Effect of Awake Prone Positioning in non-Intubated COVID-19 Patients with Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis

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Abstract

Background: Awake prone positioning (APP) has been considered as a feasible treatment for patients with acute hypoxemic respiratory failure in non-intubated coronavirus disease 2019 (COVID-19). However, the efficacy and safety of APP remain uncertain. This meta-analysis aims to assess the effect of APP on intubation rate and mortality in COVID-19 patients with acute respiratory failure.

Methods: Relevant studies published from January 1, 2020, to June 17, 2022, were systematically searched. The primary outcomes were the intubation rate and mortality; the secondary outcome was the incidence of adverse events.

Results: Of 5746 identified publications, 22 were eligible for inclusion in the meta-analysis (N = 5146 patients). In comparison to the non-APP group, APP could decrease the intubation rates (OR 0.64; 95% CI 0.48-0.83; $P = .001$), particularly in the subgroup of the daily median duration of APP > 8 h and in the subgroup of receiving high flow nasal cannula (HFNC) or non-invasive ventilation (NIV). Patients treated with APP were associated with lower mortality rates (OR 0.61; 95% CI 0.45-0.81; $P = .0008$), but no mortality benefit was found in the APP group in the subgroup of randomized controlled trials (RCTs). No significant difference was found in the incidence of adverse events between the groups (OR 1.13; 95% CI 0.75-1.71; $P = .56$).

Conclusion: Our results demonstrated that APP could be an effective strategy to avoid intubation without detrimental effects in non-intubated patients with COVID-19, especially for patients requiring HFNC or NIV, and the daily APP duration with the target of minimally eight hours was suggested. In the subgroup of RCTs, the pooled results did not demonstrate any benefit of APP on mortality. Given the limited number of RCTs, further high-quality RCTs are needed to confirm the results.

INPLASY registration number: INPLASY2021110037.

Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread quickly and has become a global pandemic. The COVID-19 disease severity ranges from mild to critical disease. Approximately 15% of COVID-19 patients are severe cases requiring oxygen support, and 5% develop the critically ill disease with respiratory failure, acute respiratory distress syndrome (ARDS), or other complications and even need to be admitted to the intensive care unit (ICU) for mechanical ventilation.[1,2] Some studies found that the mortality rates of COVID-19 patients admitted to ICU were between 26% and 53.8%.[3,4] Patients receiving invasive mechanical ventilation (IMV) have a higher mortality rate, ranging from 41% to 97%.[5–7] The best treatment to improve the outcomes of these patients remains unclear.

Prone position ventilation has several beneficial physiologic effects, including promoting the re-opening of collapsed lung alveolar, improving respiratory compliance, ameliorating the ventilation/perfusion ratio, facilitating the sputum drainage, and improving the function of the right heart.[8–10]

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So, prone position ventilation is considered one of the essential treatments for patients with moderate to severe ARDS. Previous studies have shown that prone positioning improves oxygenation and reduces mortality in intubated ARDS patients.[11–13] In non-intubated patients with acute hypoxemic respiratory failure or ARDS, some trials suggested that awake prone positioning (APP) may improve oxygenation and help avoid intubation.[14,15]

Given the high mortality rate among IMV patients, the risk of virus transmission of endotracheal intubation, and the limited medical resources during the pandemic, it is crucial to find a feasible and effective non-invasive method to stabilize respiratory status and avoid intubation in patients with COVID-19. The APP has been increasingly concerned during the COVID-19 pandemic. Some studies reported that APP effectively ameliorates blood oxygenation in non-intubated COVID-19 patients with acute respiratory failure.[16,17] As for the intubation rate and mortality, the results of different studies are inconsistent. A meta-analysis found that APP did not reduce the intubation rate and mortality in COVID-19 patients with acute respiratory failure.[18] Some recent meta-analyzes' findings on the intubation rate were consistent with that meta-analysis, but they found the beneficial effect of APP on mortality.[19,20] However, a recent randomized, controlled, meta-trial reported that APP could decrease the incidence of treatment failure and the intubation rate in subjects with hypoxemic respiratory failure due to COVID-19.[21] Several latest high-quality studies have also assessed APP's effect on the outcomes of COVID-19 patients but have produced inconsistent results.[22–25] As a result, the use of APP remains controversial. The updated Surviving Sepsis Campaign Guideline also stated that they could not issue a recommendation on using APP in non-intubated COVID-19 adults because of the uncertainty about the effect on patient's important outcomes.[26]

It is necessary to solve the controversy regarding APP's effect on intubation rate and mortality for COVID-19 patients with acute hypoxaemic respiratory failure. Thus, we systematically reviewed the current trials and performed a meta-analysis to assess whether APP can reduce the intubation rate and mortality of COVID-19 adults with acute hypoxemic respiratory failure than standard care. Several new studies are included in this meta-analysis. Moreover, some subgroup analyzes that might influence the results were also considered. The results may help clarify the APP's effects on patients with COVID-19.

Methods

Search Strategy

Databases of Pubmed, Embase, and Cochrane Library were systematically searched from January 1, 2020, to June 17, 2022. The search terms were as follows: ("COVID-19" or "COVID 19" or "COVID-19 Virus Disease" or "COVID 19 Virus Disease" or "COVID-19 Virus Diseases" or "Disease, COVID-19 Virus" or "Disease 2019, Coronavirus" or "Virus Disease, COVID-19" or "COVID-19 Virus Infection" or "COVID 19 Virus Infection" or "COVID-19 Virus Infections" or "Infection, COVID-19 Virus" or "Virus Infection, COVID-19" or "2019- nCoV" or "2019 nCoV" or "Coronavirus Disease-19" or "Coronavirus Disease 19" or "Coronavirus Disease 2019" or "2019 Novel Coronavirus" or "2019 Novel Coronaviruses" or "COVID19" or "SARS Coronavirus 2" or "Coronavirus 2, SARS" or "SARS CoV 2" or "SARS-CoV-2" or "Severe Acute Respiratory Syndrome Coronavirus 2" or "Coronavirus, 2019 Novel" or "Novel Coronavirus, 2019") and ("prone position*" or "Pron*").

In our study, two reviewers (HK, XG) independently searched and screened the study titles and abstracts, and further accessed full texts of eligible studies to select the included studies. No language restrictions were applied. The reference lists of the included studies were manually screened to identify other relevant studies. All disagreements were resolved by a third person (ZT). The INPLASY registration number is INPLASY2021110037.

