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Effectiveness of prone position with its moderating factors in non-intubated acute respiratory distress syndrome patients: a meta-analysis

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ABSTRACT

Introduction: While numerous meta-analyses have explored the efficacy of awake prone position (APP), most have concentrated solely on intubation rate among Covid-19 patients without comprehensively identifying the influencing factors. This study aims to evaluate the efficacy of APP along with its moderating factors on oxygenation, intubation rate, and mortality in non-intubated acute respiratory distress syndrome (ARDS) patients.

Methods: We conducted a systematic search in PubMed, Web of Science, and CINAHL from inception to December 2022. JBI critical appraisal tools were used to assess the study quality. Random-effects model was employed to calculate pooled standardized mean difference for continuous outcomes and risk ratio for dichotomous outcomes.

Results: Among the 39 studies included, most patients were suffering from Covid-19, using conventional oxygen therapy, and receiving APP outside the ICU. APP significantly improved the PaO2/FiO2 ratio (SMD=0.70, 95% CI=0.51-0.88) and SpO2/FiO2 ratio (SMD=0.76, 95% CI=0.51-1.01), while also reducing the risk of intubation (RR=0.66, 95% CI=0.51-0.85) and mortality (RR=0.62, 95% CI=0.49-0.78). Factors including severity, respiratory device, body mass index, detail of position, use of medication assistance, total duration, follow-up time, position at follow-up, and study design significantly influence the effectiveness of APP. APP did not lead to significant improvements in length of stay and adverse events

Conclusions: APP is a safe and beneficial intervention, enhancing oxygenation and reducing intubation and mortality rates in non-intubated ARDS patients. Importantly, various patient and intervention characteristics should be taken into account when implementing APP. Further well-designed experimental studies are needed to strengthen the evidence base.

Keywords: ARDS, awake prone positioning, intubation rate, length of stay, mortality, oxygenation

Introduction

Acute respiratory distress syndrome (ARDS) is a critical condition associated with respiratory failure, and its incidence has increased during the Covid-19 pandemic. ARDS patient, particularly those with severe cases, are at a higher risk of developing pneumonia and

ventilator-associated lung injury (VALI), leading to significant morbidity and mortality (Slutsky and Ranieri, 2013). Despite optimized standard therapies, the mortality rate remains high, necessitating additional interventions to prevent clinical deterioration and disease progression (Bellani et al., 2016; Matthay et al., 2019).

The prone position has emerged as one of the most effective interventions for preventing and treating lung injury in ARDS (Koulouras et al., 2016; Scholten et al., 2017; Guérin et al., 2020). By modifying the regional distribution of transpulmonary pressure, the prone position has been shown to reduce mortality, improve oxygenation, and enhance survival rates (Hu et al., 2014; Bloomfield, Noble and Sudlow, 2015; Kallet, 2015; Mora-Arteaga, Bernal-Ramírez and Rodríguez, 2015; Munshi et al., 2017). International practice guidelines widely recommend its use in intubated ARDS patients (Fan et al., 2017; Griffiths et al., 2019; Papazian et al., 2019; World Health Organization, 2023). However, the effectiveness of the prone position in non-intubated patients, known as the awake prone position (APP), necessitates further investigations (McNicholas, Ehrmann and Laffey, 2022).

While numerous meta-analyses have explored the efficacy of APP, their primary focus has predominantly been on intubation rates in Covid-19 patients (Beran et al., 2022; Chong, Saha and Tan, 2022; Cruz et al., 2022; Kang, Gu and Tong, 2022; Li et al., 2022; Weatherald et al., 2022; Cheema et al., 2023; Peng et al., 2023; Qin et al., 2023; Wang et al., 2023). Moreover, only one meta-analysis has delved into the influence of different patient and intervention factors on prone positioning's effectiveness, mainly in terms of oxygenation and not specifically APP (Ashra et al., 2022). Despite some studies calling for more comprehensive analyses (Aeen et al., 2021; Li et al., 2022), many have only concentrated on variables such as respiratory devices, settings, and duration. To address this gap in knowledge, our study aimed to systematically evaluate the impact of APP on oxygenation and the rate of intubation and mortality, while also considering the factors that moderate these outcomes through an extensive meta-analysis. This meta-analysis has the potential to illuminate the benefits of APP and offer valuable insights for informed clinical decision-making and improved patient care.

Materials and Methods

This meta-analysis was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database at the National Institute for Health Research on July 13, 2023. The registration number is CRD42023444945.

Eligibility criteria

The PICO (population, intervention, comparison, outcome) framework was used to determine the eligibility criteria for the required studies. We focused on studies involving non-intubated patients aged ≥18 years with ARDS or acute hypoxemic respiratory failure (AHRF) who underwent the prone position. Among these studies, we primarily investigated post-APP PaO2/FiO2 (PF) ratio, SpO2/FiO2 (SF) ratio, mortality rate, and intubation rate as the primary outcomes. Additionally, we examined secondary outcomes, which encompassed various oxygenation parameters, the length of stay (LOS) and the occurrence of adverse events. We considered all original articles published in English and used experimental or observational study designs. However, to enhance the methodological rigor, observational studies were limited to cohort studies, as they are the only ones that can distinguish cause and effect.

Search strategy

All articles included in this study were searched in three international databases from November to December 2022. The databases were PubMed, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text via EBSCOhost. The search included articles without limitations on geographic location or publication year. We employed Medical Subject Heading (MeSH) terminology and key-word such as “prone position” OR “awake prone position” AND “respiratory distress syndrome” OR “hypoxemic respiratory failure” OR “acute respiratory distress syndrome” OR “acute lung injury” OR “ARDS” AND “oxygen saturation” OR “blood gas analysis” (Supplementary file 1).

Study selection

All identified articles were collated and uploaded into the Rayyan website application for article review (Ouzzani et al., 2016). Rayyan streamlines and accelerates the systematic review process by enabling efficient study screening, unbiased collaboration, and organized data management for authors. The initial process involved removing duplicates and screening titles and abstracts. The first and second author

independently reviewed and confirmed potentially relevant articles. These articles were retrieved in full text and assessed in detail by all authors based on the eligibility criteria. The article selection process was documented in the PRISMA 2020 flow diagram (Page et al., 2021). Any disagreements during the selection process were resolved through discussion and consensus.

Data extraction

The first and second author independently extracted data from the identified articles using the Joanna Briggs Institute (JBI) data extraction instrument designed for this review's purpose. The extracted data covered article characteristics, sample details, intervention specifics, and outcomes. Data on authors, publication year, country, and study design were collected as article characteristics. For sample details, we extracted criteria, numbers, age, gender, body mass index (BMI), comorbidities, respiratory device, and room setting. Intervention specifics included the protocol or procedure, time to initiate APP from admission and/or on-set, and the actual duration and/or frequency of APP. Outcome data comprised details of follow-up time and position, mortality rate, intubation rate, adverse events reported, and the mean and standard deviation (SD) of oxygen parameters and LOS. In instances where necessary, values were converted from median and interquartile or range to mean and SD using statistical formulas from Wan et al. (2014). GetData Graph Digitizer 2.26 was used to extract data from figures or graphs. The third and fourth authors independently confirmed the extracted data, and any disagreements were resolved through discussion and consensus.

Critical appraisal

The quality of studies was appraised independently by all authors using the JBI critical appraisal tools, specifically those for RCT, quasi-experimental (Tufanaru et al., 2020), and cohort studies (Moola et al., 2020). The assessment focused on methodological quality, addressing potential bias in study design, conduct, and analysis. The studies were classified as good or poor quality based on the percentage of "Yes" responses, which had to be greater than or equal to 70%. Discrepancies in appraisal were resolved through discussion and consensus.

Data synthesis

This study utilized the standardized mean difference (SMD) along with the corresponding 95% confidence interval (95% CI) for continuous outcome data, and the risk ratio (RR) with 95% CI for dichotomous outcome data. To account for the observed variability among the included studies, the inverse variance method and random-effects model were employed to calculate pooled effect sizes and their associated CI. SMD values were interpreted as trivial (SMD < 0.2), small (SMD 0.2 to <0.5), medium (SMD 0.5 to <0.8), and large (SMD ≥0.8) (Andrade, 2020). Forest plot was used to present the result. Heterogeneity among studies was assessed using the I^2 statistic and χ^2 test. A significance level of $p<0.05$ was adopted for the χ^2 test to ascertain the presence of heterogeneity (Higgins et al., 2022). I^2 values were then categorized as low (≤25%), moderate (≤50%), or high (≤75%) to provide insights into the degree of heterogeneity (Melsen et al., 2014). Sensitivity analyses were conducted to evaluate the potential influence of outlier studies. Potential outliers were identified using Cook's distances, with a cutoff value larger than 4/N, and studentized residuals with a cutoff value larger than 2 or -2. The impact of potential outlier studies was carefully assessed by comparing the overall results with and without their inclusion. Additionally, a sensitivity analysis was performed again by excluding one study at a time to examine the stability of the results. This analysis aimed to ensure the robustness of the findings and to identify any potential sources of variation or bias in the meta-analysis. All data synthesis was performed using the statistical software package, Review Manager 5.4.1 from the Cochrane Collaboration (Oxford, UK) and R 4.3.1.

Moderator analysis

Subgroup analysis and meta-regression were conducted for several variables that could potentially influence the observed effect sizes of primary outcome. Subgroup analysis was performed for age (adult and old), severity (mild [baseline PF ratio 201-300 or SF ratio 285-323], moderate [baseline PF ratio 100-200 or SF ratio <285], and severe [baseline PF ratio <100]), respiratory device (conventional oxygen therapy [nasal cannula, face mask, or non-rebreathing mask] and noninvasive ventilation [HFNC or CPAP]), room setting (ICU and Non ICU), BMI (non-obese [BMI <30] and obese[BMI ≥30]), study design (RCT, quasi-experimental, prospective cohort, retrospective cohort), time of admission to APP (<1 day, 1-3 days, >3 days), detail of position (only prone or combined positions), medication to maintain APP (used and not used), and total duration (<1 hour, 1-6 hours, >6 hours). The total duration was measured in hour per day for intubation and mortality rates, and per follow up time for PF ratio and SF ratio. Studies were categorized into subgroups

based on majority or mean reported data. Meta-regression was performed on sample size, mean severity (baseline PF ratio and SF ratio), mean age, mean BMI, time of admission to APP (day), and total duration (hour). For the PF ratio and SF ratio, subgroup analysis was also performed for position at follow-up (prone and supine) and follow-up time (after initiation and after finish), with meta-regression also focused on follow-up time after initiation (hour) and follow-up time after finish (hour). A result with p-value less than 0.05 indicated statistically significant. The meta-regression was performed using the statistical software package, Jamovi 2.3.28.

Results

Of 3284 records identified, we retrieved 57 full-text articles and ultimately included 39 studies. The details of our study selection process were recorded in the PRISMA 2020 diagram at Figure 1.

