3 ± 12.1	62.0 ± 19.3	60.0 ± 11.0	63.3 ± 11.1	60.6 ± 8.1
Male gender, N (%)	366 (65.7)	78 (63.9)	8 (5.3)	25 (83.3)	8 (53.3)	11 (64.7)	32 (82.1)	20 (74.1)
BMI, mean ± SD (kg/m^2)	29.7 ± 6.6	N/A	N/A	25.8 ± 2.6	28.9 ± 6.3	27.3 ± 4.2	29.6 ± 4.4	31.6 ± 7.4
SpO_2:FiO_2 admission, mean ± SD	148.6 ± 43.1	303.7 ± 53.3	127.7 ± 112.5	219.9 ± 125.9	N/A	342.3 ± 62.9	156.0 ± 74.3	N/A
Initial O_2 support								
Supplemental oxygen or NRM, N (%)	0 (0)	119 (97.5)	0 (0)	30 (100)	6 (40.0)	10 (100)	0 (0)	25 (92.6)
NIMV, N (%)	0 (0)	0 (0)	15 (100)	0 (0)	0 (0)	0 (0)	10 (25.6)	1 (3.7)
HFNC, N (%)	557 (100)	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	29 (74.4)	0 (0)

APP – awake prone positioning; ARDS – acute respiratory distress syndrome; BMI – body mass index; bpm – breaths per minute; COVID-19 – coronavirus disease 2019; D – days; FiO_2 – fraction of inspired oxygen; GCS – Glasgow Coma Scale; H – hours; HFNC – high-flow nasal cannula; ICU – intensive care unit; IMV – invasive mechanical ventilation; LPM – litters per minute; N – numbers; N/A – non-available; NIMV – non-invasive mechanical ventilation; NRM – non-rebreather mask; O_2 – oxygen; $PaCO_2$ – partial pressure of carbon dioxide; PaO_2 – partial pressure of arterial oxygen; RCT – randomized controlled trial; RR – respiratory rate; SBP – systolic blood pressure; SD – standard deviation; SpO_2 – ratio of peripheral arterial oxygen saturation; Y – years

Table 2 – Clinical outcomes of eight RCTs comparing routine APP versus standard care

Author	Ehrmann et al. (2021)	Fralick et al. (2022)	Gad (2021)	Jayakumar et al. (2021)	Johnson et al. (2021)	Kharat et al. (2021)	Rosén et al. (2021)	Taylor et al. (2021)
Awake proning (N)	564	126	15	30	15	10	36	13
Outcomes								
In-hospital mortality, N (%)	117 (20.7)	1 (0.8)	3 (20.0)	3 (10.0)	2 (13.3)	N/A	6 (16.7)	0 (0)
IMV, N (%)	185 (32.8)	6 (4.8)	3 (20.0)	4 (13.3)	2 (13.3)	N/A	12 (33.3)	0 (0)
Hospital LOS, mean ± SD (D)	16.4 ± 10.5	5.7 ± 4.4	28.0 ± 5.0	N/A	N/A	N/A	16.3 ± 8.1	5.3 ± 3.7
ICU LOS, mean ± SD (D)	12.4 ± 9.0	N/A	8.0 ± 3.0	11.5 ± 6.9	4.7 ± 4.0	N/A	7.3 ± 6.7	0 (0)
Time to IMV, mean ± SD (D)	2.3 ± 2.7	N/A	20.0 ± 5.0	N/A	N/A	N/A	2.7 ± 2.9	N/A
Change in SpO_2/FiO_2 ratio, mean ± SD	N/A	53.3 ± 108.1	N/A	–3.3 ± 26.2	131.3 ± 72.3	60.7 ± 53.4	N/A	N/A
Adverse events								
Pressure sore, N (%)	8 (1.4)	N/A	N/A	N/A	N/A	N/A	2 (5.6)	0 (0)
Vomiting, N (%)	15 (2.7)	2 (1.6)	N/A	N/A	N/A	N/A	1 (2.8)	0 (0)
Line dislodgement, N (%)	26 (4.6)	N/A	N/A	N/A	N/A	N/A	0 (0)	1 (7.7)

Author	Ehrmann et al. (2021)	Fralick et al. (2022)	Gad (2021)	Jayakumar et al. (2021)	Johnson et al. (2021)	Kharat et al. (2021)	Rosén et al. (2021)	Taylor et al. (2021)
Standard care (N)	557	122	15	30	15	17	39	27
Outcomes								
In-hospital mortality, N (%)	132 (23.6)	1 (0.8)	3 (20.0)	2 (6.7)	0 (0)	N/A	3 (7.7)	0 (0)
IMV, N (%)	223 (40.0)	5 (4.1)	3 (20.0)	4 (13.3)	1 (6.7)	N/A	13 (33.3)	0 (0)
Hospital LOS, mean ± SD (D)	16.5 ± 9.7	5.0 ± 3.7	26.0 ± 5.0	N/A	N/A	N/A	19.6 ± 14.1	8.3 ± 7.4
ICU LOS, mean ± SD (D)	12.4 ± 8.4	N/A	7.0 ± 2.0	9.9 ± 5.7	4.6 ± 1.4	N/A	12.0 ± 14.1	0 (0)
Time to IMV, mean ± SD (D)	2.0 ± 2.1	N/A	25.0 ± 8.0	N/A	N/A	N/A	3.0 ± 3.7	N/A
Change in SpO_2/FiO_2 ratio, mean ± SD	N/A	61.0 ± 99.3	N/A	–11.7 ± 22.6	79.3 ± 22.7	0.0 ± 31.9	N/A	N/A
Adverse events								
Pressure sore, N (%)	10 (1.8)	N/A	N/A	N/A	N/A	N/A	9 (23.1)	0 (0)
Vomiting, N (%)	18 (3.2)	1 (0.8)	N/A	N/A	N/A	N/A	0 (0)	0 (0)
Line dislodgement, N (%)	17 (3.1)	N/A	N/A	N/A	N/A	N/A	0 (0)	0 (0)