Study Selection

The inclusion criteria were as follows: (1) adult (≥18 years old) COVID-19 patients with acute hypoxemic respiratory failure or ARDS and in the non-intubated state; (2) studies that compared the experimental group using non-invasive respiratory support in the awake prone position with the control group using non-invasive respiratory support which not in the prone position; (3) studies included required outcomes and the data could be directly extracted or calculated; (4) randomized controlled trials (RCTs) or observational cohort studies.

The exclusion criteria were as follows: (1) reviews, meta-analyzes, case reports, case series, abstract, study protocols, or expert opinions; (2) cross-over trials; (3) duplicates; (4) insufficient data; (5) multiple publications; (6) unpublished studies; (7) not related to COVID-19 patients; (8) studies that enrolled patients younger than 18 years old or animals; (9) experimental group did not receive non-invasive respiratory support combined with APP; 10) control group did not receive non-invasive respiratory support combined with non-APP; 11) studies that only compared pre-APP with post-APP in one cohort/group; 12) not reported the outcomes what we need.

Data Extraction and Risk of Bias Assessment

Two review authors (HK, XG) independently extracted data and evaluated the risk of bias of the included studies. Any disagreement was resolved by a third person (ZT). The following data were extracted from the included studies: first author, publication year, number of centers, study design, clinical setting, characteristics of the patients, respiratory support method, number of patients, description of the intervention group, description of the control group, outcomes. We e-mailed the corresponding authors when any data were insufficient. We judged the risk of bias of the included

RCTs using the Cochrane Collaboration Risk of Bias tool[27] and rated them as "low," "unclear," or "high" in each domain. And we used the Newcastle-Ottawa scale to assess the risk of bias of the included observational cohort studies. An observational study was classified as high, moderate, and low risk of bias when it achieved 1–3, 4–5, and 6–9 points, respectively.[28]

Outcomes

The primary outcomes included intubation rate and mortality. The secondary outcome was the incidence of adverse events (pain or discomfort, skin breakdown, vomiting, central or arterial line dislodgement, cardiac arrest, etc).

Statistical Analysis

All statistical analyzes were conducted with Review Manager Version 5.4 and Stata version 16.0. Values for dichotomous outcomes were presented as the odds ratios (OR) with 95% confidence intervals (CI). And values for continuous outcomes were reported as the mean (standard deviation). The Mantel-Haenszel random-effects model was used to analyze the results. The results of the meta-analysis were presented in the forest plots. Statistical heterogeneity between studies was assessed by I^2 testing. I^2 of more than 50% was regarded as moderate-to-high heterogeneity.[29] We used subgroup analyzes and sensitivity analyzes to explore the sources of heterogeneity. For the primary outcomes, subgroup analysis based on RCTs and observational studies was conducted to identify the potential sources of moderate-to-high heterogeneity. Sensitivity analyzes were also performed by excluding studies with a moderate or high risk of bias to find the potential influence. We also performed subgroup analyzes of some other factors that might influence the primary outcomes, such as the daily median duration of APP (<8 h versus >8 h) and the non-invasive respiratory support methods [conventional oxygen therapy (COT) versus high flow nasal cannula (HFNC) or non-invasive ventilation (NIV)] given to patients in APP. The publication bias was evaluated by the funnel plot and Egger tests when more than ten studies were included, and a P value less than .05 was considered a substantial publication bias. The GRADE system was used to evaluate the quality of evidence for the outcomes.

Results

Search Results

We identified 5746 publications, from which 1511 were duplicates (Figure 1). After screening the titles and abstracts, 86 records were included for full-text screening. Then, 64 articles were excluded for reasons described in the flow diagram (Figure 1). Finally, 22 studies with a total of 5146 patients were included in the meta-analysis.[21–25,30–46]

Study Characteristics and Risk of Bias

The characteristics of the included studies are shown in Supplemental Table 1. The sample size ranged from 20 to 1121 patients. Seven of these studies were RCTs,[21,22,24,25,30–32] of which one was a randomized, controlled, multinational, meta-trial.[21] The other fifteen were observational studies.[23,33–46] All the studies explored the effect of APP in COVID-19-related acute respiratory failure or ARDS patients without intubation. These patients were treated with different non-invasive respiratory support methods. In the APP group, the median duration of prone position in these included studies varied from 2 h to at least 12 h per day. The assessment of the risk of bias is presented in Supplemental Figures 1, 2, and Supplemental Table 2. Seven RCTs were assessed as low risk of bias because they had a low risk of bias in nearly all domains. For observational cohort studies, ten were considered as low risk of bias with 6–9 points assessed by the Newcastle-Ottawa Scale, and five articles were of moderate risk of bias (5 points).

Intubation Rate

22 studies[21–25,30–46] involving 5146 patients reported intubation rates (Supplemental Figure 3). The result found that APP was associated with a significant reduction in intubation rate compared with the control group (OR 0.64; 95% CI 0.48-0.83; $P = .001$), with moderate heterogeneity among these studies ($\chi^2 = 58.62$, $I^2 = 66\%$). Subgroup analysis was used to explore the source of potential heterogeneity. The result of the subgroup analysis suggested that APP could reduce intubation rate both in the RCTs subgroup (seven studies; OR 0.72; 95% CI 0.61-0.86; $P = .0004$; $I^2 = 0\%$) and the observational studies subgroup (fifteen studies; OR 0.56; 95% CI 0.36-0.86; $P = .008$; $I^2 = 74\%$), the P-value for subgroup differences was .28 (Figure 2). Then we did sensitivity analysis (Supplemental Figure 4) by excluding five articles with a moderate risk of bias. The result did not change, and the moderate-to-high heterogeneity disappeared (OR 0.66; 95% CI 0.53-0.82; $P = .0002$; $I^2 = 36\%$).

Thirteen of the 22 studies reported the actual daily median duration of APP.[21–25,30,36,37,40–43,46] In the subgroup of the daily median duration of APP > 8 h (five studies; OR 0.47; 95% CI 0.25-0.88; $P = .02$; $I^2 = 78\%$), pool analysis showed that the APP reduced the intubation rate in comparison to the control group. However, APP did not appear to reduce the intubation rate in the subgroup of the daily median duration of APP < 8 h (eight studies; OR 0.85; 95% CI 0.65-0.12; $P = .25$; $I^2 = 31\%$). The P-value for subgroup differences was .09. The details are shown in Figure 3.