Characteristics of studies

The year of publication of the included studies ranged from 2015 to 2022. Most of these studies (32/39 studies) were conducted in single-center settings, with Italy (Scaravilli et al., 2015; Coppo et al., 2020; Cammarota et al., 2021; Chiumello et al., 2021; Musso et al., 2022) and the USA (Caputo, Strayer and Levitan, 2020; Thompson et al., 2020; Dubosh et al., 2021; Ehrmann et al., 2021; Fralick et al., 2022) being the most frequently represented study locations. The study designs varied, consisting of 14 prospective cohort studies, 12 retrospective cohort studies, eight RCTs, and five quasi-experimental studies.

Most of the included studies were of good quality (Supplementary file 2, Table S3). However, a few RCTs were of poor quality (Gad, 2021; Jayakumar et al., 2021; Kharat et al., 2021; Taylor et al., 2021; Fralick et al., 2022). The identified limitation of these RCTs included lack of blinding to participants and staff, inadequate allocation concealment, and differences in group characteristics. For the cohort studies, some studies lacked strategies to deal with incomplete follow-up. Detailed characteristics of each study are available in Table 1.

Characteristics of participants

The sample sizes in the studies ranged from 15 (Scaravilli et al., 2015) to 1121 patients (Ehrmann et al., 2021), totaling 4797 non-intubated ARDS patients. The mean age of patients varied across the studies, ranging from 45.7 (Liu et al., 2021) to 70.6 years (Wormser, Romanet and Philippart, 2021), with an overall mean age of 58.4 years. The majority of patients were male (59.6%), with a mean BMI ranging from 25.8 (Altinay et al., 2022; Koike et al., 2022) to 32.1 kg/m2 (Taylor et al., 2021). Hypertension was the most prevalent comorbidity, present in 24 out of 39 studies. Out of the included studies, Ding et al. (2020) and Scaravilli et al. (2015) studies were the only ones that did not involve patients diagnosed with or suspected of Covid-19. During the course of each study, most patients received treatment outside the ICU (22/39 studies), including in the emergency department (ED), general wards, and intermediate care units (IMCU). The patients had an overall mean baseline ratio of arterial oxygen partial pressure to fractional inspired oxygen (PF ratio) and peripheral oxygen saturation to inspiratory oxygen fraction (SF ratio) of 146.8 and 209.4, respectively, indicating a moderate severity of ARDS. In terms of oxygen therapy, 22 of the 39 included studies reported that the patients used conventional oxygen therapy. For a more detailed overview of the patient characteristics in each study, please refer to Table 1.

Characteristics of intervention

Rather than being based solely on patient tolerance (Winearls et al., 2020; Cammarota et al., 2021; Chiumello et al., 2021; Dubosh et al., 2021; Khanum et al., 2021; Solverson, Weatherald and Parhar, 2021; Dos Santos Rocha et al., 2022; Fazzini, Fowler and Zolfaghari, 2022), most studies (31/39 studies) implemented APP using well-defined procedures and protocols, including duration, frequency, and/or clear initiation and termination criteria to ensure consistent implementation across studies. The procedures included combined positions such as left lateral decubitus, right lateral decubitus, and upright sitting position (Caputo, Strayer and Levitan, 2020; Thompson et al., 2020; Winearls et al., 2020; Dubosh et al., 2021; Dueñas-Castell et al., 2021; Gad, 2021; Kharat et al., 2021; Misra, Pal and Pawar, 2021; Althunayyan et al., 2022; Kumar et al., 2022), strategically designed to optimize patient outcomes and safety. Additionally, various strategies were employed to sustain APP, such as the administration of medication (mild sedation (Scaravilli et al., 2015; Cammarota et al., 2021; Koike et al., 2022; Musso et al., 2022), analgesics (Cammarota et al., 2021; Chiumello et al., 2021; Koike et al., 2022; Lupieri et al., 2022; Musso et al., 2022), neuromuscular blocking agents (Dos Santos Rocha et al., 2022), or anxiolytics (Aisa et al., 2022; Oliveira et al., 2022)) and recreational means (music and additional pillows for comfort and support) (Thompson et al., 2020; Gad, 2021; Jayakumar et al., 2021; Silva Junior et al., 2021;

Sryma et al., 2021; Fralick et al., 2022; Ibarra-Estrada et al., 2022; Kumar et al., 2022; Lupieri et al., 2022; Musso et al., 2022; Othman, El-Menshawy and Mohamed, 2022). Bed positions were also adjusted to maintain the prone position (Sryma et al., 2021). The initiation of APP occurred from immediately upon admission (Caputo, Strayer and Levitan, 2020; Dubosh et al., 2021; Althunayyan et al., 2022) to five days after admission (Liu et al., 2021), with daily duration ranging from 0.16 (Taylor et al., 2021) to 16 (Khanum et al., 2021) hours and a maximum frequency of six sessions (Fazzini, Fowler and Zolfaghari, 2022). Detailed APP characteristics in each study are available in Supplementary file 2, Table S1.

Oxygenation status

There were eight oxygen parameters evaluated before and after APP, with PF ratio and SF ratio evaluated by 18 studies and 16 studies, respectively. The other six parameters were PaO2 (13 studies), SpO2 (19 studies), respiratory rate (25 studies), ROX index (6 studies), FiO2 levels (7 studies), and SaO2 (4 studies). Regarding the follow-up time, the majority of studies (26/39 studies) evaluated the oxygen parameters after the initiation of APP, ranging from 10 minutes (Coppo et al., 2020) to three weeks (Koike et al., 2022). Thus, most of these evaluations were performed while patients were still in the prone position. Only a subset of studies (16/39 studies) conducted follow-up assessments after APP had been finished, ranging from immediately after finishing APP (Dueñas-Castell et al., 2021; Misra, Pal and Pawar, 2021; Wormser, Romanet and Philippart, 2021; Althunayyan et al., 2022; Oliveira et al., 2022) to 12 hours afterward (Elharrar et al., 2020).

Intubation and mortality rates

Intubation and mortality rates were documented in over half of the encompassed studies, constituting 31 studies each. These event rates were not only examined during the entire hospital stay but also across various time intervals (such as upon admission, 24 hours, 48 hours, 28 days, and 90 days) and settings (including both the ward and ICU). In regard to these rates, the minimum observed value was consistent across both the APP and control groups, standing at 0% (Jagan et al., 2020; Taylor et al., 2021; Othman, El-Menshawy and Mohamed, 2022). Nevertheless, the maximum rates displayed variations. Specifically, for the intubation rate, the highest rates in the APP group were recorded at 31.8% upon admission (Dubosh et al., 2021), 26% within 24 hours (Caputo, Strayer and Levitan, 2020), 36.5% within 48 hours (Oliveira et al., 2022), 32.8% at 28 days (Ehrmann et al., 2021), and 48% for the entire hospitalization duration (Thompson et al., 2020). In contrast, the control group's rates fluctuated, reaching 42.9% at 28 days (Ibarra-Estrada et al., 2022) and 82.6% for the entire hospitalization period (Altinay et al., 2022). It is noteworthy that these findings showcasing lower intubation rates within the APP group align with the mortality rates, which predominantly remained lower compared to the control group. Specifically, the APP group exhibited rates of 66.7% at 28 days (Bahloul et al., 2021), 30.4% at 90 days (Fazzini, Fowler and Zolfaghari, 2022), 7.4% in the ward (Koike et al., 2022), 20% in the ICU (Scaravilli et al., 2015; Gad, 2021), and 24.4% for the entire hospital stay (Oliveira et al., 2022). Conversely, the control group's mortality rates were 70.5% at 28 days (Bahloul et al., 2021), 0% in the ward (Koike et al., 2022), 25.8% in the ICU (Koike et al., 2022), and 37.4% for the entire hospitalization period (Perez-Nieto et al., 2022).

Length of stay

Twenty studies provided information regarding the LOS for patients. Specifically, LOS was reported for patients within the ICU (7 studies), Covid-19 units (1 study), and encompassing the entire hospitalization period (17 studies). Notably, the LOS for the APP group within the ICU exhibited variability, ranging from 6.7±5.5 days (Altinay et al., 2022) to 12.6±7.4 days (Silva Junior et al., 2021). In the control group, the LOS ranged from 7±2 days (Gad, 2021) to 11.5±6.9 days (Jayakumar et al., 2021). This finding underscores the potential for a prolonged hospital stay for non-intubated ARDS patients who undergo the APP intervention compared to the control group. Moreover, considering the overall hospitalization period, the shortest and longest mean of LOS for the APP group were also exceeded those of the control group, 5.3±4.1 days (Taylor et al., 2021) and 28±5 days (Gad, 2021) in comparison to 5±3.8 days (Fralick et al., 2022) and 26±5 days (Gad, 2021), respectively. Then, the mean LOS within Covid-19 unit was exclusively reported for the APP group, with a value of 6±3.1 days (Khanum et al., 2021).

Adverse events

Among the 24 studies that examined the occurrence of adverse events, four studies reported no adverse events in the APP group (Coppo et al., 2020; Winearls et al., 2020; Fazzini, Fowler and Zolfaghari, 2022; Lupieri et al., 2022). In total, 27 adverse events were identified across the studies. While some studies did not specify the precise number of events, pain (45 events) and line dislodgment (46 events) emerged as the most prevalent

events. Then, among the 27 adverse events, pain, discomfort, as well as nausea and vomiting emerged as the most frequently documented adverse events (8 studies each). Additionally, it is noteworthy that certain adverse events such as device removal (Scaravilli et al., 2015; Solverson, Weatherald and Parhar, 2021), hemodynamic decompensation (Solverson, Weatherald and Parhar, 2021; Sryma et al., 2021; Kumar et al., 2022), pressure ulcers (Jayakumar et al., 2021; Solverson, Weatherald and Parhar, 2021; Taylor et al., 2021; Oliveira et al., 2022), nerve compression (Scaravilli et al., 2015; Jayakumar et al., 2021), pneumothorax (Musso et al., 2022), pressure neuropathies (Scaravilli et al., 2015), and emergent intubation (Taylor et al., 2021) were recognized as potential risks but were not manifest during the course of the studies. A detailed breakdown of the adverse events is available in Supplementary Material 2, Table S2.

Meta-analysis for primary outcomes

Our comprehensive analysis encompassed 17 studies with 22 subsets of data for the PF ratio, 14 studies with 26 subsets of data for the SF ratio, 14 studies with 14 subsets of data for the intubation rate, and 13 studies with 14 subsets of data for the mortality rate. This refined selection of studies followed the exclusion of one study (Silva Junior et al., 2021) for the PF ratio due to being identified as an outlier, and two studies (Jagan et al., 2020; Taylor et al., 2021) for the SF ratio due to incomplete data.

In the initial round of our iterative sensitivity analyses, certain data subsets were flagged as potential outliers. Specifically, a subset of Ehrmann et al.'s (2021) study was identified as a potential outlier for the SF ratio (Supplementary file 2, Table S5) and intubation rate (Supplementary file 2, Table S6). Additionally, subsets from the studies conducted by Aisa et al. (2022), Liu et al. (2021), and Silva Junior et al. (2021) were flagged as potential outliers for the PF ratio (Supplementary file 2, Table S4). Further examination revealed that, except for the intubation rate, these identified subsets data were found to substantially inflate the overall effect size, reduce precision, and contribute to the observed heterogeneity. Consequently, these subsets were excluded from the analysis to enhance the overall reliability of our results. In the subsequent round, even though several other studies emerged as potential outliers for both PF ratio and SF ratio, their exclusion did not substantially affect the overall effect size and heterogeneity (Supplementary file 2, Table S8).