APP – awake prone positioning; D – days; FiO_2 – fraction of inspired oxygen; ICU – intensive care unit; IMV – invasive mechanical ventilation; LOS – length of stay; N – numbers; N/A – non-available; RCT – randomized controlled trial; SD – standard deviation; SpO_2 – ratio of peripheral arterial oxygen saturation

(ORs), mean difference (MDs), and 95% confidence intervals (CIs) were calculated, and extracted outcomes were pooled by weighted averages (DerSimonian and Laird, 1986). The random-effects model was preferred over the fixed-effects model as we suspected that clinical heterogeneity might be present due to the variability across the included studies regarding differences in criteria for escalation of oxygen therapy and IMV initiation, patient population characteristics, and clinical practices. Furthermore, we aimed to assess the mean distribution of results across the eight RCTs with various sample sizes without disregarding the results of small studies and giving extra weightage to results from larger studies. Dichotomous outcomes were assessed using Mantel-Haenszel statistical method as part of the random-effects model and measured in ORs and their 95% CIs. Continuous outcomes were evaluated by the inverse variance statistical method as part of the random-effects model and measured in MDs. The inverse variance method accounts for differing sample sizes of individual studies by weighting studies by the variance of their estimates, such that small studies with large variance have less weighting, and large studies with small variance have more weighting. Statistical heterogeneity among studies was assessed by the I^2 statistic. High heterogeneity was classified as I^2 statistics of 50% and greater, and low was with I^2 statistics of less than 50% (Higgins et al., 2003). A P-value of < 0.05 was considered statistically significant. Subgroup analysis was performed by comparing RCTs involving COVID-19 patients predominantly using NIMV and HFNC versus those using supplemental oxygen and NRM (non-rebreather mask) to determine the impact of NIMV and HFNC on primary outcomes of mortality and IMV.

Results

Study selection and characteristics

Two thousand five hundred thirty-four articles were identified through searched databases. Eight eligible RCTs were included in this meta-analysis after removing duplicates and those not meeting the inclusion criteria (Figure 1). A total of 1,631 COVID-19 patients were included, of which 809 patients received APP, and the remainder received standard of care. The study and clinical characteristics were summarized in Tables 1 and 2. The risk of bias for our primary outcome was low across most studies except for two RCTs as summarized in Table 3 (Gad, 2021; Johnson et al., 2021). Five RCTs assessed patients mainly receiving supplemental oxygen and non-rebreather mask as initial oxygen support (Jayakumar et al., 2021; Johnson et al., 2021; Kharat et al., 2021; Taylor et al., 2021; Fralick et al., 2022), whereas three RCTs by Ehrmann et al. (2021), Gad (2021), and Rosén et al. (2021), assessed patients mainly receiving NIMV and HFNC.

All-cause in-hospital mortality and IMV

The overall all-cause in-hospital mortality was similar (16.5% vs. 17.5%; OR 0.90; P=0.45) between COVID-19 patients in the routine APP group versus the standard

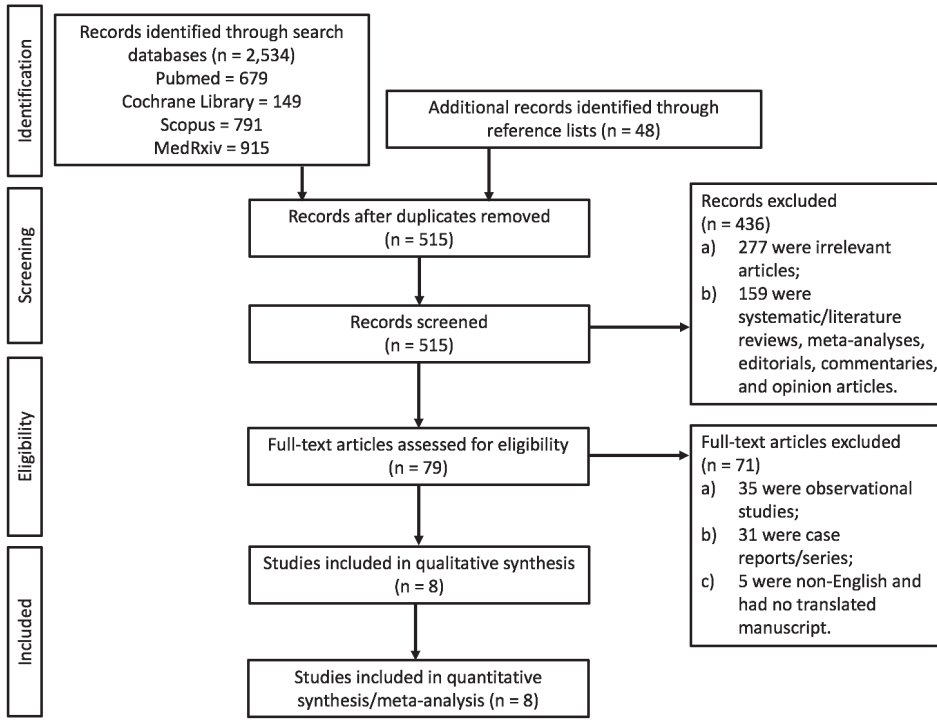

Figure 1 – Flow diagram of study selection.

