Title page

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Awake Prone Positioning in Adults with COVID-19 and Acute Hypoxemic Respiratory Failure: An Individual Participant Data Meta-analysis

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Access to data and data analysis: Dr. Luo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement: Individual participant data collected for this study will not be available due to lawful protection under data sharing agreement. Data dictionary can be available 36 months after article publication to researchers who provide a methodologically sound and ethically approved proposal, for any purpose of analysis.

Key Points

Questions: Is awake prone positioning (APP) compared to supine positioning associated with better survival without intubation in patients with COVID-19 and acute hypoxemic respiratory failure?

Findings: In this individual participant data meta-analysis, which included 3,019 patients from 14 randomized controlled trials, APP was found to improve survival without intubation and reduce the risk of both intubation and hospital mortality. A prolonged duration of APP, specifically ≥ 10 hours per day, was strongly associated with better outcomes.

Meaning: Among patients with COVID-19 and acute hypoxemic respiratory failure, APP is associated with improved clinical outcomes.

Social media post

New IPD meta-analysis of 14 RCTs (3,019 patients) shows awake prone positioning (APP) improves survival without intubation, reduces intubation & mortality in COVID-19-induced AHRF. APP ≥10 hrs/day yields better outcomes. #CriticalCare #COVID19 #Proning.

Abstract

Importance: The impact of awake prone positioning (APP) on clinical outcomes in patients with COVID-19 and acute hypoxemic respiratory failure (AHRF) remains uncertain.

Objective: To assess the effects of APP on clinical outcomes among patients with COVID-19 and AHRF and identify potential effect modifiers.

Data Sources: Pubmed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were searched through August 1st, 2024.

Study Selection: Randomized controlled trials (RCTs) examining APP in adults with COVID-19 and AHRF that reported a primary outcome were included.

Data Extraction and Synthesis: Individual participant data (IPD) were extracted according to PRISMA-IPD guidelines. For binary outcomes, logistic regression was used and odds ratio (OR) and 95% confidence interval (CI) were reported, while for continuous outcomes, linear regression was used and mean difference (MD) and 95% CI were reported.

Main Outcomes and Measures: The primary outcome was survival without intubation. Secondary outcomes included intubation, mortality, death without intubation, death after intubation, escalation of respiratory support, intensive care unit (ICU) admission, time from enrollment to intubation and death, duration of invasive mechanical ventilation, and hospital and ICU lengths of stay.

Results: 14 RCTs involving 3,019 patients were included. APP improved survival without intubation (OR 1.42 [95%CI 1.20 to 1.68]), and reduced the risk of intubation (OR 0.70 [0.59 to

0.84]), and hospital mortality (OR 0.77 [0.63 to 0.95]). APP also extended the time from enrollment to intubation (MD 0.93 days [0.43 to 1.42]). In exploratory subgroup analyses, improved survival without intubation was observed in patients under 68 years old, with a BMI of 26 to 30 kg/m^2, early implementation of APP (<1 day from hospitalization), a pulse oxygen saturation to inhaled oxygen fraction ratio of 155 to 232, respiratory rate of 20 to 26 bpm and those receiving advanced respiratory support at enrollment, but none of the subgroups had significant interaction with APP treatment. APP duration ≥10 hours/day within the first three days was associated with increased survival without intubation (OR 1.85 [1.37 to 2.49]).

Conclusions and Relevance In adults with COVID-19 and AHRF, APP increased survival without intubation and reduced the risks of intubation and mortality, including death after intubation. Prolonged APP duration (≥ 10 hours/day) was associated with better outcomes.