Our meta-analysis demonstrated a medium improvement in oxygenation levels, with a SMD of 0.70 (95% CI=0.51, 0.88) for PF ratio (Figure 2) and 0.76 (95% CI=0.51, 1.01) for SF ratio (Figure 3). Moreover, the analysis revealed a RR of 0.62 (95% CI=0.49, 0.78) for intubation rate (Figure 4) and 0.66 (95% CI=0.51, 0.85) for mortality rate (Figure 5). The robustness of these findings was reinforced by the results of the leave-one-out sensitivity analysis, which revealed that the effect size ranged from 0.65 to 0.73 for the PF ratio, 0.71 to 0.79 for the SF ratio, 0.57 to 0.65 for the intubation rate, and 0.61 to 0.71 for the mortality rate. As a result, we confidently confirm that the positive effect of APP on oxygenation, intubation rate, and mortality in non-intubated ARDS patients is consistent and reliable.

However, it is important to note that our analysis revealed significant heterogeneity across the included studies, with I^2 values of 72% (χ^2 [21] =76.33, p<0.001) for PF ratio, 93% (χ^2 [25] =333.4, p<0.001) for SF ratio, 56% (χ^2 [13] =26.98, p=0.008) for intubation rate, and 54% (χ^2 [13] = 29.13, p=0.004) for mortality rate, suggesting high and consider-able variability in the effect sizes. Despite this heterogeneity, the Egger test and funnel plot, which assess publication bias, showed no evidence of bias for the PF ratio (Egger test value = 1.291, p=0.197), SF ratio (Egger test value = -0.442, p=0.659), intubation rate (Egger test value = -0.589, p=0.555), and mortality rate (Egger test value = -0.542, p=0.587). Funnel plots are available in Supplementary file 2, Figure S1-S4.

Meta-analysis for secondary outcomes

The respiratory rate showed a substantial reduction with an SMD of -0.82 (95% CI=-1.32 to -0.41), indicating a notable improvement in the oxygenation status (Supplementary file 2, Figure S5). PaO2 demonstrated a moderate improvement with an SMD of 0.57 (95% CI=0.40 to 0.75) (Supplementary file 2, Figure S6), while SpO2 exhibited a large improvement with an SMD of 0.97 (95% CI=0.71, 1.24), indicating considerable enhancement in oxygen saturation levels (Supplementary file 2, Figure S7). Similarly, SaO2 showed a significant improvement with an SMD of 0.90 (95% CI=0.34, 1.46), further supporting the positive effect of APP on oxygenation (Supplementary file 2, Figure S8). Conversely, FiO2 presented a moderate reduction with an SMD of -0.70 (95% CI=-1.20, -0.20), indicating a decrease in the fraction of inspired oxygen required by patients (Supplementary file 2, Figure S9). The ROX index, a reliable indicator of oxygenation, demonstrated a large improvement with an SMD of 1.62 (95% CI=0.63, 2.61), further corroborating the overall positive impact of APP on oxygenation status (Supplementary file 2, Figure S10). However, it is

essential to note that the analyses showed considerable heterogeneity for all parameters, as evidenced by the high I^2 values (ranging from 63% to 99%). These results highlight the significant variability in the effect sizes across the included studies.

Regarding the LOS and adverse events, our analysis did not reveal a significant impact of APP on both of these outcomes. The RR for LOS was -0.09 (95% CI=-0.26, 0.08), suggesting no substantial difference between the APP group and control group in terms of patient duration to stay (Supplementary file 2, Figure S11). Similarly, the RR for adverse events was 0.98 (95% CI=0.73, 1.32), indicating that the occurrence of adverse events did not significantly differ between the two group (Supplementary file 2, Figure S12). These findings were associated with moderate to high heterogeneity, with I^2 values of 62% for LOS and 39% for adverse events.

Moderator analysis

Among the 12 variables assessed, it is noteworthy that only the age, room setting, BMI, and time of admission to APP were not found to be associated with the effect size of the primary outcomes.

The type of respiratory device used (p=0.02), the position at follow-up (p=0.02), and the follow-up time (p=0.03) emerged as significant contributors to the PF ratio. Patients receiving noninvasive ventilation showed a more significant improvement in oxygenation (SMD=0.82, 95% CI=0.59 to 1.05) compared to those on conventional oxygen therapy (SMD=0.43, 95% CI=0.20 to 0.67). Moreover, patients assessed in the prone position exhibited the most pronounced effect size (SMD=0.95, 95% CI=0.70 to 1.20), compared to those assessed in the supine position (SMD=0.56, 95% CI=0.35 to 0.76). Additionally, patients assessed shortly after initiation of APP demonstrated a larger improvement in the PF ratio (SMD=0.87, 95% CI=0.65 to 1.09) compared to those assessed after the completion of APP (SMD=0.50, 95% CI=0.25 to 0.76) (Table 2).

For the SF ratio, two variables were identified as significant influencers of SF ratio post-APP: the severity of ARDS (p=0.001) and the total duration per follow-up (p=0.004). Patients with moderate ARDS (SF ratio <285) displayed a more substantial improvement in oxygenation (SMD=0.82, 95% CI=0.55 to 1.08) compared to those with mild ARDS (SF ratio 285-323) (SMD=0.24, 95% CI=0.02 to 0.46). Furthermore, the patients who underwent APP for more than six hours per follow-up had a significantly greater improvement in the SF ratio (SMD=1.15, 95% CI=0.77 to 1.53) compared to those with shorter duration (Table 2).

Specific to the intubation rate, significant differences in effect sizes were observed in the subgroup analysis of study design (p=0.001), detail of position used (p=0.04), and the use of medication assistance (p=0.03). The quasi-experimental study subgroup (RR=0.33, 95% CI=0.17, 0.62) displayed the lowest risk of intubation in patient using APP, compared to the RCT subgroup (RR=0.79, 95% CI=0.69, 0.90), retrospective cohort study subgroup (RR=0.46, 95% CI=0.31, 0.67), and even prospective study subgroup, which did not show significant association. Then, patients using only the prone position in their protocol exhibited a lower intubation risk (RR=0.55, 95% CI=0.47, 0.64) compared to those using combined positions (RR=2.44, 95% CI=0.59, 10.04), which was not statistically significant. Moreover, patients receiving any medication to maintain APP were associated with a lower risk of intubation (RR=0.31, 95% CI=0.17, 0.59) compared to those without medication (RR=0.67, 95% CI=0.54, 0.84).

Moving to the analysis of the mortality rate, the effect size was significantly difference in the subgroup analysis of the respiratory device used (p=0.04) and study design (p=0.001). Specifically, within the conventional oxygen therapy subgroup, APP was associated with a substantial reduction in the risk of mortality (RR=0.54, 95% CI=0.44, 0.66) compared to noninvasive ventilation (RR=0.78, 95% CI=0.58, 1.05). Additionally, the subgroup of quasi-experimental studies (RR=0.33, 95% CI=0.18, 0.58) and retrospective cohort studies (RR=0.51, 95% CI=0.35, 0.76) exhibited a more pronounced reduction in mortality risk associated with APP compared to other study designs, which did not show significant association.

In our meta-regression analysis for the PF ratio, intubation rate, and mortality, none of the examined potential moderator variables, including sample size, mean severity, mean age, mean BMI, total duration, follow-up time after initiation, and follow-up time after finish, were found to be significantly associated with the effect size of APP in non-intubated ARDS patients (p>0.05). Additionally, due to the inclusion of fewer than 10 studies, certain variables were not estimable for the PF ratio, mortality rate, and intubation rate. On the other hand, in the case of the SF ratio, our meta-regression revealed that mean severity (SMD=-0.004, 95% CI=-0.009 to -0.001), mean body mass index (SMD=-0.228, 95% CI=-0.414 to -0.041), total duration per follow-up (SMD=0.016, 95% CI=0.005 to 0.028), and follow-up time after initiation (SMD=0.003, 95% CI=0.002 to 0.005) had a significant impact on the effectiveness of APP (p<0.05). Patients with more severe

ARDS, lower body mass index, longer total duration per follow-up, and longer follow-up time after initiation showed a larger improvement in SF ratio with the implementation of APP. The other potential moderator variables did not show a significant association with the effect size of APP on SF ratio (p>0.05) (Table 3).

Discussions

This comprehensive meta-analysis amalgamated findings from a diverse array of studies, encompassing 13 experimental studies and 26 cohort studies, collectively involving a substantial cohort of 4,797 non-intubated ARDS patients, predominantly afflicted by Covid-19. The culmination of these efforts yielded robust evidence supporting the substantial efficacy of the prone position in enhancing oxygenation status among this patient population. Notably, the implementation of APP also exerted a considerable impact in reducing both intubation and mortality rates in comparison to the control groups.

In line with the consistent improvement in oxygenation observed in previous studies (Aeen et al., 2021; Fazzini et al., 2021; Reddy et al., 2021; Ashra et al., 2022; Peng et al., 2023), our analysis unveiled a broader positive effect across additional parameters, including PaO2, SpO2, SaO2, ROX index, respiratory rate, and FiO2. Moreover, our further investigations highlighted that these enhancements were significantly influenced by various patient and intervention characteristics. The augmentation of the SF ratio was particularly pronounced in patients who exhibited moderate to severe ARDS, non-obese, and underwent APP for more than six hours before evaluation. Concerning duration, the included studies consistently maintained or repeated the APP until the follow-up time, contributing to the sustained improvement in oxygenation over the longer follow-up periods. Interestingly, this finding contrasts with the study by Ashra et al. (2022), which reported a significant positive effect size on obese patients, while also aligning with the study of Fazzini et al. (2021), who noted improvement after more than four hours of APP.

Our findings suggest that the limited impact of APP on higher BMI could be attributed to potential challenges in administering the intervention effectively. Higher BMI patients might require additional adjustments or personalized approaches during prone position (Guérin et al., 2013). Furthermore, Ashra et al. (2022) did not exclusively focus on non-intubated patients and had smaller sample size. Further well-controlled investigations are required to clarify this relationship.

As for the PF ratio, it exhibited more substantial improvements in patients who were subjected to noninvasive ventilation and were assessed while in the prone position. A similar trend was also evident in the context of the SF ratio when considering the influence of respiratory devices, although the subgroup differences in this case did not reach statistical significance. This finding aligns with Chilkoti et al. (2022) who observed that noninvasive ventilation during PP improves oxygenation without significant side effects and has a feasibility ranging from 36-100%.

Moreover, both the SF ratio and PF ratio showed more noticeable improvements when evaluated from the initiation of the intervention, during its administration, as opposed to post-intervention completion. This suggests that the immediate effects of APP may be more substantial during the intervention itself, with a potential decline in the immediate improvements after the completion of prone positioning. Some studies have also posited that this could be attributed to lung recruitment dynamics and time-dependent effects (Coppo et al., 2020; Jayakumar et al., 2021). Furthermore, considering factors such as the influence of other therapies, patient-specific characteristics, or even the possibility of recurrence of lung collapse, further investigation is needed to validate and comprehend the underlying mechanisms responsible for these observed associations.