care group (Figure 2). The mortality rate remained unchanged (3.2% vs. 1.5%; OR 1.79; P=0.41) in the four RCTs, mainly receiving supplemental oxygen and NRM as initial oxygen support (Jayakumar et al., 2021; Johnson et al., 2021; Taylor et al., 2021; Fralick et al., 2022). For the three RCTs assessing patients mainly receiving NIMV and HFNC as initial oxygen support, the mortality rate was equal (20.5% vs. 22.6%; OR 0.88; P=0.35) (Ehrmann et al., 2021; Gad, 2021; Rosén et al., 2021).

The overall IMV requirement was lower (26.5% vs. 30.9%; OR 0.77; P=0.03) in the routine APP group than in the standard care group (Figure 3). Although patients mainly receiving NIMV and HFNC in the routine APP group benefited from lower (32.5% vs. 39.1%; OR 0.75; P=0.02) IMV requirements than the standard care group, a similar outcome was not seen for those mainly receiving supplemental oxygen and NRM. The time to IMV initiation for patients mainly receiving NIMV and HFNC was comparable between the routine APP and standard care groups (Figure 4). Indications for IMV were described in two RCTs with COVID-19 patient deterioration involving respiratory rate > 40 breaths per minute, respiratory muscle fatigue, respiratory acidosis with pH < 7.25, copious tracheal secretions, respiratory distress with PaO_2/FiO_2 ratio < 100 mm Hg or SpO_2 < 90% at 100% FiO_2 for at

Table 3 – Results of the Cochrane Collaboration's Risk of Bias Tool for the eight randomized controlled trials

Randomized controlled trials	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ehrmann et al. (2021)	+	+	–	–	+	+	+
Fralick et al. (2022)	+	+	–	–	+	+	+
Gad (2021)	+	+	–	–	–	+	–
Jayakumar et al. (2021)	+	+	–	–	+	+	+
Johnson et al. (2021)	–	–	–	–	+	+	+
Kharat et al. (2021)	+	?	–	–	+	+	+
Rosén et al. (2021)	+	+	–	–	+	+	+
Taylor et al. (2021)	+	?	–	–	+	+	+