Four of the 22 studies reported that patients were treated with COT in APP.[32,34,41,43] In the subgroups of COT, no significant difference in intubation rate was found between the APP group and the control group (four studies; OR 1.04; 95% CI 0.22-4.87; $P = .96$; $I^2 = 82\%$). And five of the 22 studies reported that patients were treated with HFNC or NIV in APP.[21,24,30,37,46] The results showed that APP appeared to decrease the intubation rate in the subgroup of HFNC or NIV (five studies; OR
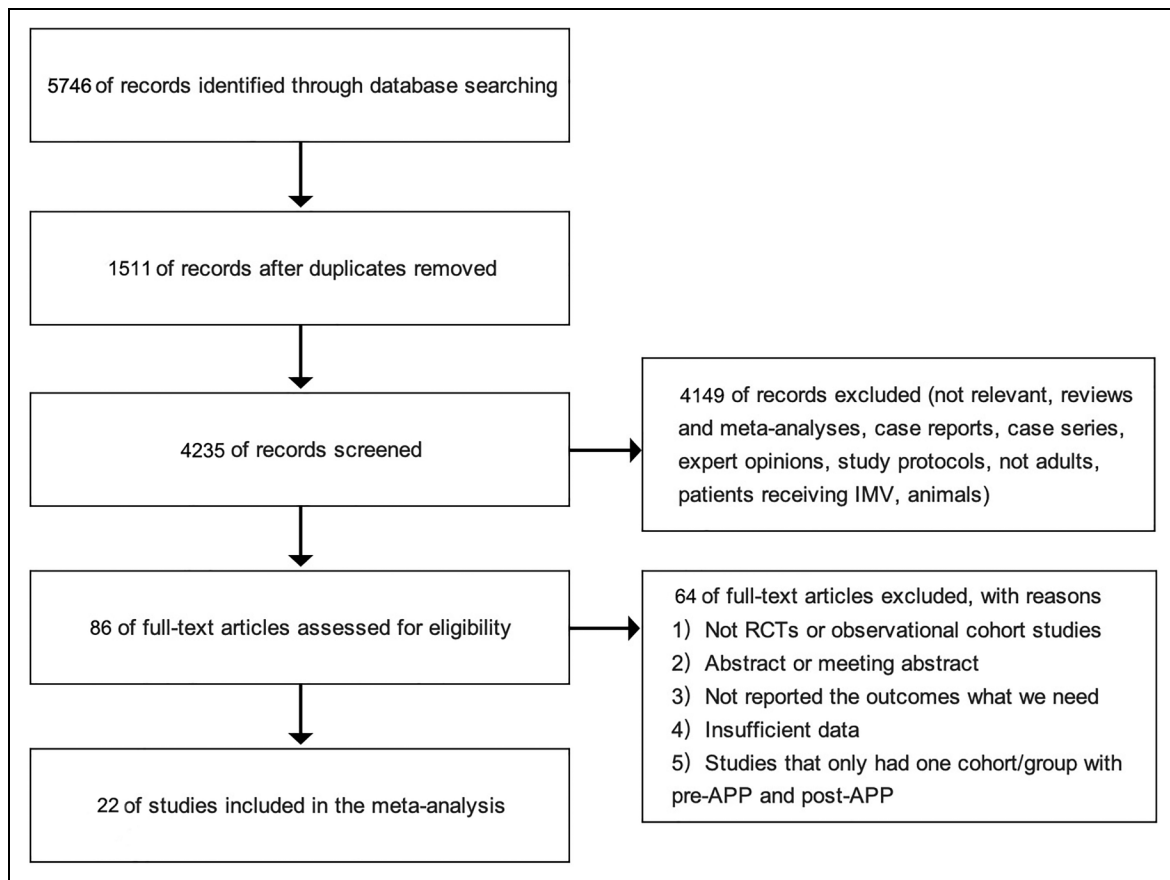
Figure 1. Flow chart of the study selection.

0.60; 95% CI 0.39-0.93; $P = .02$; $I^2 = 76\%$). The *P*-value for subgroup differences was .51. The result of the subgroup analysis is shown in Figure 4.

Mortality

20 studies[21–25,30–41,43,45,46] estimated the effect of APP on mortality (Supplemental Figure 5). Pooled analysis showed that APP reduced mortality in comparison to the control group (OR 0.61; 95% CI 0.45-0.81; $P = .0008$), with moderate heterogeneity ($\chi^2 = 47.86$, $I^2 = 60\%$). The heterogeneity was explored by subgroup analysis (Figure 5). The results indicated that APP was associated with a reduction in mortality in the subgroup of observational studies (thirteen studies; OR 0.44; 95% CI 0.29-0.66; $P < .0001$; $I^2 = 61\%$), but there was no difference between the APP group and non-APP group in the subgroup of RCTs (seven studies; OR 0.89; 95% CI 0.73-1.09; $P = .26$; $I^2 = 0\%$); the *P*-value for subgroup differences was .002. We also did sensitivity analyzes by excluding articles with a moderate risk of bias (Supplemental Figure 6), and no change was found in the result, which suggested this result was robust.

Twelve of the 20 studies reported the daily median duration of APP.[21–25,30,36,37,40,41,43,46] APP did not appear to reduce mortality in both subgroups of the daily median duration of APP > 8 h (five studies; OR 0.65; 95% CI 0.31-1.34; $P = .24$; $I^2 = 77\%$) and <8 h (seven studies; OR 0.85; 95% CI

0.65-1.11; $P = .24$; $I^2 = 20\%$) (Supplemental Figure 7). The *P*-value for subgroup differences was .49. Four studies analyzed mortality among the COT subgroup,[32,34,41,43] and the results showed that APP could reduce mortality (OR 0.37; 95% CI 0.17-0.81; $P = .01$; $I^2 = 31\%$); there were five studies in the HFNC or NIV subgroup,[21,24,30,37,46] APP did not appear to reduce mortality (OR 0.76; 95% CI 0.46-1.26; $P = .29$; $I^2 = 76\%$); the *P*-value for subgroup differences was .14. The details are presented in Supplemental Figure 8.

Adverse Events

For adverse events (Figure 6), three studies[22,24,43] reported the incidence of pain or discomfort, four studies[21,24,30,42] reported the incidence of skin breakdown, and six trials[21,22,24,30,42,43] reported the incidence of central or arterial line dislodgement, four studies[21,22,24,30] reported the incidence of vomiting and cardiac arrest. In general, APP did not increase the incidence of adverse events (OR 1.13; 95% CI 0.75-1.71; $P = .56$), with mild heterogeneity ($\chi^2 = 23.50$, $I^2 = 32\%$).