The distinct physiological and clinical insights captured by the SF ratio and PF ratio underscore their significance in contributing valuable inputs to the decision-making process. This not only enriches our understanding of their respective influencing factors but also holds implications for tailoring patient care and optimizing treatment protocols in non-intubated ARDS cases. The results of this meta-analysis further consolidate the evolving body of evidence, affirming the vital role of the prone position and its potential to reshape the management landscape for critically ill patients, particularly those grappling with Covid-19-related respiratory challenges.

In the context of intubation risk reduction, the insight provided by Peng et al. (2023) highlights that the observed reduction might not reach statistically significant within observational studies. Interestingly, our analysis introduces a nuanced perspective, revealing that retrospective cohort studies exhibit a more pronounced reduction in intubation risk, surpassing RCTs and being second only to quasi-experimental

studies. This intriguing trend also extends to mortality risk, diverging from previous study outcomes that reported no significant reduction. This revelation underscores the potential influences of study design on the efficacy of APP, suggesting that real-world clinical scenarios captured by cohort studies might offer unique insight into the impact of this intervention.

Upon delving into the nuanced examination of intubation and mortality rates, although not all analyzed variables exhibited statistically significant subgroup differences, certain patient characteristics emerged as significant determinants. Notably, patients under the age of 60, with moderate severity of ARDS, non-obese, receiving conventional oxygen therapy, and treated outside the ICU experienced significantly lower risks of intubation and mortality. These discernible patient attributes underscore the potential benefits of implementing the prone position as an early intervention in the management of non-intubated ARDS, particularly when the patient's lung condition has not deteriorated significantly. Furthermore, these findings underscore the importance of timely and strategic use of the prone position, especially in cases where the patient's respiratory status is relatively stable.

For the characteristics of the APP itself, a noteworthy observation emerges: an intervention protocol centered exclusively on the prone position, omitting other positional changes, and not relying on medication assistance, but administered for a duration of more than six hours per day, resulted in a significant reduction in both intubation and mortality risks. While these findings necessitate further corroboration through additional studies, they underscore the inherent potency of the prone position as a primary and self-sufficient intervention strategy. This emphasizes the pivotal significance of upholding consistent and dedicated prone positioning for extended durations to harness its maximum potential and achieve improved outcomes.

Moreover, concerning intubation rates, a lower risk of intubation was also observed in patients who underwent APP initiation within one day of admission, reinforcing the notion of implementing APP as early as feasible. Additionally, it's noteworthy that a lower risk of events was also evident in patients who utilized medication to maintain the prone position. However, the confidence interval of the effect size was wide, and the limited number of studies may introduce some degree of uncertainty, particularly regarding the use of medication in conjunction with the prone position. Further research is warranted to provide a more comprehensive understanding of the potential benefits and limitations associated with this aspect of intervention.

Notably, no significant variation in the LOS was evident between the APP and control groups, whether measured in the ICU or across the entire hospital stay. This could potentially be attributed to the limited power in assessing LOS as a secondary outcome in the included studies. Therefore, a more detailed and dedicated investigation is necessary to elucidate this finding comprehensively. Nevertheless, our findings provide reassurance regarding the safety of APP, as the analysis indicates that its implementation did not lead to a significant increase in the risk of adverse events. Notably, no serious adverse events like hemodynamic decompensation or emergent intubation were reported during the process. Among the encountered adverse events, the most frequent were pain and line dislodgment.

While our analysis yields promising outcomes and does not solely rely on sample size, as studies with smaller sample sizes can provide reliable effect size estimates, we acknowledge the limitation that our included RCTs were limited in number and exhibited poor quality. Consistent with the finding from Cruz et al. (2022), which highlighted a high risk of bias, particularly the performance bias, in all of the included RCTs. Although the nature of APP might inherently preclude blinding in the study, measures to minimize bias, especially toward the assessors, such as concealing participant allocation, should be considered. Rigorous, well-designed trials remain essential cornerstones of evidence-based practice, providing a stronger foundation for understanding the true impact of APP. Therefore, the imperative for more robust and well-designed studies is clear, both to bolster the evidence base and to address potential biases in assessing the effectiveness of APP in non-intubated ARDS patients. Future research should prioritize improved study designs, including blinding measures, to enhance the validity and reliability of findings in investigating APP as an oxygenation strategy for non-intubated ARDS patients.

Our methodology approach, which exclusively focused on cohort and experimental designs yielded in a more extensive patient cohort, encompassing cases beyond those affected by Covid-19, even though the representation was limited to before pandemic. Additionally, the study successfully incorporated feedback obtained from previous research efforts, especially in facilitating advanced analysis of primary

outcomes, which encompassed various moderating factors and summarized a comprehensive protocol (Aeen et al., 2021; Li et al., 2022; Peng et al., 2023; Wang et al., 2023). As a result, we believe this study can significantly enhance the depth of perspectives on the efficacy of prone positioning in non-intubated ARDS patients and provide a valuable contribution to inform the clinical decision-making process.

However, this study is not without its limitations, which warrant careful consideration. First, a major limitation in analyzing the outcomes is the uneven distribution of experimental and observational studies, and especially for the oxygenation parameter is the reliance on single-arm data. While observational studies are valuable in providing real-world insights, the lack of control groups in some included studies may introduce bias and limit the ability to establish direct cause-and effect-relationships. Some of the included RCTs were of poor quality, designed primarily for feasibility assessment or as pilot studies, which can introduce bias and affect the overall robustness of the findings. Second, several data had to be derived using statistical formulas and extracted from the graphs, potentially impacting the accuracy and precision of the results. Lastly, several subgroups had a small number of studies, and the presence of heterogeneity across studies remains a challenge. Although sensitivity analyses were conducted to address this issue, the influence of unmeasured confounders and the potential for residual heterogeneity should be acknowledged.

The limited number of experimental studies and the potential biases in some included studies highlight the need for rigorous and controlled trials to establish a more solid evidence base for the efficacy of APP in non-intubated ARDS patients. Healthcare providers can utilize our findings to develop well-structured APP protocol. This protocol should involve early initiation for non-intubated ARDS patients under 60-year-old, non-obese, with moderate severity, using conventional oxygen therapy, and treated outside the ICU. It should also incorporate APP for over six hour per day, avoiding combined position and medication assistance.

Conclusion

Our study provides evidence that supports the safety and effectiveness of the prone position in improving oxygen levels, while also reducing intubation and mortality rates among non-intubated ARDS patients. However, we did not find significant benefits in reducing LOS. To make APP more effective, factors like the patient's severity, the type of respiratory device, BMI, detail of position, use of medication assistance, total duration, time to follow-up, and position at follow-up should be considered. This study underscores the importance of a holistic approach in implementing prone positioning. While our findings are robust, further research and trials are needed to refine prone positioning protocols for non-intubated ARDS patients.

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Competing interests

The authors declare no conflict of interest that could have influenced the work described in this paper

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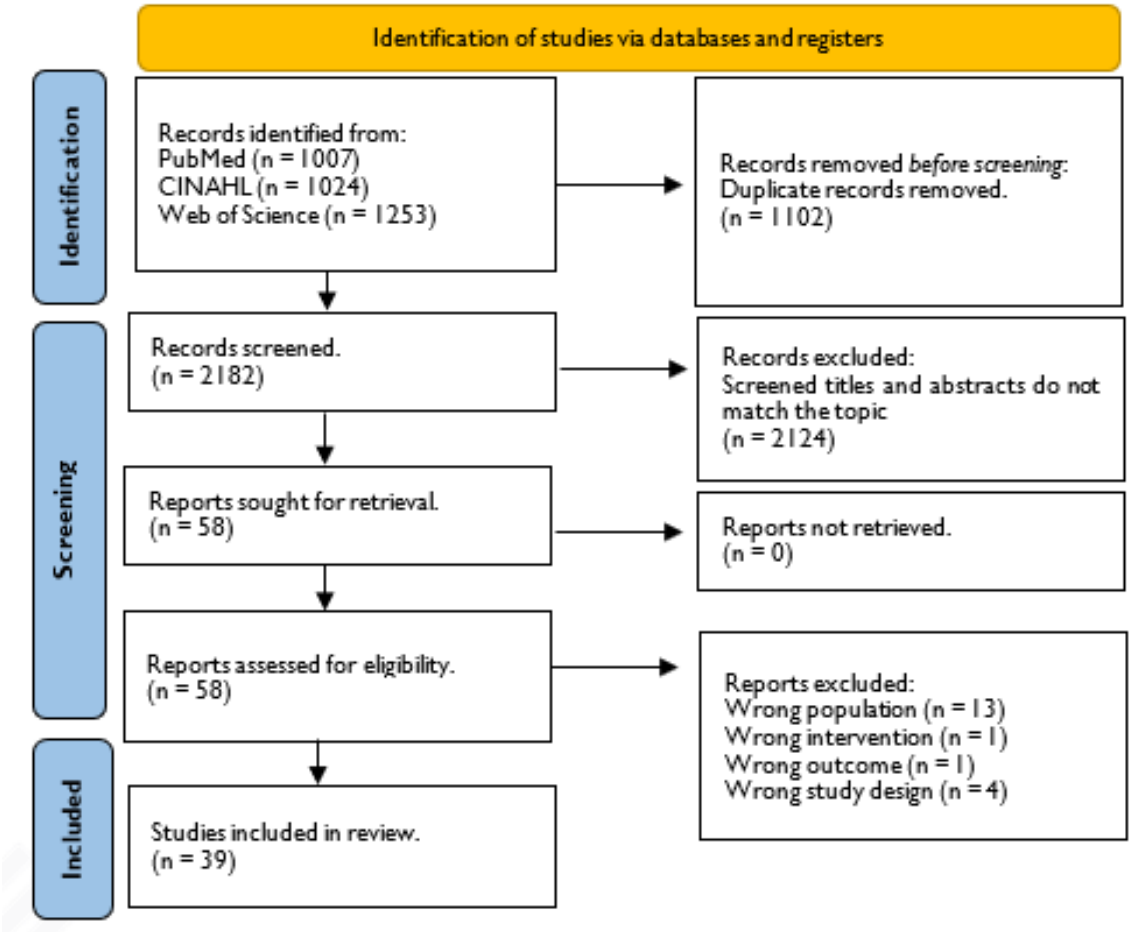