"+" risk of bias low; "–" risk of bias high; "?" unknown risk of bias

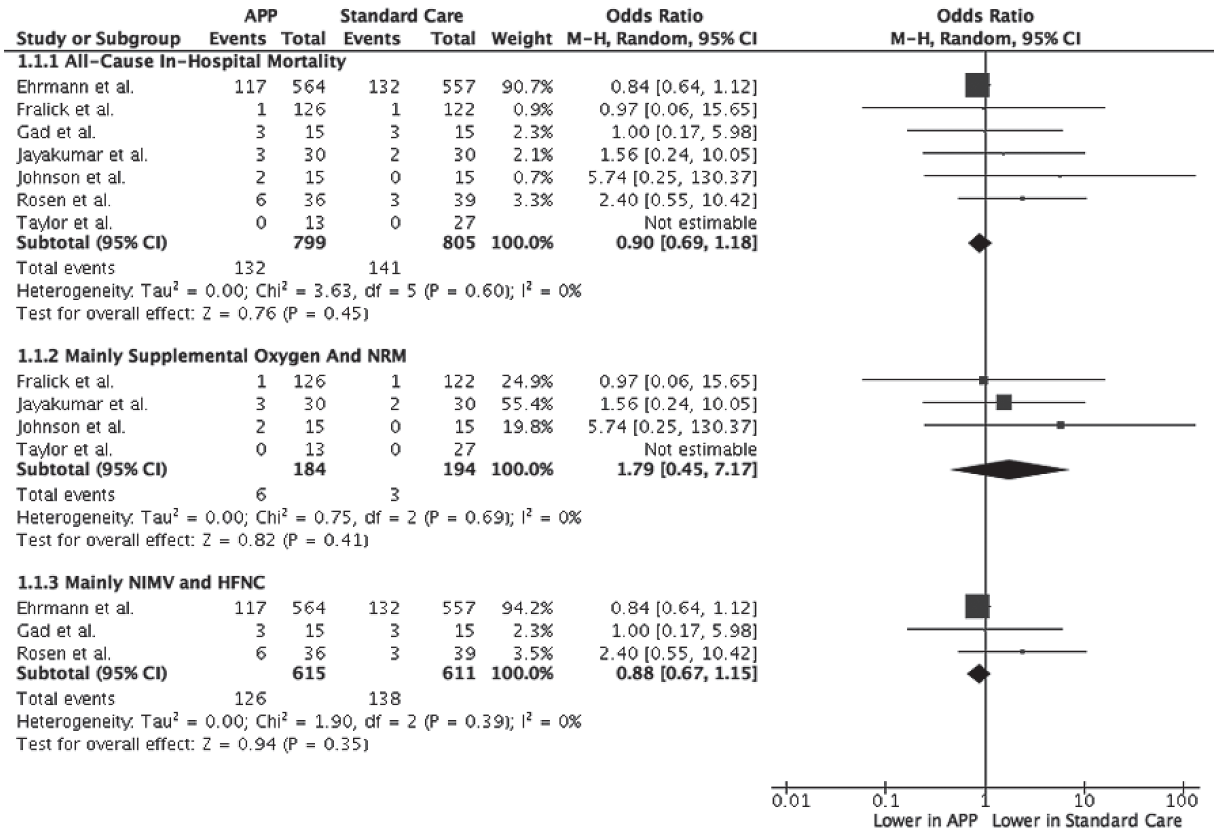

Figure 2 – Forrest plot of COVID-19 patients divided into routine APP versus standard care. Outcomes of overall all-cause in-hospital mortality was assessed. Sensitivity analysis was also performed for overall mortality dividing RCTs into patients mainly requiring supplemental oxygen and NRM, and patients mainly requiring NIMV and HFNC. The odds ratio was calculated by the Mantel-Haenszel method with a random-effects model (APP – awake prone positioning; CI – confidence interval; HFNC – high-flow nasal cannula; M-H – Mantel-Haenszel; NIMV – non-invasive mechanical ventilation; NRM – non-rebreather mask; RCTs – randomized controlled trials).

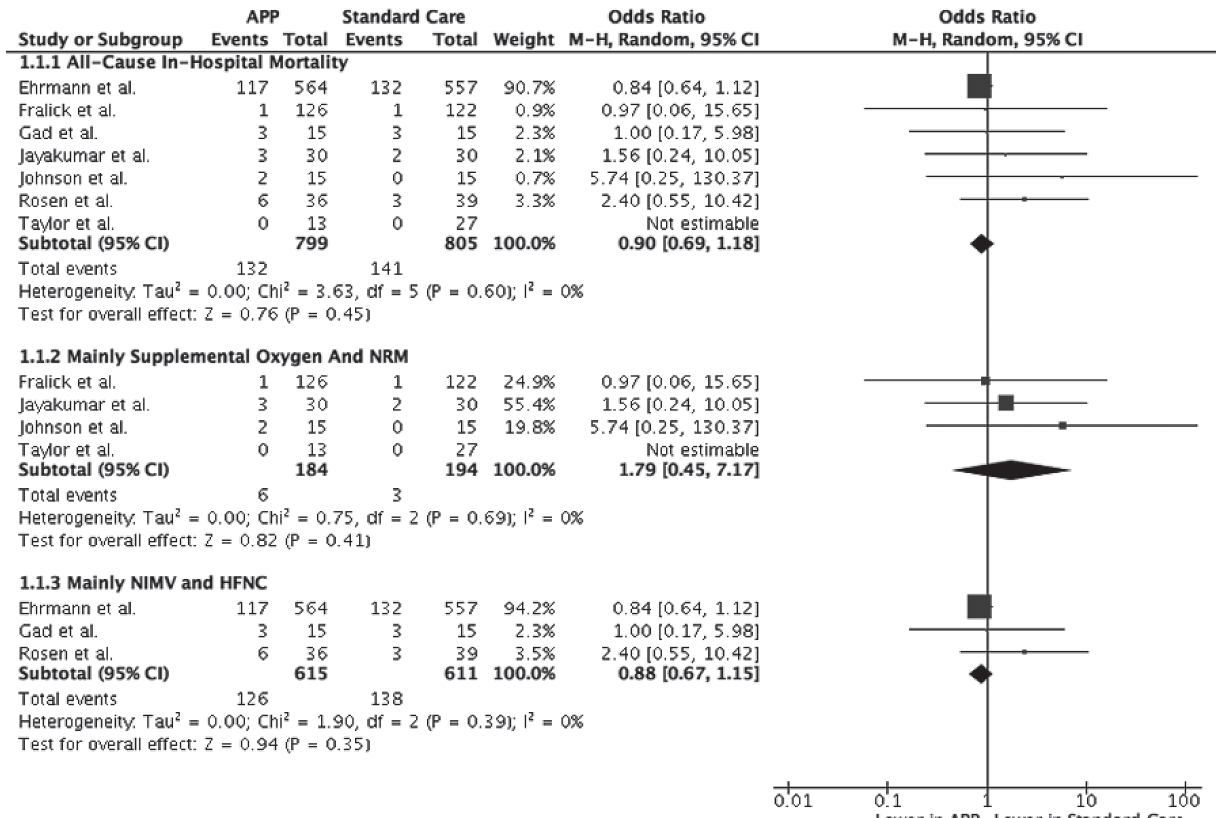

Figure 3 – Forrest plot of COVID-19 patients divided into routine APP versus standard care. Outcomes of IMV requirement was assessed. Sensitivity analysis was also performed for overall IMV requirement dividing RCTs into patients mainly requiring supplemental oxygen and NRM, and patients mainly requiring NIMV and HFNC (APP – awake prone positioning; CI – confidence interval; HFNC – high-flow nasal cannula; IMV – invasive mechanical ventilation; M-H – Mantel-Haenszel; NIMV – non-invasive mechanical ventilation; NRM – non-rebreather mask; RCTs – randomized controlled trials).