Publication Bias

More than ten studies reported the primary outcomes of intubation rate and mortality, so we used funnel plots (Supplemental Figures 9 and 10) and Egger's test to assess the publication bias.
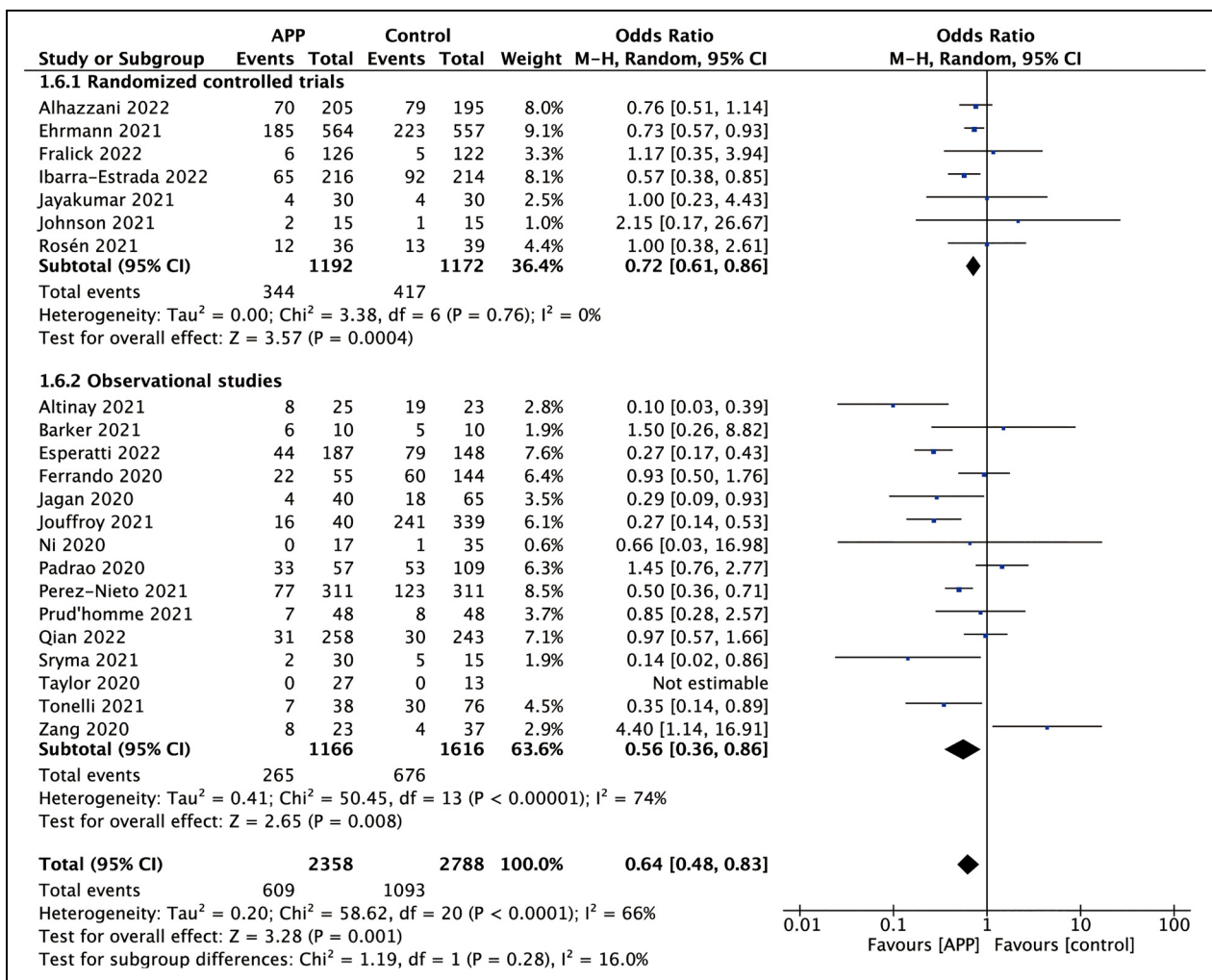
Figure 2. Forest plot for subgroup analysis of intubation rate according to randomized controlled trials or observational studies.

No significant publication bias was found for the primary outcomes (P values for intubation rate and mortality were .7429 and .3398, respectively).

Quality of the Meta-Analysis Evidence

The GRADE summary of evidence is shown in Supplemental Table 3. For the primary outcomes, the principles of the GRADE system indicated that the quality of evidence for both intubation rate and mortality in the subgroups of RCTs was of high quality. However, the quality of evidence for intubation rate and mortality in the observational studies subgroup was very low.

Discussion

Our systematic review and meta-analysis demonstrated that APP could reduce the incidence of endotracheal intubation without increasing the incidence of adverse events in COVID-19-related acute hypoxemic respiratory failure or

ARDS patients requiring non-invasive respiratory support. Overall, the findings support the application of APP to avoid intubation in non-intubated patients with acute hypoxemic respiratory failure or ARDS due to COVID-19. The results differed from another systematic review and meta-analysis,[18] which reported that APP was not associated with the reduced intubation rate and mortality of COVID-19 patients with acute respiratory failure.