Figure 1. Process of study selection

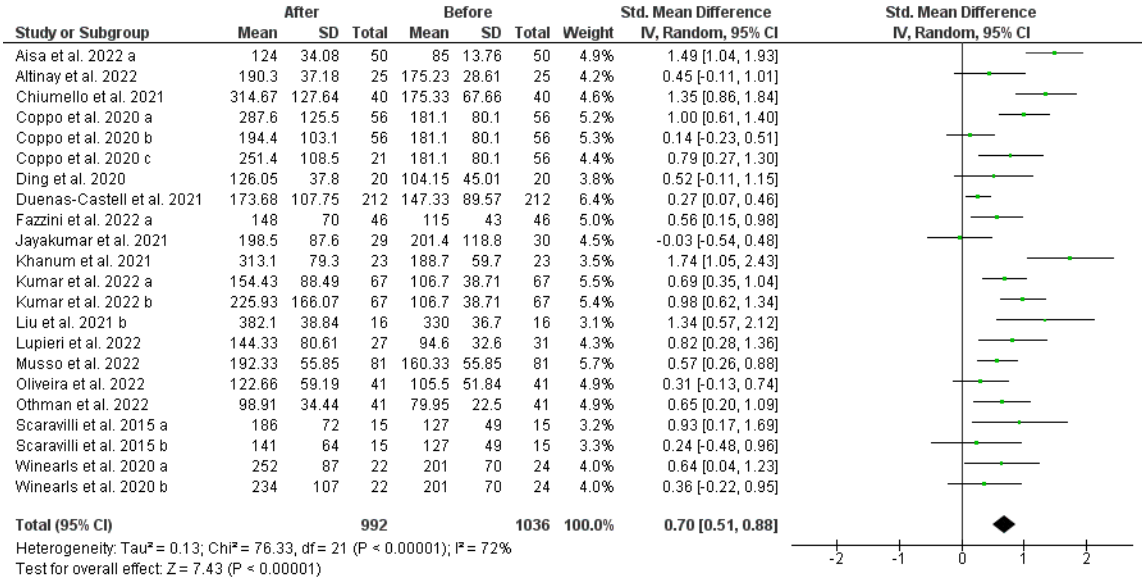

Figure 2. Forest plot of the effect of awake prone position on PF ratio

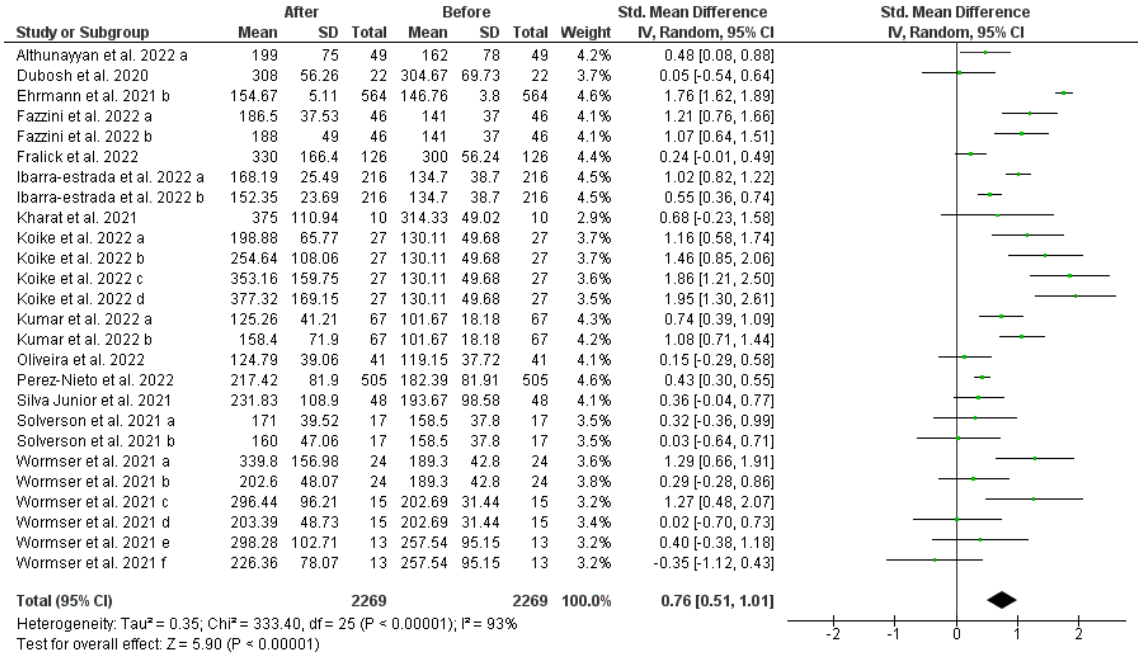

Figure 3. Forest plot of the effect of awake prone position on SF ratio

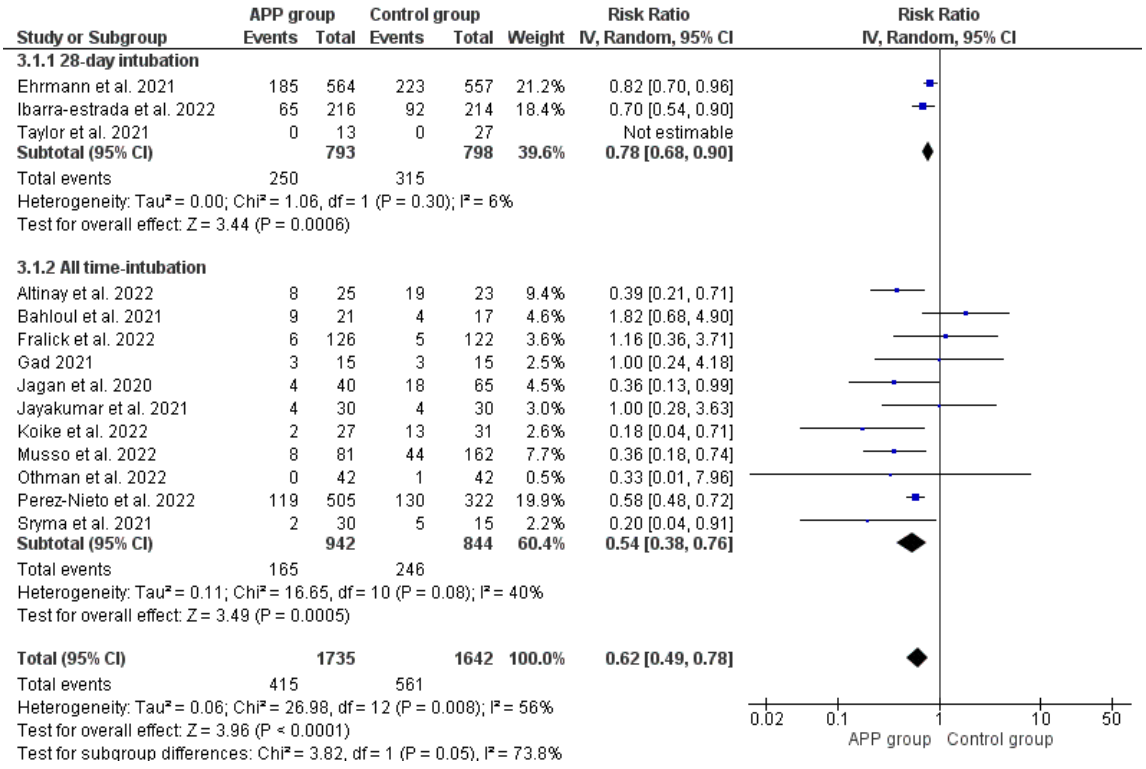

Figure 4. Forest plot of the effect of awake prone position on intubation rate

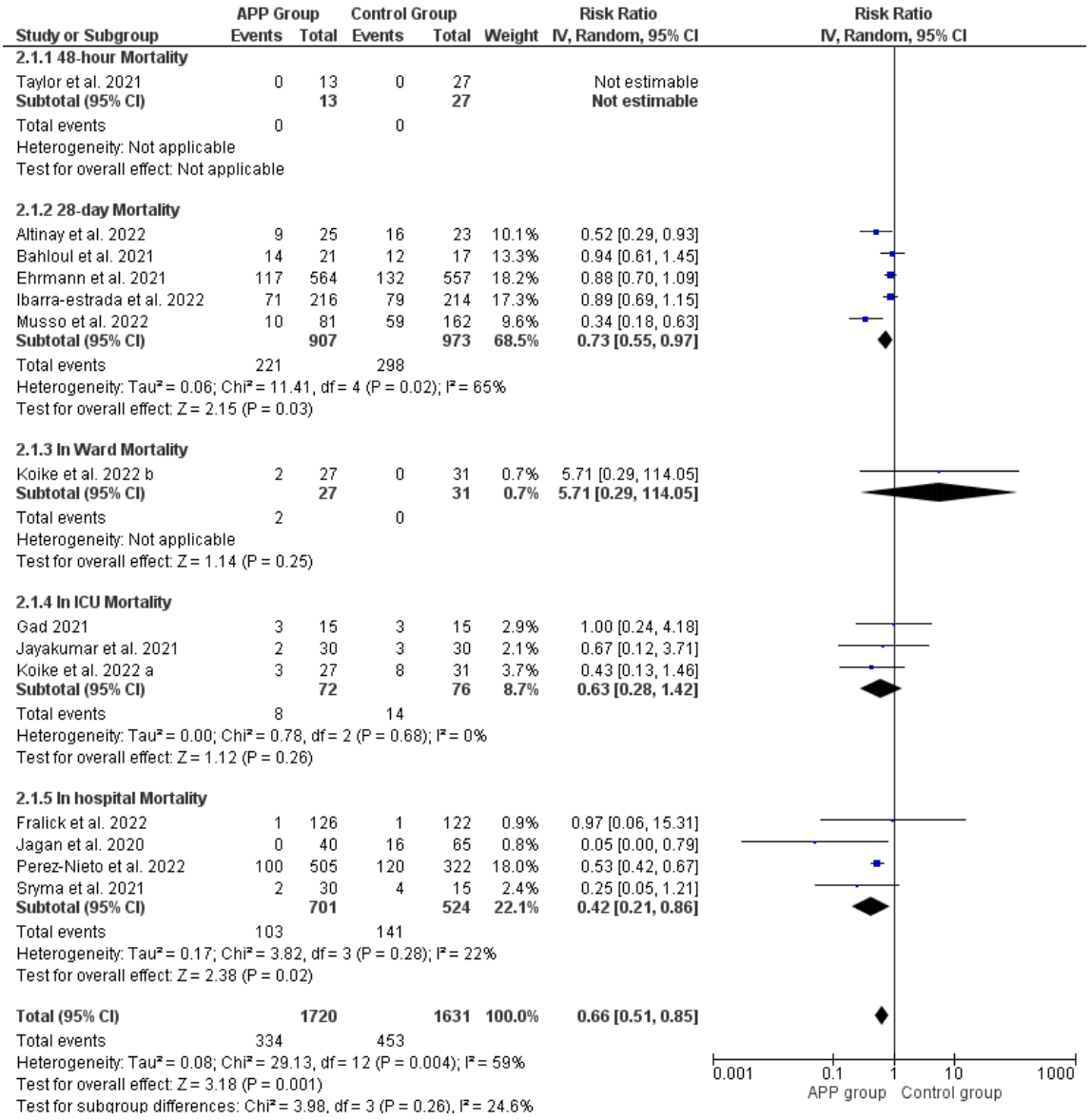

Figure 5. Forest plot of the effect of awake prone position on mortality rate

Table 1. Detail of included studies

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP[a]	Oxygenation Parameters	Time to follow up (position)
Aisa et al./2022	Single center, Drogheda, Ireland	Prospective cohort	Covid-19 patients with SpO_2 <90% or PaO_2 <10 kPa requiring any oxygen support	50	23 (46%)	56.2±11.9	29.5±3.7	PF ratio 85±13.7	**Hypertension**; COPD; CKD; Asthma; Autoimmune disease	HFNC, NIV	Ward	**Duration**: 8.5 ± 3.13 hours/day	PF ratio; PaO_2; SpO_2; FiO_2; RR	30 mins after initiated (prone); 1 hour after initiated (prone)
Althunayyan et al./2022	Single center, Riyadh, Saudi Arabia	Prospective cohort	Covid-19 patients with SpO_2 <94%, RR >30, and accessory muscle usage	49	40 (81.6%)	53.4±11.3	Obese excluded	SF ratio 162±78	Hypertension; **Diabetes**; Sickle cell anemia; Hypothyroidism; Asthma; Parkinson; Ischemic heart disease	**Face mask**, NRM, nasal cannula	ED	**Duration**: 4 hours/day	SF ratio; SpO_2; RR	After finished (supine)
Altinay et al./2022	Single center, Istanbul, Turkey	Retrospective cohort	Covid-19 patients with PF ratio <300 despite using NRM 6 L/min	48 PP: 25 CG: 23	20 (41.7%) PP: 11 (44%) CG: 9 (39.1%)	67.3±11.7 PP: 62.4±10.9 CG: 72.6±10.1	25.8±2.9 PP: 25.1±2.5 CG: 26.6±3.1	PF ratio: 177.6±36.1 PP: 175.2±28.6 CG: 180.2±42.6	**Hypertension**; Diabetes; CAD; COPD; CHF; CKD; Cancer; Other	NRM	ICU	**Duration**: 12 hours/day	PF ratio; PaO_2; SpO_2	1 day after initiated (supine)
Bahloul et al./2021	Single center, Sfax, Tunisia	Prospective cohort	Covid-19 patients with SpO_2 <92% despite using face mask or HFNC	38 PP: 21 CG: 17	PP: 16 (76%) CG: NR	60.8±10.7 PP: 61.4±9.5 CG: 60±12	Obese 14 (36.8%) PP: 10 (48%) CG: 4 (24%)	PF ratio 84.4±30.8 PP: 88±37 CG: 80±20	**Hypertension**; Diabetes; COPD	Face mask, **HFNC**	ICU	**Duration**: NR	SpO_2; RR	1 hour after initiated (prone)
Cammarota et al./2021	Single center, Italy	Prospective cohort	Covid-19 patients with PF ratio <200 mmHg	20	16 (80%)	63.7±14.4	28.3±4	NR	**Hypertension**; Other; Cancer; Diabetes; Dyslipidemia; CKD; Cardiovascular disease;	NIV	ICU	**Duration**: NR	SpO_2; RR	1 hour after initiated (prone)
Caputo, Strayer and Levitan /2020	Single center, New York, USA	Prospective cohort	Covid-19 patients with SpO_2 <90% and without resolution (SpO_2 >93%) despite any oxygen support	50	30 (60%)	59±13.7	NR	NR	NR	Nasal cannula, NRM	ED	**Duration**: NR	SpO_2	5 mins after initiated (prone)
Chiumello et al./2021	Single center, Milan, Italy	Quasi-experimental	Covid-19 patients with PF ratio <300mmHg and PEEP ≥5 cmH_2O	40	26 (65%)	60±11.5	27.7±4.6	PF ratio 175.3±67.7	**Hypertension**; Diabetes; Tumor; Immunosuppression	Helmet CPAP	IMCU	**Duration**: 3 hours/day	PF ratio; PaO_2; RR	3 hours after initiated (prone)
Coppo et al./2020	Single center, Monza, Italy	Prospective cohort	Covid-19 patients, required any oxygen support	56	44 (79%)	57.4±7.4	27.5±3.7	PF ratio 181.1±80.1	**Hypertension**; Myocardial infarction; Vascular disease; Chronic bronchopulmonary disease; Gastric or liver disease; Diabetes; Cancer	**Helmet CPAP**, NRM, venturi mask	Ward, ED, IMCU	**Duration**: 3.33±0.76 hours/day	PF ratio; PaO_2; SpO_2; SaO_2; FiO_2; RR	10 mins after initiated (prone); 1 hour after finished (supine); 5 days after initiated (supine)