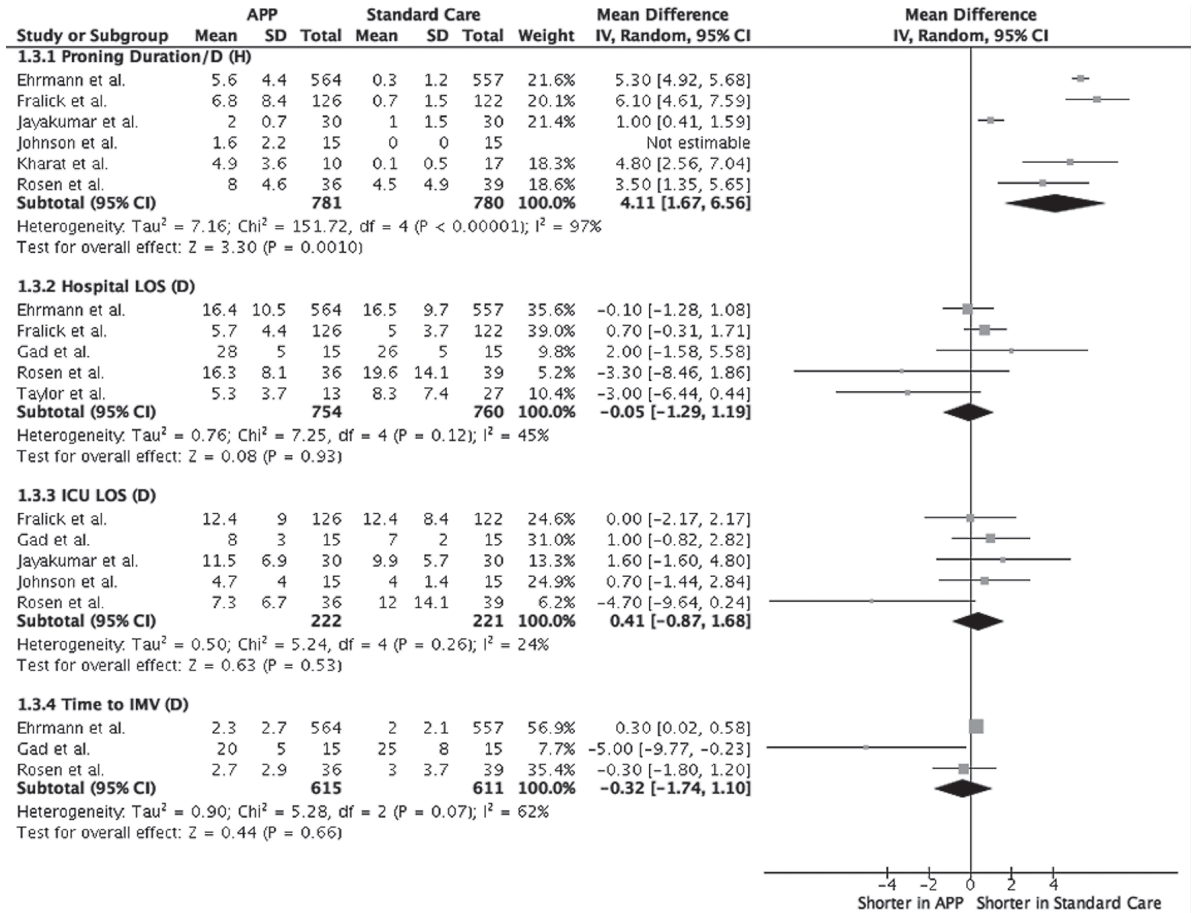

Figure 4 – Forrest plot of COVID-19 patients divided into routine APP versus standard care. Outcomes of proning duration daily, hospital and ICU LOS, and time to IMV were assessed. Mean differences were calculated by the inverse variance statistical method with a random-effects model (APP – awake prone positioning; CI – confidence interval; D – days; ICU – intensive care unit; IMV – invasive mechanical ventilation; IV – inverse variance; LOS – length of stay; SD – standard deviation).

Figure 5 – Forrest plot of COVID-19 patients divided into routine APP versus standard care. Outcome of SpO_2/FiO_2 change on supplemental oxygen and NRM was assessed (APP – awake prone positioning; CI – confidence interval; NRM – non-rebreather mask; SD – standard deviation).