Introduction

Awake prone positioning (APP), a non-invasive and low-cost treatment, has been widely used in patients with acute hypoxemic respiratory failure (AHRF) since the COVID-19 pandemic.[1] Physiological studies have shown that, in addition to improving oxygenation, APP can significantly reduce the work of breathing and enhance ventilation homogeneity,[2-4] potentially lowering the risk of lung injury.[5,6] In contrast, a recent physiological study showed that APP was associated with more intense inspiratory effort when compared to supine position, due to positional increases in airway resistance and prolonged expiratory time[7]. These heterogeneous physiological responses to APP may account for the variability in outcomes observed across randomized controlled trials (RCTs). Indeed, despite the publication of numerous RCTs[8-20] and meta-analyses,[21-24] several key questions remain unanswered. First, the impact of APP on mortality remains unclear. While earlier meta-analyses[21,22] did not find a mortality benefit, a recent RCT[25] has demonstrated that prolonged APP can reduce the risk of death. Second, while patients receiving advanced respiratory support, such as high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or noninvasive ventilation (NIV), have been reported to benefit most from APP[21,22], its effectiveness in patients receiving conventional oxygen therapy remains uncertain.[26,27] Third, it is unclear which patient populations, beyond those on advanced respiratory support, are most likely to benefit from APP, and what factors contribute to treatment success. To address these uncertainties, we conducted an individual participant data meta-analysis (IPD-MA) of RCTs comparing APP to supine positioning in patients with COVID-19 and AHRF.

Method

Literature search

We prospectively registered the protocol for this IPD-MA in International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42022343625) and conducted the review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[28] Two reviewers (AK & YP), independently and in duplicate, conducted a systematic electronic search of Pubmed, EMBASE, the Cochrane Library, and ClinicalTrials.gov from January 1st, 2021 to August 1st, 2024, based on our previous work[21]. We searched for studies published in English only. The detailed search strategies are available in the supplementary file (Supplementary Search strategy). We included published and unpublished RCTs that compared APP with standard care in adult, non-intubated patients with COVID-19 and AHRF, if they reported our primary outcome of interest (see below). Studies that randomized patients undergoing invasive mechanical ventilation or extracorporeal membrane oxygenation were excluded. Quasi-RCTs were included only in secondary sensitivity analyses. A group of investigators (JLuo, JLi, & IP) resolved discrepancies concerning study eligibility by discussion and consensus. All included studies obtained approval from the local research ethics boards and required obtaining informed consent from participants.

Outcomes

The primary outcome was survival without intubation. Secondary outcomes included intubation, death during ICU and hospital stay, death without intubation, death after intubation, escalation of respiratory support (defined as a sequential increase in oxygen or respiratory support levels [room air < conventional oxygen therapy < HFNC < CPAP/NIV < invasive mechanical ventilation]), ICU admission, time from enrollment to intubation, time from

enrollment to death, duration of invasive mechanical ventilation, and lengths of stay in hospital and ICU.

Data collection and integration

The corresponding authors of eligible trials were invited to participate and share de-identified IPD. A data usage agreement was established before distributing a standardized data collection form, which included demographics, comorbidities, type of respiratory support, baseline oxygenation and vital signs, duration of APP, and outcomes. To ensure uniformity in data analysis, the primary outcome was censored to days 28 to 30 if data was available, otherwise it was reported as originally collected. APP duration was reported as the daily average time (hrs) spent on APP (Daily average time on APP [D0-D3]). This metric was calculated as the total APP duration divided by the number of days APP was actually applied from day 0 to day 3 (data beyond day 3 were largely incomplete).

Assessment of data integrity and risk of bias

Data integrity and completeness were verified against the original study publications, when available, and any invalid, inconsistent, or missing data were sought for correction by communication with the respective study investigators. Two independent groups of investigators (SE & BM and JLuo & JLi) assessed the risk of bias for each included study using the revised tools for randomized trials (RoB 2) and cluster-randomized trials (RoB 2 CRT).[29] For each study, reviewers assigned one of the following risk-of-bias categories (low risk, some concerns, and high risk) based on an assessment of the following domains: 1) randomization process, 2) intended intervention (effect of assignment/adhering to intervention), 3) missing outcome data,

4) outcome measurement, and 5) selection of the reported result. Any discrepancies were resolved by additional two reviewers (AK and YP).

Imputation of missing data

Patterns of missing data were tested using Little's test for missing completely at random (MCAR) at both study and intervention levels. Missing data was imputed using multivariate imputation by chained equations (MICE) under a fully conditional specification approach, accounting for the clustering of participants within studies.[30] Two models were attempted for multiple imputation, including Bayesian linear regression ('norm') and predictive mean matching ('pmm'). The consistency of imputed data was further assessed by intraclass correlation with higher intraclass correlation indicating better representation. Imputation of missing data was conducted only for confounding variables, not for outcome variables. Complete-case, which removed participants with missing data, was used for primary analyses, while imputed data was used only for sensitivity analyses.