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP[a]	Oxygenation Parameters	Time to follow up (position)
Ding et al./2020	Multicenter, PR China	Prospective cohort	ARDS patients on PEEP ≥ 5 cmH_2O and FiO_2 0.5 with PF ratio <200 mmHg	20	13 (65%)	50±10	NR	PF ratio 104.2±45	NR	HFNC, NIV	ICU	**Duration**: 1.84±1.07 hours/session **Frequency**: 2.04±1.22 session/day **Given for**: 3.32±3.09 days	PF ratio	30 mins after initiated (prone)
Dubosh et al./2021	Single center, Massachusetts, USA	Prospective cohort	Covid-19 patients dependent on nasal cannula or NRM to maintain SpO_2 >93%	22	14 (64%)	58.7±11.9	32±4.6	SF ratio 304.7±69.7	**Hypertension**; Diabetes; CAD; Cancer; COPD; Arrhythmia; Hyperlipidemia; Renal disease; Thyroid disease; Asthma	Nasal cannula, NRM	ED	**Duration**: 111±74.49 minutes	SF ratio; SpO_2; FiO_2; RR	30 mins after initiated (prone)
Duenas-Castell et al./2021	Single center, Cartagena, Colombia	Retrospective cohort	AHRF and suspected Covid-19 patients with PF ratio <300 mmHg	212	142 (67%)	61.6±18.06	Obese: 11 (5.2%)	PF ratio 147.3±89.6	**Hypertension**; Diabetes; Asthma; COPD; CKD	Nasal cannula, face mask	ED, ward, ICU	**Duration**: NR **Given for**: 1.73±1.64 days	PF ratio; SpO_2; RR	After finished (supine)
Ehrmann et al./2021	Multicenter, Canada; France; Ireland; Mexico; USA; Spain	RCT	Covid-19 patients on HFNC and SF ratio ≤315	1121 PP: 564 CG: 557	746 (66.5%) PP: 380 (67%) CG: 366 (66%)	61.1±13.7 PP: 61.5±13.3 CG: 60.7±14.0	29.7±4.6 PP: 29.7±4.6 CG: 29.7±4.6	SF ratio 148.2±43.5 PP: 146.7±3.8 CG: 148.6±43.1	Chronic heart disease; COPD; CKD; Severe liver disease; **Diabetes**; Cancer	HFNC	Ward, **ICU**, IMCU, ED	**Duration**: 5.6±4.4 hours/day; 2.73±2.08 hours/session **Given for**: 14 days	SF ratio; RR; ROX index	30 min to 1 hour after initiated (prone); 30 min to 1 hour after finished (supine)
Elharrar et al./2020	Single center, France	Quasi-experimental	Covid-19 and hypoxic respiratory failure patients required any oxygen support	24	16 (67%)	66.1±10.2	Obese: 5 (23%)	NR	Hypertension	**Nasal cannula**, HFNC	Outside ICU	**Duration**: >3 hours/day	PaO_2	1-2 hours after initiated (prone); 6-12 hours after finished (supine)
Fazzini, Fowler and Zolfagh/2022	Single center, London, UK	Prospective cohort	Covid-19 patients on face mask, HFNC or CPAP	46	NR	53.5±42.2	Obese excluded	PF ratio 115±43	NR	**HFNC**, face mask	Ward	**Duration**: 6.3±9.9 hours/session **Frequency**: 1-6 session/day	PF ratio; SF ratio; RR	During (prone); 1-4 hours after finished (supine)
Fralick et al./2022	Multicenter, Canada, USA	RCT	Highly suspected or confirmed Covid-19 patients required any oxygen support with FiO_2 >0.5	248 PP: 126 CG: 122	159 (64.1%) PP: 82 (65%) CG: 77 (63%)	55.4±15.6 PP: 57.5±17.2 CG: 53.3±13.5	NR	SF ratio 301.8±55.2 PP: 300±56.2 CG: 303.7±54	Diabetes; **Hypertension**; COPD or asthma; CHF	**Nasal cannula**, face mask, HFNC	Ward	**Duration**: 2.5 hours/day; 6.76±8.47 hours/3days **Given for**: 3 days	SF ratio	3 days after initiated (supine)
Gad/2021	Single center, Qena, Egypt	RCT	Covid-19 patients with PF ratio <200mmHg	30 PP: 15 CG: 15	17 (56.7%) PP: 9 (60%) CG: 8 (53%)	46.5±17.6 PP: 49.7±19.6 CG: 43.3±14.7	Obese 5 (16.7%) PP: 3 (20%) CG: 2 (13.3%)	PF ratio 126.9±63 PP: 126±62.1 CG: 127.7±63.8	**Hypertension**; Diabetes; COPD	**NRM**, NIV	ICU	**Duration**: 1-2 hours/session **Given for**: 3 days	PaO_2; SaO_2	3 days after initiated (supine)