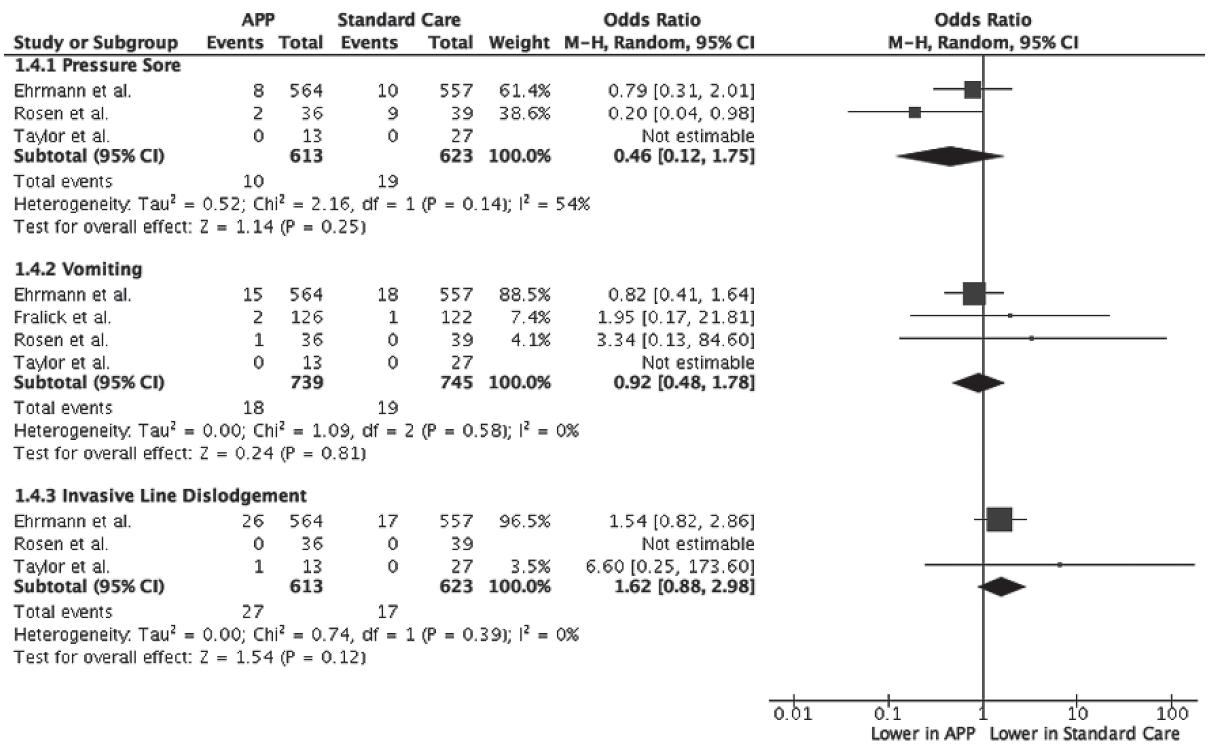

Figure 6 – Forrest plot of COVID-19 patients divided into routine APP versus standard care. Adverse events involving pressure sore, vomiting, and invasive line dislodgement were assessed (APP – awake prone positioning; CI – confidence interval; M-H – Mantel-Haenszel).

least 5 minutes, altered mental status, and hypotension or shock (Ehrmann et al., 2021; Gad, 2021).

Hospital and ICU LOS, change in SpO_2/FiO_2 ratio

In the six RCTs, the total duration of proning daily was significantly longer (mean 4.8 vs. 1.1 hours; MD 4.11; P=0.001) in the routine APP group than in the standard care group (Figure 4) (Ehrmann et al., 2021; Jayakumar et al., 2021; Johnson et al., 2021; Kharat et al., 2021; Rosén et al., 2021; Fralick et al., 2022). Five RCTs demonstrated that the routine APP and standard care groups had comparable hospital LOS (Figure 4) (Ehrmann et al., 2021; Gad, 2021; Rosén et al., 2021; Taylor et al., 2021; Fralick et al., 2022). Similarly, the ICU LOS differed between the two groups according to five RCTs (Figure 4) (Gad, 2021; Jayakumar et al., 2021; Johnson et al., 2021; Rosén et al., 2021; Fralick et al., 2022). Among the four RCTs assessing patients mainly receiving supplemental oxygen and NRM, the change in SpO_2/FiO_2 ratio was higher (mean 80.6 vs. 42.8; MD 24.30; P=0.09) in the routine APP group than the standard care group, but statistical difference was not achieved (Figure 5) (Jayakumar et al., 2021; Johnson et al., 2021; Kharat et al., 2021; Fralick et al., 2022).

Adverse events

Four RCTs assessing patients receiving routine APP versus standard care found no difference in the incidence of vomiting (Figure 6) (Ehrmann et al., 2021; Rosén et al., 2021; Taylor et al., 2021; Fralick et al., 2022). The incidence of other adverse events involving pressure sores and invasive line dislodgements were similar in both groups (Figure 6) as described in three RCTs (Ehrmann et al., 2021; Rosén et al., 2021; Taylor et al., 2021).

Discussion

APP has emerged as an important and effective adjunct therapy in managing COVID-19 patients with acute hypoxic respiratory failure due to the known physiological benefits in gaseous exchange, prevention in respiratory support escalation, good safety profile, and ease of implementation, even in non-intensive care and resource-limited setting. While prone positioning benefited critically ill patients with IMV requirements, our meta-analysis of RCTs demonstrated that routine APP in non-intubated COVID-19 patients would reduce overall IMV requirement, especially in those requiring HFNC and NIMV oxygen support. The lack of blinding and IMV indications might influence the decision-making of treating clinicians by having a lower threshold for initiating IMV in the standard care group, mainly requiring HFNC and NIMV. Though, the time to IMV initiation for patients requiring HFNC and NIMV was similar between the routine APP and standard care groups. Despite the lack of statistical difference, the improvement in SpO_2/FiO_2 ratio in patients, mainly requiring supplemental oxygen and NRM, might create a false perception of clinical improvement and lead to the potential harm caused by delayed

IMV initiation. However, no difference in all-cause in-hospital mortality, hospital and ICU LOS, and incidence of adverse events (pressure sores, vomiting, invasive line dislodgements) were observed in both groups. These findings suggested that the clinicians treated COVID-19 patients correctly and appropriately identified those that did not require IMV. Our pragmatic results supported the notion that routine APP was a valuable tool for managing acute hypoxic respiratory failure considering recent findings of comparable mortality rate and IMV duration in critically ill COVID-19 patients receiving early versus late intubation (Papoutsi et al., 2021).