Statistical analysis

To estimate the overall treatment effect of APP for IPD-MA, a one-stage approach was conducted using a generalized linear mixed model with stratified trial intercept and trial-specific centering of treatment variable to account for both clustering of participants within trials and heterogeneity across trials.[31,32] For binary outcomes, logistic regression was used and odds ratio (OR) and 95% confidence interval (CI) were reported, while for continuous outcomes, linear regression was used and mean difference (MD) and 95% CI were reported. For time-to-event outcomes, a Cox proportional hazards model was used and reported as hazard ratio (HR). For

the identification of patient-level treatment effect modifiers, treatment-covariate interaction was estimated between intervention and variables including age, body mass index (BMI), time from hospitalization to enrollment, ratio of pulse oxygen saturation to fraction of inhaled oxygen (SpO_2:FiO_2), respiratory rate, the unit of care at enrollment (ICU vs non-ICU), and type of respiratory support at enrollment (advanced respiratory support [HFNC, NIV or CPAP] vs conventional oxygen therapy). Exploratory subgroup analyses were performed based on tertiles of continuous variables or categories of binary variables using the same regression model within each categorized analysis, and significance level was adjusted for multiple testing using the Bonferroni method[33].

To assess the independent association of APP duration with binary outcomes, univariate and multivariable logistic regression were performed in the APP group, using a full model with predictors chosen as a priori and confirmed by stepwise predictors selection based on Akaike Information Criteria value. Cutoff values of APP duration were defined as the inflection time point where the trend in the percentage of outcome events changed, depicted graphically by the number and percentage of patients who had an event in 2-hour bins.

For conventional meta-analyses of aggregate data, treatment effects were estimated using the Mantel-Haenszel method for fixed-effects models and the inverse variance method for random-effect models, respectively. Two sets of conventional meta-analyses were conducted separately for the studies providing IPD and those with aggregate data.

Heterogeneity was evaluated by Cochran's Q test and the degree of heterogeneity was quantified by I^2: insignificant heterogeneity (0% to 30%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%), and considerable heterogeneity (75% to 100%).[34]

All analyses were performed on intention-to-treat population and conducted separately on complete-case data and imputed data from RCTs, both without and with quasi-RCTs. Results of complete-case IPD from RCTs were reported primarily, while results of IPD from imputation or quasi-RCTs and results of conventional meta-analyses were used as sensitivity analyses. All tests were two-sided with a significance level of 0.05. All data were analyzed using R software version 4.2.2.

Results

Study selection and quality assessment

Our search identified a total of 3,139 records, and 26 studies (5,333 patients) were eligible for inclusion, out of which, 5 studies (796 patients) were not published, resulting in 21 studies[8-20,25,35-41] with 4,537 patients (APP 2,315 vs Control 2,222) included in a conventional meta-analysis (Figure 1). After contacting corresponding authors to share individual participant data, 6 (1,017 patients, 22.4%) were not included for the reasons listed in Figure 1, and the other 15 (3,520 patients, 77.6%) agreed to participate. We obtained IPD from 14 RCTs[8-17,20,25,35,36], comprising 3,019 patients (APP 1,542 vs Control 1,477). In addition, we included data from one quasi-RCT[19], resulting in 3,520 patients (APP 1,800 vs Control 1,720) for sensitivity analyses. Details of studies included in IPD-MA were summarized in supplementary Table S1. From 1,719 patients (~60% of total patients) on HFNC or NIV, data on flow was reported in 1,241 patients (72%). Using the new definition of ARDS[42], i.e., flow ≥ 30 L/min and SpO_2:F_IO_2 ≤ 315, 1,229 patients (99%) had ARDS based on the assumption of bilateral opacities. Baseline characteristics of the patients were summarized in supplementary Tables S2 and S3, showing no significant imbalances across variables.