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP [a]	Oxygenation Parameters	Time to follow up (position)
Ibarra-Estrada et al./2022	Multicenter, Mexico	RCT	Covid-19 patients with SpO_2 <90% despite using NRM 15 L/min	430 PP: 216 CG: 214	258 (60%) PP: 132 (61.1%) CG: 126 (58.8%)	58.4±15.8 PP: 58.6±15.8 CG: 58.2±15.8	30.2±4.2 PP: 30.3±4.6 CG: 30±3.8	SF ratio 135.1±38.3 PP: 134.7±38.7 CG: 135.5±37.9	Hypertension; CAD; Heart failure; CLD; CKD; Severe liver disease	HFNC	ICU, **IMCU**	**Duration**: 9.3±5.4 hours/day; 3.33±0.44 hours/session **Frequency**: 4±1.5 session/day **Given for**: 6.23±3.95 days	SF ratio; ROX index; RR	1 hour after initiated (prone); 1 hours after finished (supine)
Jagan et al./2020	Single center, Grand Island, Nebraska	Retrospective cohort	Covid-19 patients with hypoxic respiratory failure	105 PP: 40 CG: 65	57 (54.3%) PP: 37 (56.9%) CG: 20 (50%)	59.7±15.9 PP: 65.8±16.3 CG: 56±14.4	30.1±7.8 PP: 31.7±8.5 CG: 29.1±7.2	NR	**Hypertension**; Diabetes; COPD; CKD; Asthma; Heart failure; CAD; Rheumatoid arthritis; Cancer; Immunocompromised	NR	Outside ICU	**Duration**: NR **Given for**: 28 days	SF ratio	Every 4 hour for the first 48 hours (NR)
Jayakumar et al./2021	Multicenter, India	RCT	Covid-19 patients with PF ratio 100-300 mmHg, or required any oxygen support ≥4 L/min to maintain SpO_2 ≥92%	60 PP: 30 CG: 30	50 (83.3%) PP: 25 (83.3%) CG: 25 (83.3%)	56.1±11.7 PP: 54.8±11.1 CG: 57.3±12.1	27±4.6 PP: 28.2±5.7 CG: 25.8±2.6	PF ratio 193.5±122.8 PP: 201.4±118.8 CG: 185.6±126.1	Hypertension; **Diabetes**; Asthma, Pulmonary fibrosis	**Face mask**, NRM, HFNC, NIV, nasal cannula	ICU	**Duration**: 1.67±0.7 hours/session; 4 hours/day	PF ratio	2 hours after finished (supine)
Khanum et al./2021	Single center, Karachi, Pakistan	Retrospective cohort	Covid-19 patients with SpO2 room air <94%	23	21 (91.3%)	54.5±11.7	27.5±3.3	PF ratio 188.7±59.7	**Hypertension**; Diabetes; Ischemic heart disease; CKD; COPD; Malignancy; Immunocompromised	NIV	IMCU	**Duration**: 2.5-16 hours/day **Given for**: 6±3.16 days	PF ratio	At the last session (supine)
Kharat et al./2021	Single center, Geneva, Switzerland	RCT	Covid-19 patients required nasal cannula 1-6L/min to obtain SpO_2 90-92%	27 PP: 10 CG: 17	17 (63%) PP: 6 (60%) CG: 11 (65%)	57.8±12.5 PP: 54±14 CG: 60±11	28.2±4.8 PP: 29.7±5.3 CG: 27.3±4.2	SF ratio 331.9±63.6 PP: 314.3±49 CG: 342.3±68.7	**Hypertension**; Diabetes; CKD	Nasal cannula	Ward	**Duration**: 4.91±3.6 hours/day	SF ratio; RR	24 hour after initiated (supine for 1 hour)
Koike et al./2022	Single center, Sagamihara, Japan	Retrospective cohort	Covid-19 patients with FiO_2 ≥0.4	58 PP: 27 CG: 31	28 (48.3%) PP: 20 (74%) CG: 8 (25.8%)	64±17.1 PP: 67.7±17.2 CG: 60.7±16.3	25.8±5.4 PP: 26±5.4 CG: 25.7±5.4	SF ratio 153±52.1 PP: 130.1±49.7 CG: 172.9±45.6	**Hypertension**; Diabetes; Hyperlipidemia; CKD; Hemodialysis; COPD; Asthma; Interstitial pneumonia	**Face mask**, HFNC, NPPV	ICU	**Duration**: 3±1.56 hours/session **Frequency**: 2.3±0.7 session/day **Given for**: 12±7.04 days	SF ratio; ROX index; RR	3 days after initiated (NR); 1 week after initiated (NR); 2 weeks after initiated (supine); 3 weeks after initiated (supine)
Kumar et al./2022	Single center, Delhi, India	Prospective cohort	Covid-19 patients with SpO_2 <94% and RR ≥25 despite using nasal cannula 6 L/min or NRM 15 L/min	102	65 (63.7%)	57.9±10	Obese excluded	PF ratio 106.7±38.71	NR	HFNC	ICU	**Duration**: 6.8±3.9 hours/session	PF ratio; SF ratio; PaO_2; RR;	After first session (supine); After last session (supine)

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP [a]	Oxygenation Parameters	Time to follow up (position)
Liu et al./2021	Single center, Sichuan, PR China	Retrospective cohort	Mild Covid-19 patients	28 Early PP: 13 Late PP: 16	12 (42.9%) Early PP: 5 (38%) Late PP: 7 (43%)	45.7±14.2 Early PP: 42.6±13.2 Late PP: 48.3±14.5	NR	PF ratio 328.2±32.4 Early PP: 326±25.9 Late PP: 330±36.7	NR	Nasal cannula	Outside ICU	**Duration of early PP**: 12.5±0.66 hours/day **Duration of late PP**: 12.6±0.78 hours/day **Early PP given for**: 11.1±4.17 days **Late PP given for**: 16.9±5.2 days	PF ratio; RR	1 day after initiated (supine)
Lupieri et al./2022	Single center, Lausanne, Switzerland	Retrospective cohort	Covid-19 patients with PF ratio <200mmHg	31	23 (74%)	60±12	28.3±5.7	PF ratio 94.6±32.6	Cardiovascular disease; Hypertension; Diabetes; Respiratory comorbidities; Immunocompromised	NR	ICU	**Duration**: ≥45 minutes/session **Frequency**: 3.3±3.9 session/patient	PF ratio; PaO_2; SpO_2; FiO_2; RR;	After the first session initiated (prone)
Misra, Pal and Pawar/2021	Single center, Madhya Pradesh, India	Quasi-experimental	Covid-19 patients required any COT	400	NR	NR	NR	NR	NR	COT	Ward, ICU	**Duration**: NR	SpO_2	After finished (supine)
Musso et al./2022	Single center, Turin, Italy	Quasi-experimental	Covid-19 patients with PF ratio <200mmHg using FiO2 50% or NRM, and required NIV	243 PP: 81 CG: 162	178 (73.3%) PP: 62 (76%) CG: 116 (72%)	68.8±12.3 PP: 67.7±11.3 CG: 69.3±12.7	28±4.8 PP: 27.8±4.6 CG: 28.1±4.9	PF ratio 156.3±61.1 PP: 160.3±55.8 CG: 154.3±63.5	Diabetes; **Hypertension**; COPD; Asthma; CAD; CKD; Chronic atrial fibrillation; Cancer; Immunocompromised	NIV	IMCU	**Duration**: 12.03±2.79 hours/day **Frequency**: 2±1.5 sessions/day **Given for**: 6.3±2.2 days	PF ratio; PaO_2; FiO_2; RR	7 days after initiated (supine for 1 hour)
Oliveira et al./2022	Single center, Rio Grande do Sul, Brazil	Prospective cohort	Moderate Covid-19 patients required any oxygen support	41	28 (68.2%)	53.5±14.2	30.8±6.7	PF ratio 105.5±51.8	Diabetes; **Hypertension**; Neoplasm; Heart disease; Pulmonary disease; Asthma	HFNC, NIV, **NRM**, nasal cannula	ICU	**Duration**: 1.78±0.6 hours/session **Frequency**: 1.84±2.01 sessions/day **Given for**: 1.5±1.2 days	PF ratio; SF ratio; PaO_2; SpO_2; FiO_2; RR	After 1st session finished (supine)
Othman, El-Menshawy and Mohamed/2022	Single center, Damanhur, Egypt	RCT	Covid-19 patients with PF ratio ≤150mmHg required NRM or CPAP	82 PP: 41 CG: 41	52 (63.4%) PP: 29 (70.7%) CG: 23 (56.1%)	51.6±14.6 PP: 51.2±13.1 CG: 52±16	NR	PF ratio 84.3±29.3 PP: 79.9±22.5 CG: 88.6±34.3	**Hypertension**; Diabetes; CHF; Kidney disease	**NRM**, CPAP	ICU	**Duration**: ≥3 hours/session	PF ratio; PaO_2; SpO_2; SaO_2; RR; ROX index;	10 minutes after initiated (prone); 1 hour after initiated (prone)
Perez-Nieto et al./2022	Multicenter, Mexico; Ecuador	Retrospective cohort	Covid-19 patients with SpO_2 <94% upon admission to ED	827 PP: 505 CG: 322	600 (72.6%) PP: 370 (73.3%) CG: 230 (71.4%)	54.3±14.2 PP: 53.4±13.9 CG: 55.8±14.5	Obese 119 (14.4%) PP: 74 (14.7%) CG: 45 (14%)	SF ratio PP: 182.4±81.9 CG: NR	**Diabetes**; Hypertension; Heart disease; Lung disease; Cancer; CKD; Liver disease	**Nasal cannula**, HFNC, NRM	**ED, ward**, ICU	**Duration**: 14.6±11.8 hours during in-hospital stay	SF ratio	Within 1 hour after initiated (prone)

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP[a]	Oxygenation Parameters	Time to follow up (position)
Dos Santos Rocha et al./2022	Single center, Geneva, Switzerland	Prospective cohort	Covid-19 patients under NIV	28 PP: 13 CG: 15	21 (75%) PP: 9 (69%) CG: 12 (80%)	64.8±8.7 PP: 61±9 CG: 68±7	28.1±6.7 PP: 26.3±3.5 CG: 29.7±8.3	NR	**Hypertension**; Diabetes	CPAP, HFNC	IMCU	**Duration**: NR	SpO_2; FiO_2; RR	1 hour after initiated (prone)
Scaravilli et al./2015	Single center, Monza, Italy	Retrospective cohort	AHRF patients with PF ratio <300 mmHg	15	10 (66%)	58.3±22.8	NR	PF ratio 127±49	COPD; Malignancy; **Immunocompromised**	**Face mask**, HFNC, helmet CPAP, NIV	ICU	**Duration**: 3±1.63 hours/session **Frequency**: 2±1.63 session/patient	PF ratio; PaO_2; RR	Last hour of PP (prone); 6 hour after finished (supine)
Silva Junior et al./2021	Single center, Sao Paulo, Brazil	Prospective cohort	Covid-19 patients required any oxygen support	48	31 (65%)	59.4±12.6	30.1±8.1	PF ratio 153±7.41	**Hypertension**; Diabetes; CKD; Asthma; Other	**Nasal cannula**, NRM, HFNC, CPAP	Ward, ED	**Duration**: 1.9±0.9 hours/session	PF ratio; SF ratio; PaO_2; SaO_2; SpO_2; RR;	During first session (prone)
Solverson, Weatherald and Parhar/2021	Multicenter, Calgary, Canada	Retrospective cohort	Covid-19 patients using ≥5L/min oxygen to maintain SpO_2 90% or SF ratio ≤250	17	12 (71%)	55.3±13.0	Obese: 3 (18%)	SF ratio 158.5±37.8	**Hypertension**; CAD; Obstructive sleep apnea	**Nasal cannula**, HFNC	Ward, **ICU**	**Duration**: 2.75±2.08 hours/session **Frequency**: 2.75±1.39 session/day **Given for**: 2.5±1.67 days	SF ratio; SpO_2; RR	20 minutes after initiated (supine); 1-2 hours after finished (supine)
Sryma et al./2021	Single center, Delhi, India	Quasi-experimental	Covid-19 patients with room air SpO_2 <94%	45 PP: 30 CG: 15	38 (84.4%) PP: 29 (96.7%) CG: 9 (60%)	52.6±11.4 PP: 50.1±10.1 CG: 57.5±12.2	Obese excluded	NR	Hypertension; Diabetes; **Other**	**COT**, NIV, HFNC	NR	**Duration**: 7.7±1.9 hours/day	SpO_2; ROX index; RR;	30 minutes after initiated (prone); 12 hours after initiated (supine)
Taylor et al./2021	Single center, Charlotte, North Carolina	RCT	Covid-19 patients with room air SpO_2 <93%	40 PP: 13 CG: 27	27 (67.5%) PP: 7 (53.8%) CG: 20 (74%)	57.4±10.2 PP: 50.6±9.9 CG: 60.6±8.6	32.1±9.6 PP: 33±12.4 CG: 31.6±7.8	NR	**Diabetes**; Heart failure; CKD; CLD	**Nasal cannula**, MFNC, Bi-PAP	Ward	**Duration**: 10-120 minutes/day	SF ratio	2 days after initiated (NR)
Thompson et al./2020	Single center, New York, USA	Prospective cohort	Covid-19 patients with SpO_2 ≤93% required nasal cannula (6 L/min) or NRM (15 L/min)	25	18 (72%)	65.1±9.4	29.5±6.3	NR	**Hypertension**; Diabetes; Hyperlipidemia; CAD; CLD; CKD	Nasal cannula, NRM	IMCU	**Duration**: 8.7±6.9 hours/day **Given for**: 2.2±0.9 days	SpO_2	1 hour after initiated (NR)
Winearls et al./2020	Single center, Bristol, UK	Retrospective cohort	Covid-19 patients required CPAP	24	15 (63%)	62±13	NR	PF ratio 201±70	**Hypertension**; Diabetes; Renal failure; Heart failure; Cancer; Immunocompromised	CPAP	IMCU	**Duration**: 8±5 hours/day **Given for**: 10±5 days	PF ratio; SpO_2; ROX index; RR	15 minutes after initiated (prone); 1 hour after finished (supine)
Wormser, Romanet and Philippart/2021	Single center, Paris, France	Retrospective cohort	Covid-19 patients using any oxygen support ≥4 L/min	24	16 (59%)	70.6±14.8	28.7±5.8	SF ratio 189.3±42.8	**Hypertension**; COPD; Diabetes	COT	Ward	**Duration**: NR	SF ratio	During implementation in each session (prone); After finished in each session (supine)