In the study, we found that APP reduced the intubation rate compared with standard care, contrary to the results of a recent meta-analysis.[20] Our result was consistent with a previous study about non-COVID-19 related ARDS patients done by Ding et al,[15] which showed that early use of prone position ventilation combined with HFNC might help decrease the rate of intubation in patients with moderate ARDS. Several reasons may account for the lower incidence of intubation rate. First, the ventilation distribution can be more homogeneous in the prone position than in the supine position, thereby promoting ventilation to match perfusion and decreasing the alveolar shunt.[47,48] Second, prone positioning is more conducive to the clearance
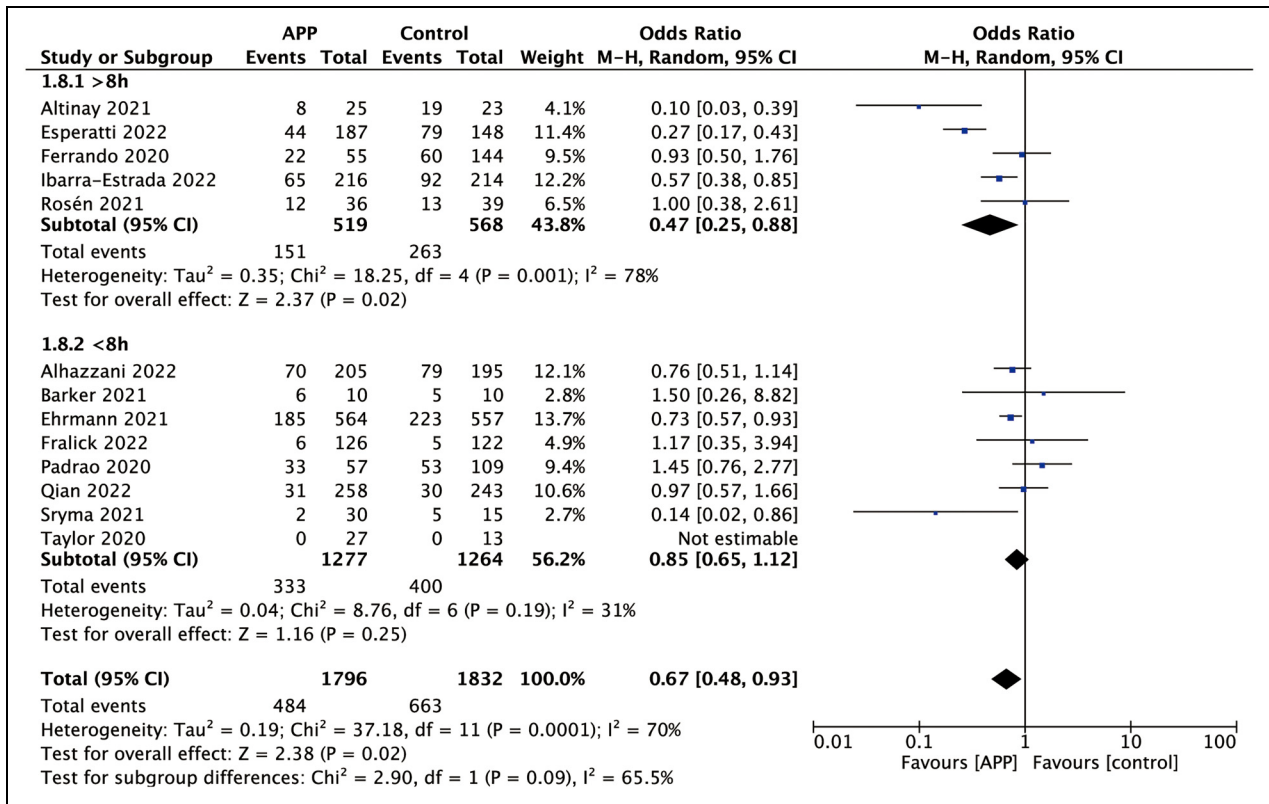
Figure 3. Forest plot for subgroup analysis of intubation rate according to the daily median duration of APP.
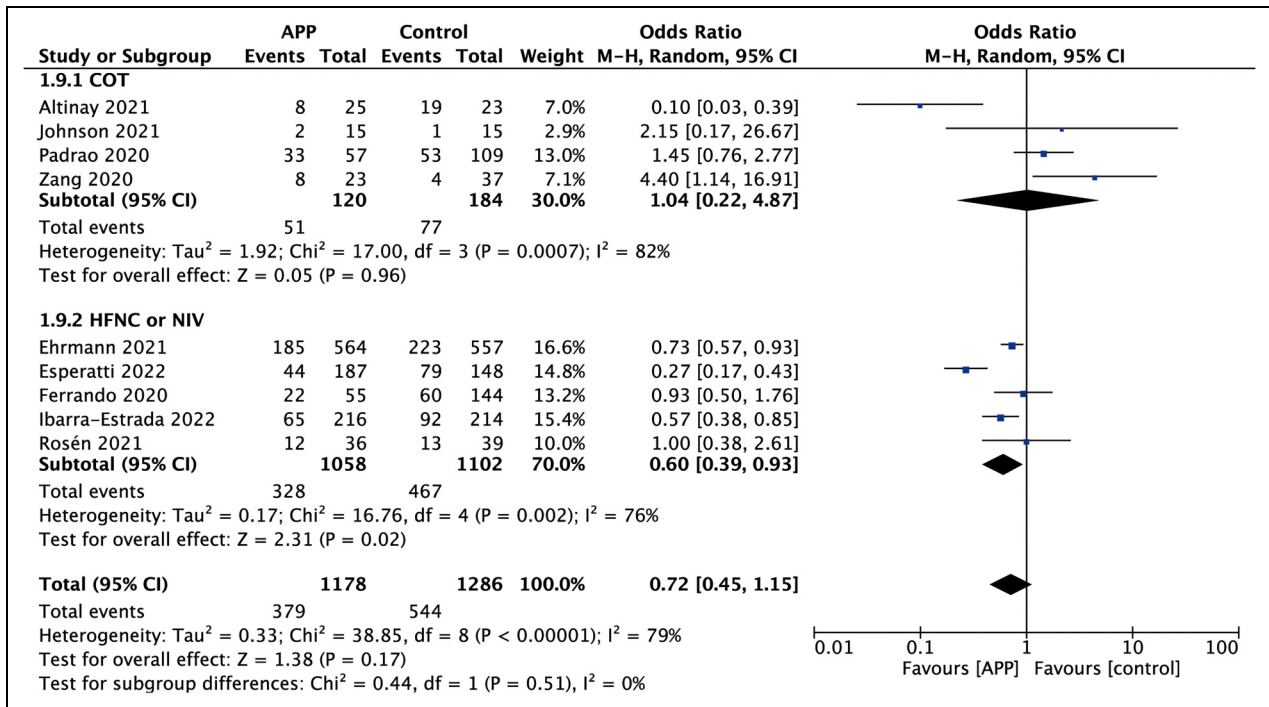
Figure 4. Forest plot for subgroup analysis of intubation rate according to the non-invasive respiratory support methods.