No data was missing for the primary outcome. At the intervention level, all treatment effect modifiers were consistent with MCAR (Little's test, $p>0.05$). However, at the study level, systematic missingness occurred, with only BMI, time from hospitalization to enrollment, and respiratory rate identified as not missing at random (Little's test, $p<0.001$). Although blinding participants and healthcare staff was not feasible due to the nature of the intervention, 17 trials[8-14,16,18,20,25,35-37,39-41] were judged as low risk of bias, while two cluster-randomized trials[15,17] were considered high risk of bias (Supplementary Figures S1 and S2).

Overall treatment effects of APP

Compared to supine positioning, APP increased survival without intubation (OR 1.42 [95%CI 1.20 to 1.68]) and reduced the odds of intubation (OR 0.70 [95%CI 0.59 to 0.84]) and hospital mortality (OR 0.77 [95%CI 0.63 to 0.95]) (Table 1). While the overall patients (intention-to-treat population) in the APP group had a lower risk of death after intubation than the control group (OR 0.76 [95%CI 0.61 to 0.96]), mortality was similar between APP and control groups within the selected subgroup of intubated patients (OR of 1.07 [95% CI 0.79 to 1.46]). APP extended the time to intubation compared to supine positioning (MD 0.93 days [95%CI 0.43 to 1.42]). No significant differences were observed between APP and control groups in terms of ICU mortality, need for escalation of respiratory support, need for ICU admission, duration of invasive mechanical ventilation, ICU length of stay, hospital length of stay, or adverse events.

In the time-to-event analysis, APP reduced the risk of the composite outcome of mortality or intubation (HR 0.75 [95%CI 0.65 to 0.86]) (Figure 2), intubation (HR 0.74 [95%CI 0.64 to

0.86]) (Supplementary Figure S3) and mortality (HR 0.81 [95%CI 0.67 to 0.98]) (Supplementary Figure S4) within 30 days.

Similar results were found in the sensitivity analyses which excluded cluster-randomized trials (Supplementary Table S4) and included the quasi-RCT (Supplementary Table S5 and Figures S5-7) and conventional meta-analyses (Table 1 and Supplementary Table S6 and S7), except for mortality in the analyses involving the quasi-RCT.

Exploratory subgroup and interaction analyses

For survival without intubation, the p values for interaction were not significant (Figure 3). The treatment effect of APP on survival without intubation was estimated as follows: OR 1.57 [95%CI 1.19 to 2.07] in patients aged 55 and 68 years, OR 1.67 [95%CI 1.18 to 2.35]) in patients under 55 years old, OR 1.57 [95%CI 1.18 to 2.08] in patients with a BMI of 26 to 30 kg/ m^2, OR 1.60 [95%CI 1.12 to 2.28] in patients who received APP between 0.8 to 1 day of hospitalization, OR 1.50 [95%CI 1.11 to 2.04] in patients who received APP within 0.8 day of hospitalization, OR 1.85 [95%CI 1.25 to 2.72] in patients with SpO_2:FiO_2 between 155 and 232, OR 1.53 [95%CI 1.15 to 2.03] in patients with respiratory rates between 20 and 26 bpm, and OR 1.46 [95%CI 1.21 to 1.77] in patients receiving advanced respiratory support at enrollment (Figure 3). These findings were consistent across both imputed data (Supplementary Figures S8 and S9) and data from the quasi-RCT (Supplementary Figures S10-12).

Similar results were also found for intubation (Supplementary Figures S13) and confirmed by imputed data and data from the quasi-RCT (Supplementary Figures S14-18), but significant treatment effect modification by age was found in the latter (p-interaction=0.047). No significant treatment effect modifiers were identified for mortality (Supplementary Figures S19-

24), death without intubation (Supplementary Figures S25-30), or death after intubation (Supplementary Figures S31-36).