Authors/ Year	Location	Design	Sample	N	Gender (Male, %)	Mean age (years)	BMI (kg/m^2)[a]	Mean baseline PF ratio/SF ratio	Comorbidities	Respiratory device	Setting	Actual duration and/or frequency of PP[a]	Oxygenation Parameters	Time to follow up (position)

Definition of abbreviations: a Data presented as mean ± SD or otherwise stated; bolded text indicates the most common finding; PP, prone position; CG, control group; NR, not reported; PF ratio, arterial partial pressure of oxygen to inspired fraction of oxygen ratio; SF ratio, peripheral oxygen saturation to inspired fraction of oxygen ratio; ROX index, ratio of SF ratio to respiratory rate; PaO2, arterial pressure of oxygen; SaO2, oxygen saturation in arterial blood; SpO2, peripheral oxygen saturation; RR, respiratory rate; FiO2, inspired fraction of oxygen; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; CLD, chronic lung disease; HFNC, high flow nasal cannula; NIV, noninvasive ventilation; NRM, non-rebreathing mask; CPAP, continuous positive air pressure; NPPV, noninvasive positive-pressure ventilation; Bi-PAP, bi-level positive airway pressure; COT, conventional oxygen therapy; ICU, intensive care unit; IMCU, intermediate care unit; ED, emergency department.

Table 2. Subgroup analysis

Variable	PF ratio				SF ratio				Intubation rate				Mortality rate			
	n	SMD (95% CI)	p	I^2	n	SMD (95% CI)	p	I^2	n	RR (95% CI)	p	I^2	n	RR (95% CI)	p	I^2
Age			0.52	0			0.07	69.3			0.72	0			0.86	0
Adult (18-59 years)	15	0.74 (0.50, 0.97)			15	0.59 (0.40, 0.77)			9	0.62 (0.54, 0.73)			8	0.63 (0.41, 0.96)		
Elder (≥60 years)	7	0.61 (0.33, 0.90)			11	1.04 (0.58, 1.49)			5	0.56 (0.31, 1.00)			6	0.66 (0.45, 0.98)		
Severity			0.44	0			**0.001**	90.5			0.09	59			0.52	0
Milda	4	0.53 (0.00, 1.05)			3	0.24 (0.02, 0.46)			2	1.09 (0.46, 2.57)			2	0.74 (0.17, 3.18)		
Moderateb	15	0.67 (0.47, 0.88)			23	0.82 (0.55, 1.08)			6	0.59 (0.42, 0.81)			7	0.69 (0.50, 0.95)		
Severec	3	0.99 (0.46, 1.52)							2	1.56 (0.60, 4.05)			1	0.94 (0.61, 1.45)		
Respiratory device			**0.02**	80.6			0.22	33.4			0.16	48.9			0.04	76.3
COT	8	0.43 (0.20, 0.67)			21	0.64 (0.45, 0.90)			9	0.53 (0.38, 0.75)			9	0.54 (0.44, 0.66)		
NIV	13	0.82 (0.59, 1.05)			5	1.03 (0.50, 1.56)			4	0.74 (0.54, 1.01)			4	0.78 (0.58, 1.05)		
Setting			0.10	63.5			0.06	72.1			0.63	0			0.10	63
ICU	10	0.57 (0.37, 0.78)			10	1.05 (0.60, 1.51)			7	0.69 (0.42, 1.12)			7	0.84 (0.70, 1.00)		
Non ICU	11	0.88 (0.58, 1.17)			16	0.58 (0.38, 0.77)			6	0.60 (0.48, 0.75)			6	0.55 (0.34, 0.88)		
Body Mass Index			0.13	57			0.11	61.8			0.94	0			0.59	0
Non obese (<30 kg/m2)	13	0.69 (0.45, 0.93)			20	0.87 (0.55, 1.20)			9	0.59 (0.43, 0.82)			10	0.63 (0.47, 0.84)		
Obese (≥30 kg/m2)	1	0.31 (-0.13, 0.74)			5	0.48 (0.13, 0.83)			3	0.61 (0.36, 1.03)			3	0.29 (0.02, 4.67)		
Design			0.64	0			0.79	0			**0.001**	81.6			0.001	81.4
RCT	2	0.32 (-0.34, 0.98)			5	0.86 (0.22, 1.50)			7	0.79 (0.69, 0.90)			6	0.88 (0.75, 1.04)		
Quasi-experimental	2	0.94 (0.17, 1.70)							2	0.33 (0.17, 0.62)			2	0.33 (0.18, 0.58)		
Prospective cohort	9	0.72 (0.45, 0.99)			8	0.66 (0.37, 0.95)			1	1.82 (0.68, 4.90)			1	0.94 (0.61, 1.45)		
Retrospective cohort	9	0.70 (0.38, 1.03)			13	0.78 (0.43, 1.14)			4	0.46 (0.31, 0.67)			5	0.51 (0.35, 0.76)		
Time of admission to APP			0.61	0			0.90	0			0.69	0			0.59	0
Less than 1 day					4	0.62 (0.34, 0.91)			4	0.70 (0.51, 0.97)			4	0.75 (0.51, 1.11)		
1-3 days	5	0.96 (0.46, 1.46)			9	0.58 (-0.07, 1.23)			2	0.59 (0.27, 1.29)			2	0.57 (0.23, 1.44)		

Variable	PF ratio				SF ratio				Intubation rate				Mortality rate			
	n	SMD (95% CI)	p	I^2	n	SMD (95% CI)	p	I^2	n	RR (95% CI)	p	I^2	n	RR (95% CI)	p	I^2
More than 3 days	4	0.77 (0.26, 1.29)														
Detail of position			0.44	0			0.51	0			**0.04**	78.3			0.11	61.5
Combined positions	5	0.58 (0.27, 0.90)			5	0.64 (0.31, 0.97)			1	2.44 (0.59, 10.04)			1	0.94 (0.61, 1.45)		
Only prone	17	0.74 (0.51, 0.96)			21	0.79 (0.50, 1.08)			13	0.55 (0.47, 0.64)			13	0.62 (0.46, 0.82)		
Medication assistance			0.38	0			0.10	63.6			**0.03**	80			0.38	0
Used	7	0.82 (0.45, 1.19)			5	1.29 (0.57, 2.02)			2	0.31 (0.17, 0.59)			3	0.46 (0.19, 1.16)		
Not used	15	0.64 (0.43, 0.84)			21	0.64 (0.36, 0.91)			13	0.67 (0.54, 0.84)			11	0.71 (0.55, 0.92)		
Total duration[d,e]			0.12	52.3			**0.004**	82			0.05	73.5			0.51	0
Less than 1 hour	5	0.94 (0.60, 1.27)			2	0.17 (-0.28, 0.61)										
1-6 hours	9	0.49 (0.22, 0.76)			9	0.63 (0.18, 1.08)			5	0.72 (0.56, 0.94)			4	0.69 (0.45, 1.04)		
More than 6 hours	7	0.68 (0.49, 0.87)			9	1.15 (0.77, 1.53)			5	0.41 (0.25, 0.68)			6	0.55 (0.32, 0.92)		
Position at follow-up			**0.02**	82.5			0.94	0								
Prone	8	0.95 (0.70, 1.20)			8	0.74 (0.42, 1.06)										
Supine	14	0.56 (0.35, 0.76)			16	0.76 (0.41, 1.11)										
Follow-up time			**0.03**	78.1			0.23	29.8								
After initiation	11	0.87 (0.65, 1.09)			15	0.88 (0.61, 1.15)										
After finish	10	0.50 (0.25, 0.76)			11	0.56 (0.11, 1.02)										

Definition of abbreviations: PF ratio, partial pressure of oxygen to fraction of inspired oxygen ratio; SF ratio, oxygen saturation to fraction of inspired oxygen ratio; n, study size; SMD, standardized mean difference; RR, risk ratio; CI, confidence interval; APP, awake prone position; a, PF ratio 201-300 or SF ratio 285-323; b, PF ratio 100-200 or SF ratio <285; c, PF ratio <100; d, total duration per follow up for PF ratio and SF ratio; e, total duration per day for mortality rate and intubation rate.

Table 3. Meta-regression

Variable	PF ratio			SF ratio			Intubation rate			Mortality rate		
	n	SMD (95% CI)	p	n	SMD (95% CI)	p	n	RR (95% CI)	p	n	RR (95% CI)	p
Sample size	22	-0.002 (-0.006, 0.002)	0.27	26	7.55e-4 (-0.001, 0.002)	0.38	14	1.0003 (1, 1.001)	0.24	14	1.0001 (1, 1.001)	0.58
Mean age	22	-0.016 (-0.059, 0.026)	0.44	26	0.019 (-0.017, 0.056)	0.29	14	0.978 (0.929, 1.029)	0.39	14	1.015 (0.962, 1.071)	0.57
Mean BMI	11	0.005 (-0.241, 0.252)	0.96	18	-0.228 (-0.414, -0.041)	**0.01**		Not estimable		10	0.983 (0.822, 1.174)	0.85
Mean severity	22	4.27e-4 (-0.003, 0.004)	0.81	26	-0.004 (-0.009, -0.001)	**0.01**		Not estimable			Not estimable	
Time of admission to APP (day)		Not estimable		12	-0.142 (-0.688, 0.405)	0.61		Not estimable			Not estimable	
Total duration per follow-up (hour)	20	-0.001 (-0.012, 0.009)	0.81	19	0.016 (0.005, 0.028)	**0.005**						
Follow up time after initiation (hour)	11	-0.002 (-0.005, 0.001)	0.24	10	0.003 (0.002, 0.005)	**<0.001**						
Follow up time after finish (hour)	10	-0.109 (-0.277, 0.060)	0.20	17	0.001 (-0.001, 0.003)	0.33						

Definition of abbreviations: PF ratio, partial pressure of oxygen to fraction of inspired oxygen ratio; SF ratio, oxygen saturation to fraction of inspired oxygen ratio; n, study size; SMD, standardized mean difference; RR, risk ratio; CI, confidence interval; BMI, body mass index; APP, awake prone position.