of the secretion on the dorsal lung because of the influence of gravity.[9] Last but not least, when prone ventilation strategies are applied in patients, collapsed alveoli in dorsal lung regions tend to re-open.[49] In a word, the physiological benefits of the position change might help improve oxygenation, prevent the exacerbation of the disease, and further reduce the
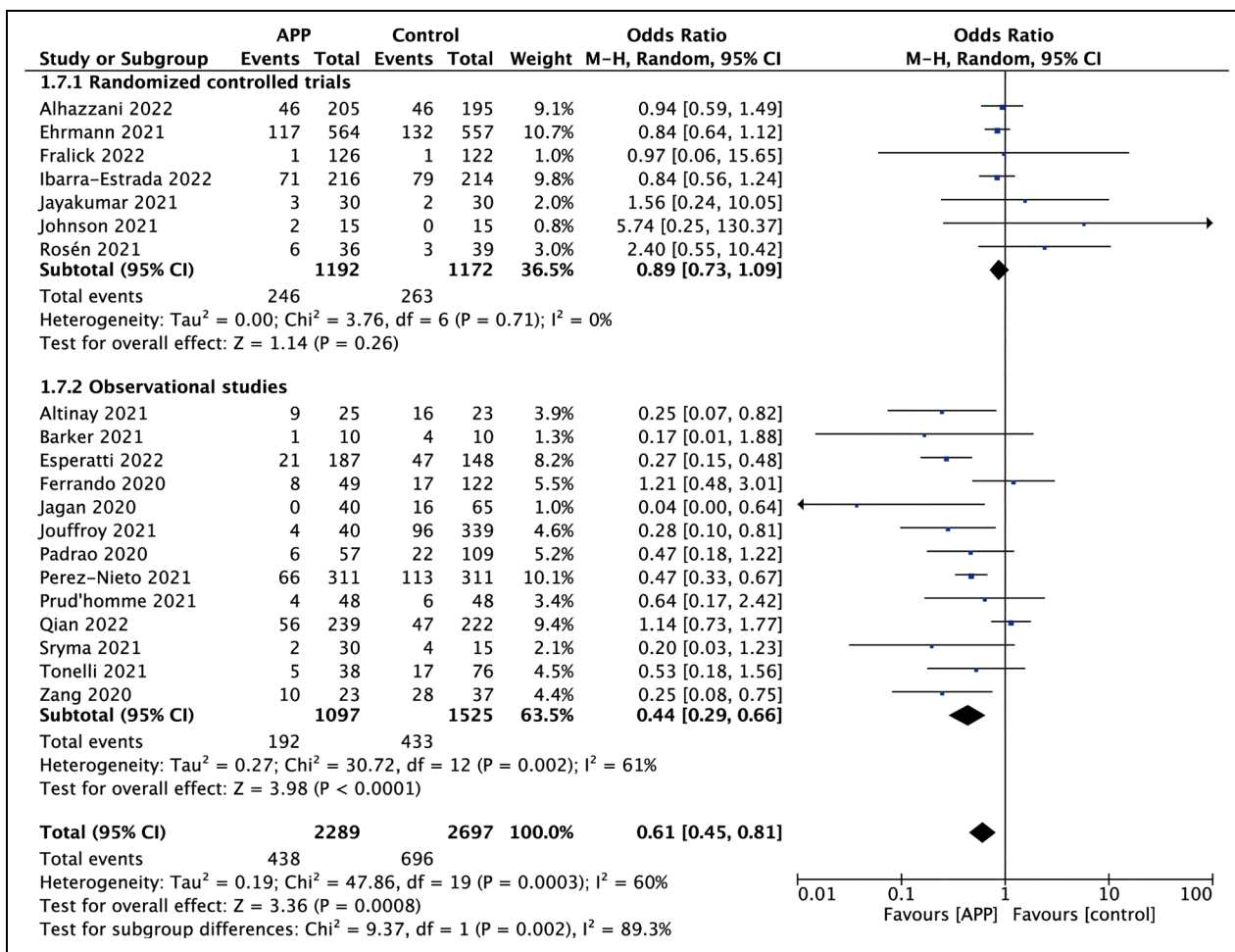
Figure 5. Forest plot for subgroup analysis of mortality according to randomized controlled trials or observational studies.

intubation rate. Then, the need for IMV may be lower, which could relieve the stress of lacking ICU resources during the pandemic and reduce the risk of disease transmission through aerosols generated during endotracheal intubation. However, it has been reported that delayed intubation was associated with increased mortality in ARDS patients.[50] Therefore, we need to closely monitor patients' responses and the progress of the disease during APP, and if necessary, timely intubation is required to avoid delay.

In the subgroup analysis regarding the daily median duration of APP, we found that APP significantly reduced the intubation rate of COVID-19 patients with acute hypoxaemic respiratory failure, especially among patients in the subgroup with a daily median duration of APP > 8 h. A recent study also demonstrated that the APP duration was associated with APP success, and a longer APP duration with the target of minimally 8 h/day was suggested,[24] which was consistent with our subgroup analysis results. However, the goal of minimally 8 h/day was not reached in many studies due to the poor adherence to APP, which may affect the APP's effectiveness to some extent. Thus, it is crucial to improve the compliance and comfort of APP in clinical practice. In the subgroup analysis regarding

the non-invasive respiratory support methods, we found that APP significantly decreased the intubation rate of COVID-19 patients with acute hypoxaemic respiratory failure among patients in the subgroup receiving HFNC or NIV was as same as the latest meta-analysis.[51] The reason may be because patients receiving COT had less severe diseases and were less likely to progress to endotracheal intubation than patients receiving HFNC or NIV.