The association of APP duration and outcomes

In 11 RCTs[8,9,11-13,16,17,20,25,35,36] with data on APP duration, more than 93% (1174/1258) of patients started APP on day 0 or day 1 from enrollment. After adjustment for age, BMI, time from hospitalization to enrollment, SpO_2:FiO_2, respiratory rate, unit of care at enrollment and type of respiratory support at enrollment, multivariable logistic regression showed that APP duration was an independent factor associated with survival without intubation. There was a 3% increase in the odds of survival without intubation for every hour increase in APP duration (OR 1.03 [95%CI 1.00 to 1.07]) (Supplementary Table S8). We identified a significant inflection cutoff at 10 hours/day within the first three days (Figure 4). Patients with APP ≥10 hours/day had significantly lower baseline SpO_2:FiO_2 compared to those with APP <10 hours/day, with similar baseline respiratory rates (Supplementary Figure S37). Patients with APP ≥10 hours/day had higher odds of survival without intubation (OR 1.85 [95%CI 1.37 to 2.49]), especially those who were consecutively proned for the first three days (OR 2.59 [95%CI 1.30 to 5.14]) (Supplementary Table S9). These findings were confirmed by sensitivity analyses (Supplementary Table S8, S10 and S11 and Figures S38-40). Although APP duration was not an independent predictor for intubation (OR 0.97 [95%CI 0.94-1.00]) (Supplementary Table S12 and S13) or mortality (OR 0.98 [95%CI 0.95-1.02]) (Supplementary Table S14 and S15), significant differences were observed when comparing patients with an APP duration of ≥10 hours/day to those with <10 hours/day during the first three days. Patients with APP ≥10 hours/day had reduced odds of intubation (OR 0.69 [95%CI 0.50 to 0.94]) (Supplementary Table

S9 and S11 and Figures S41-44) and mortality (OR 0.49 [95%CI 0.34 to 0.70]) (Supplementary Table S9 and S11 and Figures S45-48), especially those who were consecutively proned for the three first days (intubation: OR 0.54 [95%CI 0.30 to 0.95]; mortality: OR 0.38 [95%CI 0.15 to 0.97]) (Supplementary Table S9 and S11).

Discussion

This study presents the most comprehensive analysis to date of APP for COVID-19 and AHRF. We have confirmed that APP reduces intubation and mortality, and identified key factors that influence its success, offering actionable insights for clinical practice.

Consistent with previous meta-analyses of aggregated data, our findings confirm that APP significantly reduces the risk of intubation compared to the supine position.[21-24] Unlike prior meta-analyses of RCTs,[21-23] which found no significant impact on hospital mortality, our study demonstrates that APP reduces mortality in patients with COVID-19 and AHRF. This outcome is likely attributed to larger sample sizes and particularly to analyses conducted at the individual participant level. However, in our sensitivity analysis that included a quasi-RCT,[19] we did not observe a significant difference in mortality. This discrepancy is presumably due to the high number of patients with "do-not-intubate" orders in the quasi-RCT,[19] because a significant reduction in the post-intubation mortality by APP was still observed. More insights are expected from the ongoing CORONA trial[43], which will further explore this issue. Among patients who failed treatment and ultimately required intubation, the APP group experienced longer durations between enrollment and intubation, yet their mortality did not significantly differ from those intubated in the supine position group. While assessing outcomes only in intubated patients can

introduce bias compared to a strict intention-to-treat analysis of all randomized patients, these findings help alleviate clinicians' concerns that APP may delay intubation and thereby increase post-intubation mortality.[44-46]–

In addition to confirming that APP benefits most patients receiving advanced respiratory support,[21] our exploratory subgroup analyses revealed new insights. Specifically, patients under 68 years old, with a BMI of 26 to 30 kg/m^2, early implementation of APP (within 1 day), a SpO_2:FiO_2 of 155 to 232 at enrollment, a respiratory rate of 20 to 26 bpm at enrollment, and those treated in ICU were significantly associated with improved survival without intubation. Although interaction analyses did not show significant treatment effect modification by any of these factors potentially due to limited sample size[47], the treatment effect in these subgroups remained significant after adjusting for multiple comparisons using the Bonferroni method[33]. These findings may help identify the patients most likely to benefit from APP, but should not preclude implementation of APP in patients who do not exhibit these beneficial characteristics since no significant increase of severe adverse events were observed with APP.