Several meta-analyses published to date comparing the outcomes of APP versus standard of care in COVID-19 patients suffer from the same limitations as the majority of studies included were observational studies, lack a control group, unmeasured confounding variables, variable sample sizes, and susceptible to selection and publication bias (Ponnapa Reddy et al., 2021; Fazzini et al., 2022; Pavlov et al., 2022; Schmid et al., 2022). Furthermore, many of these studies were performed during the first and second pandemic wave, where rapid data collection and dissemination was prioritized. Hence, the reported outcomes might not be accurate and reflective of current clinical outcomes, considering the rapid advancement of COVID-19 therapies. The effectiveness of APP remains to be established in RCTs, likely due to multiple implementation barriers such as adoption, feasibility, and tolerability. Although APP is a more cost-effective therapy than IMV and extracorporeal membrane oxygenation (ECMO) for managing ARDS, APP is perceived as a labor-intensive intervention and often deferred due to the desire to minimize staff exposure and use of personal protective equipment (Poor et al., 2020; Weatherald et al., 2021). Our meta-analysis was restricted to eight RCTs, and the huge weightage of the RCT by Ehrmann et al. (2021) might have influenced the outcomes of our meta-analysis. However, the outcomes would likely not be different as Ehrmann et al. (2021) conducted a meta-trial of six RCTs to achieve a large sample size to overcome known barriers to performing a RCT. These barriers would have been further exacerbated during the ongoing pandemic in which clinicians and research staffs were relocated to meet the increasing demands of the overwhelmed healthcare setting. Other important clinical outcomes such as mortality, IMV requirement, ICU and hospital LOS, and adverse events were assessed because APP might provide a false sense of reassurance leading to potentially delayed escalation of respiratory support and IMV initiation. We also included RCTs from the grey literature of medRxiv to reduce publication bias and used mortality from the longest follow-up period to avoid missing important data contributed by the delayed clinical decompensation from the atypical COVID-19 phenotype (Chong et al., 2021, 2022). The prolonged duration of patient enrolment as the RCTs were conducted between April 2020 and May 2021 would increase the generalizability due to the rapid advancement in COVID-19 therapies and the increase in APP experience gained among healthcare providers from previous waves of the ongoing pandemic.

There are several possible reasons for the similarity in outcomes of all-cause in-hospital mortality, hospital and ICU LOS observed in COVID-19 patients receiving APP versus standard care. 1) Crossover with the use of APP as part of rescue therapy at the discretion of the treating clinician due to the known physiological benefit in the standard care group; and 2) the mean daily duration of APP was 4.8 hours compared to 1.1 hours in the standard care group might not be significant enough to demonstrate any difference in outcomes (Ehrmann et al., 2021; Jayakumar et al., 2021; Rosén et al., 2021; Fralick et al., 2022). Prone positioning when applied for a longer period (12 hours or more) has been demonstrated to improve oxygenation and mortality in non-COVID-19 patients on IMV (Beitler et al., 2014; Lee et al., 2014; Bloomfield et al., 2015; Park et al., 2015; Munshi et al., 2017). Possibly because of the physiological benefit of prone positioning to facilitate lung recruitment, improve compliance and promote ventilation-perfusion homogeneity is a time-dependent event. However, similar to multiple studies and meta-analyses assessing the benefits of prone positioning in non-COVID-19 patients with ARDS, the exact threshold of minimum daily duration and cumulative hours in which prone positioning will confer benefit remains unknown (Sud et al., 2010; Abroug et al., 2011; Park et al., 2015; Munshi et al., 2017). Although the mean daily duration of proning was recorded in our meta-analysis, the number of APP sessions and patients adhering to APP remain uncertain. Furthermore, the mean daily duration of proning was highly variable across different RCTs (Table 1), which might be explained by the crossover from standard care to the APP group and poor patient compliance to APP due to discomfort ranging from musculoskeletal discomfort, vomiting, coughing, and anxiety, despite repeated encouragements (Touchon et al., 2021). Considering that IMV patients are often heavily sedated and paralyzed to tolerate prone positioning, these explain the difficulty of achieving a similar prone positioning duration in non-IMV patients. Nevertheless, poor tolerance and adherence to APP likely reflect real-world challenges for critically ill COVID-19 patients with underlying acute hypoxic respiratory failure, multi-organ dysfunction, and a lack of high nursing-to-patient ratio to reinforce APP.

Despite the known benefit of prone positioning, there remains a lack of evidence guiding the timing of APP initiation for COVID-19 patients to achieve optimal outcomes. Early initiation (within two days of ICU admission) of prone positioning was associated with lower mortality among mechanically ventilated COVID-19 patients with moderate to severe ARDS (Mathews et al., 2021). A prospective study observed that APP COVID-19 responders (more remarkable improvement in oxygenation parameters) were those who had shorter time from hospital admission to receiving APP (mean 2.7 vs. 4.6 days) when the duration and number of APP sessions were similar (Coppo et al., 2020). A RCT that compared outcomes among 125 COVID-19 patients receiving early APP (less than 24 hours) compared to delayed APP with HFNC showed improved oxygenation parameters and 28-day mortality (Kaur et al., 2021). However, patients in the early APP had a longer daily

duration of APP (mean 5.1 vs. 3 hours) than the delayed group.