Our meta-analysis suggested that APP was associated with decreased mortality in acute hypoxemic respiratory failure or ARDS patients due to COVID-19. Other meta-analyzes also found evidence of the prone position on reducing mortality rate in non-intubated COVID-19 patients.[19,52] The application of APP could help stabilize COVID-19 patients' respiratory status and avoid intubation, which may partially explain the survival benefit. However, we found that APP did not reduce the mortality rate in the subgroup analysis of the RCTs group. In the subgroup analysis of the observational studies group, we still found that the mortality rate was lower in patients treated with APP. The results of the subgroup analysis suggested that the study design might have a potential impact on patients' outcomes. More high-quality RCTs are needed to confirm the findings in the future. Besides,
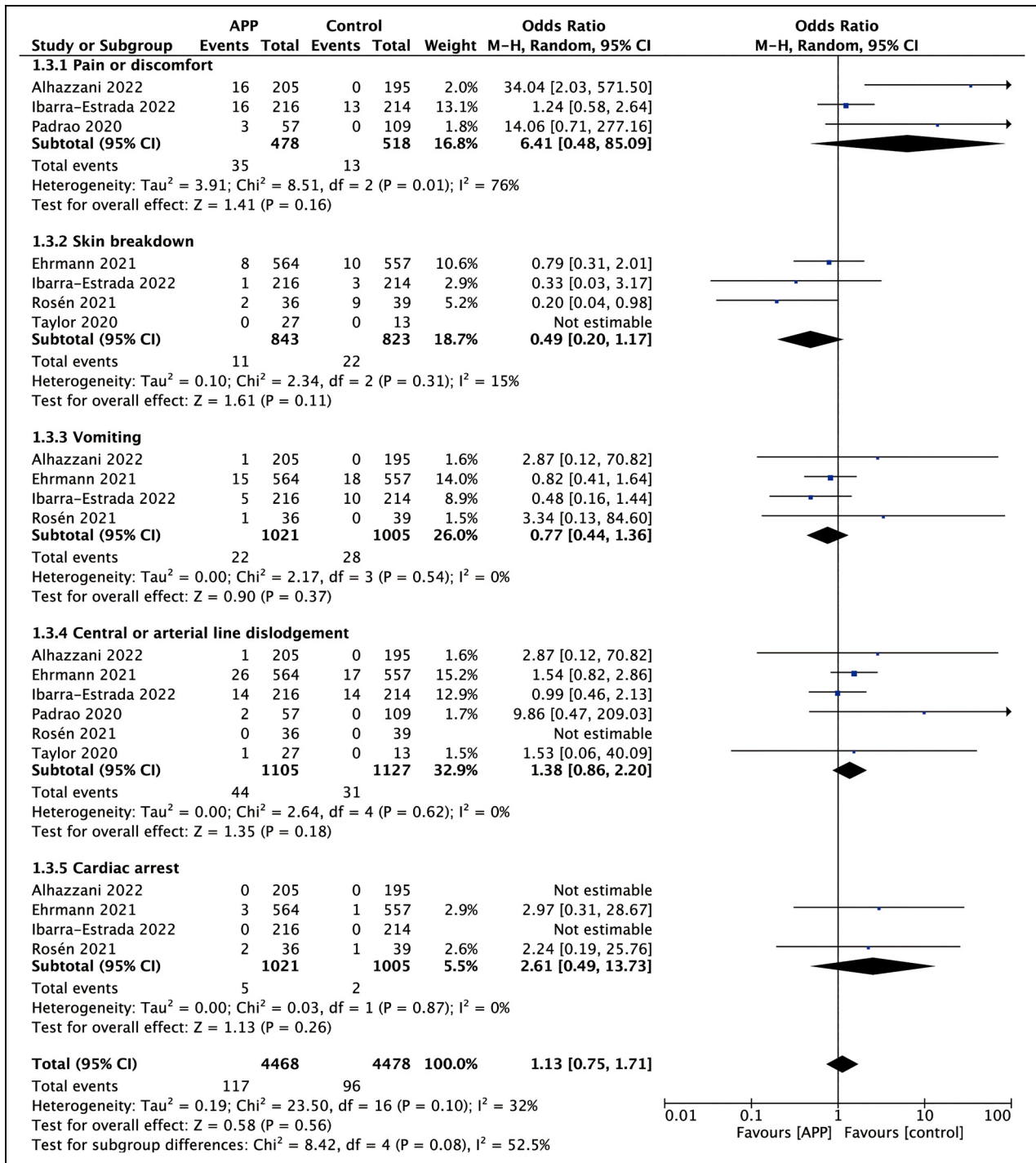
Study or Subgroup	APP Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Odds Ratio M–H, Random, 95% CI
1.3.1 Pain or discomfort							
Alhazzani 2022	16	205	0	195	2.0%	34.04 [2.03, 571.50]	
Ibarra–Estrada 2022	16	216	13	214	13.1%	1.24 [0.58, 2.64]	
Padrao 2020	3	57	0	109	1.8%	14.06 [0.71, 277.16]	
Subtotal (95% CI)		**478**		**518**	**16.8%**	**6.41 [0.48, 85.09]**	
Total events	35		13				
Heterogeneity: Tau² = 3.91; Chi² = 8.51, df = 2 (P = 0.01); I² = 76%							
Test for overall effect: Z = 1.41 (P = 0.16)							
1.3.2 Skin breakdown							
Ehrmann 2021	8	564	10	557	10.6%	0.79 [0.31, 2.01]	
Ibarra–Estrada 2022	1	216	3	214	2.9%	0.33 [0.03, 3.17]	
Rosén 2021	2	36	9	39	5.2%	0.20 [0.04, 0.98]	
Taylor 2020	0	27	0	13		Not estimable	
Subtotal (95% CI)		**843**		**823**	**18.7%**	**0.49 [0.20, 1.17]**	
Total events	11		22				
Heterogeneity: Tau² = 0.10; Chi² = 2.34, df = 2 (P = 0.31); I² = 15%							
Test for overall effect: Z = 1.61 (P = 0.11)							
1.3.3 Vomiting							
Alhazzani 2022	1	205	0	195	1.6%	2.87 [0.12, 70.82]	
Ehrmann 2021	15	564	18	557	14.0%	0.82 [0.41, 1.64]	
Ibarra–Estrada 2022	5	216	10	214	8.9%	0.48 [0.16, 1.44]	
Rosén 2021	1	36	0	39	1.5%	3.34 [0.13, 84.60]	
Subtotal (95% CI)		**1021**		**1005**	**26.0%**	**0.77 [0.44, 1.36]**	
Total events	22		28				
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.90 (P = 0.37)							
1.3.4 Central or arterial line dislodgement							
Alhazzani 2022	1	205	0	195	1.6%	2.87 [0.12, 70.82]	
Ehrmann 2021	26	564	17	557	15.2%	1.54 [0.82, 2.86]	
Ibarra–Estrada 2022	14	216	14	214	12.9%	0.99 [0.46, 2.13]	
Padrao 2020	2	57	0	109	1.7%	9.86 [0.47, 209.03]	
Rosén 2021	0	36	0	39		Not estimable	
Taylor 2020	1	27	0	13	1.5%	1.53 [0.06, 40.09]	
Subtotal (95% CI)		**1105**		**1127**	**32.9%**	**1.38 [0.86, 2.20]**	
Total events	44		31				
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.35 (P = 0.18)							
1.3.5 Cardiac arrest							
Alhazzani 2022	0	205	0	195		Not estimable	
Ehrmann 2021	3	564	1	557	2.9%	2.97 [0.31, 28.67]	
Ibarra–Estrada 2022	0	216	0	214		Not estimable	
Rosén 2021	2	36	1	39	2.6%	2.24 [0.19, 25.76]	
Subtotal (95% CI)		**1021**		**1005**	**5.5%**	**2.61 [0.49, 13.73]**	
Total events	5		2				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%							
Test for overall effect: Z = 1.13 (P = 0.26)							
Total (95% CI)		**4468**		**4478**	**100.0%**	**1.13 [0.75, 1.71]**	
Total events	117		96				
Heterogeneity: Tau² = 0.19; Chi² = 23.50, df = 16 (P = 0.10); I² = 32%							
Test for overall effect: Z = 0.58 (P = 0.56)							
Test for subgroup differences: Chi² = 8.42, df = 4 (P = 0.08), I² = 52.5%							