APP duration is an independent factor associated with treatment success, efforts should be made to improve patient compliance and comfort in the prone position in order to extend APP duration.[48] Although this finding aligns with previous studies,[8,49,50] our study analyzed data at the individual participant level after adjustment of other confounding factors, highlighting the importance of sustained prone positioning for optimal clinical outcomes, with a preferred daily duration of ~10 hours in the first three days. Furthermore, the use of IPD allowed us to address potential biases in patient severity between those with longer and shorter APP duration. Given that the duration of APP was not randomized in the original RCTs, there was a concern that the observed benefit of longer APP might be driven by a "healthy worker" bias, with healthier

patients tolerating longer durations of APP. This assumption is not borne out in our IPD meta-analysis, as patients with longer APP durations (≥10 hours/day) had worse baseline oxygenation, reinforcing the conclusion that longer APP is independently associated with better clinical outcomes. In addition, approximately 44% of patients were intubated or dead within the first three days of enrollment, which necessarily resulted in shorter exposure to APP and could have introduced immortal time bias into our analysis of the dose-response relationship of APP on the outcomes. Reassuringly, the benefit of longer duration of APP was even stronger in a subgroup analysis restricted to patients who did not encounter the outcomes during the first three days, and had therefore an equal window of opportunity for exposure to APP.

Our study has several strengths. First, this study features the largest sample size to date, utilizing IPD from all eligible RCTs, representing the highest level of evidence. The findings from the comprehensive analyses are confirmed by sensitivity analyses including the most updated conventional meta-analysis of 21 RCTs, making them conclusive. Second, our findings are also practical for guiding clinical practice, including identifying the patient population that benefits most from APP and the optimal APP duration. Third, these results offer a valuable reference for future studies involving non-COVID-19 patients. However, our study also has some limitations. First, despite extensive efforts, we could not obtain data from all RCTs for various reasons, among them regulatory complexities concerning sharing data collected across multiple sites. Second, not all studies collected all outcomes, resulting in several outcomes having data from only a few RCTs with limited sample sizes, which could result in insignificant differences in findings for those outcomes. Third, the impact of pandemic timing on the benefits of APP has not been fully addressed. Subgroup analyses based on pandemic timing indicated a stronger treatment effect of APP during the first and second waves compared to the control

group. However, these findings should be interpreted with caution. Pandemic timing was analyzed as a study-level covariate, limiting the granularity of the analysis, and the sample size for patients enrolled during the third and fourth wave subgroups was relatively small (less than 20% of the total patients in each treatment arm), which reduces statistical power and precision and increases the potential for bias. Additionally, heterogeneity in co-interventions, virus variants, and clinical practices across pandemic periods may have influenced outcomes. For example, earlier trials with longer APP durations may have shown greater benefit, while later trials with shorter APP durations may have shown diminished benefits due to changes in co-treatments, virus variants, or overall care practices. These factors complicate efforts to attribute differences in outcomes solely to APP duration. Finally, while our models accounted for clustering within trials, they did not explicitly adjust for the time period of enrollment as a random effect, which could have introduced residual confounding.

Conclusion

This IPD meta-analysis establishes the efficacy of APP in improving survival outcomes and reducing intubation for adult patients with COVID-19-induced AHRF, with potential benefits in specific patient subgroups and with sustained application. APP was also associated with significant reductions in mortality, including death after intubation. These findings support the broader implementation of APP in clinical practice.

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Figure legends

Figure 1. Study flow diagram.

IPD, individual participant data; RCTs, randomized controlled trials.

Figure 2 Comparison of time-to-composite outcome of mortality or intubation in RCTs.

APP, awake prone positioning; HR, hazard ratio; RCTs, randomized controlled trials.

Figure 3 Interaction and subgroup analyses of primary outcome in RCTs.

APP, awake prone positioning; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SpO_2:FiO_2, the ratio of pulse oxygen saturation to the fraction of inhaled oxygen.

Figure 4 Dose effect of APP duration on APP success for the primary outcome in RCTs.

The number of patients who survived without intubation (Yes) and those who did not (No), and the percentage of patients who survived without intubation in the total number of patients, are depicted at each APP duration (Daily average time on APP during day 0 to day 3) interval of 2 hours/day by stacked bars (left y-axis) and connected points (right y-axis), respectively.
APP, awake prone positioning; RCTs, randomized controlled trials.

Table 1 Primary and secondary outcomes in RCTs.