In our meta-analysis, COVID-19 patients predominantly receiving NIMV and HFNC during APP had reduced need for IMV requirements, although the time to IMV initiation, mortality, and hospital/ICU LOS were similar. The rate of escalation and the number of days free from HFNC and NIMV were not assessed in RCTs requiring supplemental oxygen and NRM. Only one RCT demonstrated no difference in mortality and IMV requirement among COVID-19 patients receiving APP combined with NRM versus those solely receiving NIMV in the standard care group (Gad, 2021). There remains a lack of studies comparing the outcomes of COVID-19 patients receiving either HFNC or NIMV during APP. Multiple prospective observational COVID-19 studies assessing APP as an adjunctive to HFNC compared to HFNC alone showed conflicting results in mortality rate and IMV requirement despite increasing oxygenation parameters in the APP group (Ferrando et al., 2020; Esperatti et al., 2022). Other small retrospective studies revealed a reduction in respiratory rate and increased oxygenation parameters among COVID-19 patients receiving NIMV with APP than those receiving NIMV alone (Winearls et al., 2020; Chiumello et al., 2021). A small retrospective observational study involving 48 COVID-19 patients receiving APP revealed that patients managed by NIMV alone had a lower mortality rate than those who transitioned from NIMV to HFNC (Hallifax et al., 2020). However, it was possible that COVID-19 patients who were transitioned from NIMV to HFNC had poor tolerance and demonstrated clinical decompensation with failure to respond to existing oxygen support. Historically, HFNC was favoured over NIMV in critically ill non-COVID-19 patients with ARDS as HFNC provided a lower level of positive pressure compared to high levels of positive pressure delivered by NIMV that may lead to patient self-induced lung injury (P-SILI) in a spontaneous breathing patient, regardless of prone positioning status (Walkey and Wiener, 2013; Spinelli et al., 2020). Therefore, current evidence supporting the use of HFNC over NIMV is limited to observational non-COVID-19 ARDS studies in which HFNC was not demonstrated to be superior over NIMV in improving gaseous exchange during APP, although clinical outcomes such as mortality were not examined (Ding et al., 2020; Pérez-Nieto et al., 2020).

Prone positioning for patients requiring IMV is associated with an increased risk of dislodgement of invasive lines that arise when turning, and pressure sores from prolonged static positioning frequently in those receiving IMV, sedation, and NMB (Venus et al., 2020). Multiple meta-analyses of non-COVID-19 patients requiring IMV showed a similar incidence of line dislodgements but increased in pressures sores during prone positioning compared to supine (Sud et al., 2010; Abroug et al., 2011; Lee et al., 2014; Bloomfield et al., 2015; Park et al., 2015; Munshi et al., 2017). However, the risks of pressure sores may be mitigated in an awake patient who can change position independently for comfort. In our meta-analysis, adverse events involving pressure sores, vomiting, and invasive line dislodgements were low (less than 5%), and there was no difference between the routine APP and standard

care groups. The lack of difference in pressure sore incidence is vital as pressure sore has been associated with higher morbidity and mortality among critically ill non-COVID-19 patients and constitutes a significant burden to the healthcare system (Labeau et al., 2021).

There were several limitations to our meta-analysis. 1) The included RCTs were diverse based on the inclusion criteria employed, unclear ARDS severity, time to APP initiation from hospital admission, missing IMV indication (only discussed in two RCTs) (Ehrmann et al., 2021; Gad, 2021), and associated-COVID-19 therapy provided. The use of a random-effect model might have resulted in wider CIs and a more conservative treatment effect; 2) As more than three-quarters of the studies were conducted in Europe and the USA, there was a lack of generalizability toward other populations of different demographics; 3) The exclusion of non-English studies might preclude the extrapolation of our results towards low- and middle-income countries that were equally burdened by COVID-19; 4) Because of the nature of APP intervention, blinding of the patients and treating clinicians will not be feasible leading to increased risk of bias; 5) Other essential clinical data that might affect the efficacy of the intervention, management, and outcomes such as the number of cycles of APP, severity and duration of illness before randomization, and existing do-not-intubate status were not well-described. Clinical outcomes that have important implications for patient care, such as changes in respiratory rate and oxygenation parameters after proning, and time to the escalation of oxygen requirement, were inconsistently assessed that might be used as a marker for P-SILI development (Venus et al., 2020); and 6) Publication bias was not assessed due to the low number of RCTs included, although RCT from grey literature of medRxiv was included (Fralick et al., 2022). Future trials should ideally minimize crossover from supine to APP, improve compliance to longer APP duration, compare the utility of different forms of respiratory support during APP, and assess the clinical benefit of specific interventions and devices for APP comfort and adherence are required.

Conclusion

When applied in an optimal manner and to the targeted COVID-19 population, APP is associated with a reduction in IMV requirement, especially in patients requiring NIMV and HFNC, and improvement in SpO_2/FiO_2 ratio in patients requiring supplemental oxygen and NRM. Current evidence cannot determine the optimal timing of initiation, duration, and frequency of APP sessions for COVID-19 patients.

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