0.01   0.1   1   10   100
Favours [APP]   Favours [control]

Figure 6. Forest plot showing the effect of awake prone positioning on the incidence of adverse events of non-intubated COVID-19 patients with acute hypoxemic respiratory failure.

we did not find different effects of APP on mortality between subgroups with a duration of APP > 8 h/day and subgroups with APP duration of fewer than 8 h/day. Nevertheless, the results of subgroup analysis regarding the non-invasive respiratory support methods showed that the type of non-invasive respiratory support strategies might affect APP's effect on patients' mortality. However, as the number of high-quality RCTs was limited in our included studies, the impact of APP on mortality rate in COVID-19-related acute hypoxemic respiratory failure or ARDS patients remains uncertain. Many factors may influence patients' mortality. On the one hand, the characteristics of patients can affect the outcomes. For instance, several studies have found that patients' age,[53] the severity of disease,[54] and the patient's response to prone positioning[55] were associated with the mortality

rate. On the other hand, the strategies of APP in the included studies are inconsistent due to lacking standardized procedures. The duration of APP,[56] the timing of APP initiation,[57,58] and the type of non-invasive respiratory support methods combined with APP[15] have been considered as potential factors affecting mortality in some previous studies. Future studies should focus more on these possible factors influencing patient outcomes.

Complications, such as pressure ulcers, device displacement, vomiting, and hemodynamic instability, can occur in patients in prone positioning.[10,59] In our study, we explored the safety of APP. We found that APP did not increase the incidence of adverse events compared with the non-APP group. The possible reason is that patients treated with APP remain conscious and can spontaneously breathe, actively express their discomfort during prone positioning and adequately adjust the body position according to their tolerance. As a result, the risk of adverse events could be reduced. Although two studies reported the occurrence of cardiac arrest,[21,30] both mentioned that the cardiac arrest was unrelated to APP.

Moderate heterogeneity could be detected in primary outcomes (intubation rate and mortality). For intubation rate, the subgroup analysis based on RCTs and observational studies could not completely explain the heterogeneity. Although no heterogeneity was found in the subgroup analysis of the RCTs group, the subgroup of observational studies still had potential heterogeneity. Except for five observational studies with a moderate risk of bias, nearly all included studies had a low risk of bias. So, we further did sensitivity analysis by excluding trials with a moderate risk of bias. We found the result was consistent, but the heterogeneity could not be detected. For mortality, subgroup analysis was performed to explore the source of heterogeneity. The results showed that the determined statistical heterogeneity disappeared in the RCTs subgroup. Further sensitivity analyzes were done by excluding studies with a moderate risk of bias. We found that moderate-to-high heterogeneity could not be detected. Hence, we concluded that the included non-RCTs and the risk of bias in some domains potentially impacted the primary outcomes.

To our knowledge, this is the latest meta-analysis focused on the feasibility and safety of APP in non-intubated COVID-19 patients, which includes some recent high-quality RCTs. Another advantage is that our review's inclusion criteria are more stringent and just included studies that compared APP group with a control group of non-APP, and studies without a control group that only compared pre-APP with post-APP were excluded. Furthermore, we explored more subgroup analyzes and found that APP could reduce the intubation rate in COVID-19 patients, particularly in the subgroup with a median APP duration >8 h/day and those patients treated with HFNC or NIV.

Our study also has some limitations. First, due to the limited number of RCTs, most included studies were observational cohort studies; more high-quality RCTs are required to confirm APP's effects on COVID-19 patients in the future. Second, there were no standardized strategies for APP in our included studies. The initiation time, the duration of APP, and the combined respiratory support methods varied in these trials, which might affect the outcomes. The potential heterogeneity needs attention, and the optimal APP strategy needs further exploration. Third, given the absence of available patients' individual data, we couldn't evaluate the effect of demographic characteristics, severity of disease, and the different response to APP on patients' outcomes. Future studies should pay more attention to the individual subject's data that may impact a patient's prognosis. The appropriate selection of patients for an individualized APP strategy may be more helpful in improving non-intubated COVID-19 patients' outcomes. Finally, considering the credibility of the results, we only included published studies and not included unpublished grey studies which were not peer-reviewed. Although we evaluated the publication bias of the primary outcomes by the funnel plot and Egger tests, no significant publication bias was found. There is still the potential for publication bias.

Conclusions

In summary, applying APP with close monitoring by professionals may be feasible and safe in non-intubated patients with COVID-19. Our results suggested that APP was associated with reduced intubation rate and mortality of adults with COVID-19-related acute hypoxemic respiratory failure or ARDS without increasing the incidence of adverse events. However, no benefit of APP on mortality was found in the subgroup of RCTs. Because of the limitations of the meta-analysis, more high-quality RCTs should be performed further to confirm the influences of APP on non-intubated COVID-19 patients.

Abbreviations

COVID-19	the coronavirus disease 2019
ARS-CoV-2	severe acute respiratory syndrome coronavirus 2
ARDS	acute respiratory distress syndrome
ICU	intensive care unit
APP	awake prone positioning
IMV	invasive mechanical ventilation
RCTs	randomized controlled trials
OR	odds ratios
CI	confidence intervals
HFNC	high flow nasal cannula
NIV	non-invasive ventilation

Authors' Contributions

ZT came up with the idea, HK and XG contributed to the literature search, data collection, study design, and data analysis. HK drafted the manuscript. ZT revised the final manuscript.

Availability of Data and Materials

All data analyzed during this meta-analysis are included in this published article and its supplementary information files.

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