Outcomes	No. of study	APP (Event or Mean/Total)	Control (Event or Mean/Total)	OR/MD (95%CI)		I^2 (95%CI)
				IPD-MA	Conventional MA	
Primary outcome						
Survival without intubation	14	1149/1542	1004/1477	OR 1.42 (1.20, 1.68)	OR 1.43 (1.20, 1.69)	0% (0%, 58%)
Secondary outcomes						
Intubation	14	336/1542	413/1477	OR 0.70 (0.59, 0.84)	OR 0.70 (0.59, 0.83)	0% (0%, 58%)
Mortality	14	215/1542	255/1477	OR 0.77 (0.63, 0.95)	OR 0.78 (0.64, 0.96)	0% (0%, 58%)
Death without intubation	14	57/1542	61/1477	OR 0.88 (0.60, 1.28)	OR 0.81 (0.50, 1.33)	0% (0%, 71%)
Death after intubation	14	158/1542	194/1477	OR 0.76 (0.61, 0.96)	OR 0.77 (0.61, 0.97)	0% (0%, 58%)
Death in non-intubated patients	14	57/1206	61/1064	OR 0.72 (0.46, 1.13)	OR 0.68 (0.40, 1.18)	8% (0%, 73%)
Death in intubated patients	12	158/336	194/413	OR 1.07 (0.79, 1.46)	OR 1.08 (0.79, 1.47)	0% (0%, 60%)
ICU mortality	9	86/807	89/781	OR 0.91 (0.66, 1.25)	OR 0.90 (0.66, 1.24)	0% (0%, 71%)
Need for escalation of respiratory support	13	412/1501	464/1435	OR 0.83 (0.59, 1.18)	OR 0.83 (0.59, 1.19)	53% (11%, 75%)
Need for ICU admission	10	112/518	95/468	OR 0.92 (0.60, 1.40)	OR 0.88 (0.57, 1.36)	34% (0%, 71%)
Time to intubation (days)	8	4.5/308	3.6/375	MD 0.93 (0.43, 1.42)	MD 0.96 (0.30, 1.63)	0% (0%, 79%)
Time to death (days)	10	13.0/211	13.0/248	MD -0.25 (-2.25, 1.75)	MD -0.18 (-2.25, 1.88)	45% (0%, 78%)
Duration of IMV (days)	5	11.9/233	11.5/273	MD -0.78 (-3.11, 1.55)	MD -0.72 (-3.16, 1.73)	57% (0%, 86%)
ICU LOS (days)	8	12.2/696	13.2/705	MD -1.97 (-4.37,	MD -2.01 (-4.38,	81% (62%,

				0.44)	0.35)	91%)
Hospital LOS (days)	12	14.1/1434	14.6/1380	MD -0.81 (-2.07, 0.45)	MD -0.81 (-2.04, 0.42)	62% (27%, 80%)
Adverse events						
Skin breakdown	10	26/1191	27/1143	OR 0.84 (0.48, 1.47)	OR 0.84 (0.48, 1.47)	0% (0%, 79%)
Vomiting	9	31/1195	32/1154	OR 0.78 (0.46, 1.34)	OR 0.78 (0.45, 1.34)	0% (0%, 90%)
Central arterial line dislodgement	9	38/1311	30/1228	OR 1.14 (0.69, 1.90)	OR 1.08 (0.54, 2.15)	0% (0%, 85%)
Back pain	6	18/367	9/349	OR 1.59 (0.64, 3.93)	OR 1.52 (0.62, 3.72)	0% (0%, 90%)
Bloating sensation	5	21/357	12/332	OR 1.31 (0.52, 3.35)	OR 1.31 (0.51, 3.35)	NA*
Discomfort	8	76/567	58/524	OR 3.47 (0.64, 18.86)	OR 2.64 (0.52, 13.40)	80% (52%, 91%)
Cardiac arrest	9	13/1164	11/1130	OR 0.82 (0.33, 2.02)	OR 1.03 (0.26, 4.09)	23% (0%, 92%)

* Four out of 5 studies reported no event on bloating sensation, resulting in only 1 study contributing to the final meta-analysis result, therefore, I^2 was not available.

APP, awake prone positioning; CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; IPD-MA, individual participant meta-analyses; LOS, length of stay; MA, meta-analyses; MD, mean difference; NA, not available; OR, odds ratio.