
Systematic Review

Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: A systematic review of proportional outcomes comparing observational studies with and without awake prone positioning in the setting of COVID-19

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Title page

Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: A systematic review of proportional outcomes comparing observational studies with and without awake prone positioning in the setting of COVID-19

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Abstract

Background Awake prone positioning (APP) has been advocated to improve oxygenation and prevent intubations of patients with acute hypoxemic respiratory failure due to coronavirus disease 2019 (COVID-19). This paper aims to synthesize the available evidence on the efficacy of APP.

Methods: We performed a systematic review of proportional outcomes from observational studies to compare intubation rate in patients treated with APP or with standard care.

Results: A total of 46 published and 4 unpublished observational studies that included 2994 patients were included, of which 921 patients were managed with APP, and 870 patients were managed with usual care. APP was associated with significant improvement of oxygenation parameters in 381 cases of 19 studies that reported this outcome. Among the 41 studies assessing intubation rates (870 patients treated with APP, and 852 patients treated with usual care), the intubation rate was 27%(95%CI, 19 to 37%), as compared to 30%(95%CI, 20 to 42%)($p=0.71$), even when duration of application, use of adjunctive respiratory assist device (high flow nasal cannula or non-invasive ventilation) and severity of oxygenation deficit were taken into account. There appeared to be a trend toward improved mortality when treated with APP was compared with usual care (11% v.s. 22%), which was not statistically significant.

Conclusions: APP was associated with improvement of oxygenation but did not reduce the intubation rate in patients with acute respiratory failure due to COVID-19. This finding is limited by the high heterogeneity and the observational nature of included studies. Randomized controlled clinical studies are needed to definitively assess whether APP could improve key outcome such as intubation and mortality rate in these patients.

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Keywords:

Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), Acute respiratory distress syndrome (ARDS), Acute hypoxemic respiratory failure (AHRF), Acute respiratory failure (ARF), High-flow nasal cannula (HFNC), Awake prone positioning (APP), Non-invasive ventilation (NIV), Continuous positive airway pressure (CPAP)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to a sudden surge of hospital admissions for acute hypoxemic respiratory failure. A significant proportion of patients who are

hospitalized for COVID-19 fulfill the criteria for the acute respiratory distress syndrome (ARDS)¹, and require prolonged mechanical ventilation.

Prone positioning is one of the few interventions that has been proven to reduce mortality in intubated and mechanically ventilated patients with moderate to severe ARDS^{2,3}. This effect is likely mediated through a combination of better lung recruitment, reduced ventilation/perfusion mismatch, and prevention of alveolar strain and ventilator-induced lung injury by a more homogenous distribution of pleural pressures throughout the lung parenchyma⁴.

Groups worldwide have reported on the use of APP in acute hypoxemic respiratory failure due to COVID-19, and showed improvement of oxygenation, and reduction of respiratory rate in populations with various disease severity⁵⁻¹¹. Despite studies reporting outcomes being limited to case series and cohort studies, awake prone positioning has been widely adopted and included in the guidelines on management of COVID-19 pneumonia without any evidence that improvement of surrogate physiological endpoints translates into better clinical outcomes, such as reduced incidence of intubation, or reduced mortality, remains unknown.

The aim of this systematic review of proportional outcomes from observational studies was to investigate the hypothesis that APP of non-intubated patients with acute hypoxemic respiratory failure due to COVID-19 results in reduced intubation rate. The impact of APP on intubation rate is the primary outcome, and its effects on oxygenation, mortality, and the tolerability of APP are reported as exploratory secondary outcomes. We also explored the impacts of the duration of APP, the severity of the acute hypoxemic respiratory failure, the type

of respiratory support, such as conventional oxygen therapy, high flow nasal canula(HFNC), or non-invasive ventilation(NIV) on respiratory parameters, intubation rate, and mortality.

Methods

This study was registered on PROSPERO (CRD42020201947), and the detailed protocol is available at [https://www.crd.york.ac.uk/prospERO/display_record.php?RecordID=201947]. Our findings are presented in conformity with the PRISMA guidelines¹².

Search strategy and study selection

Two investigators (HH and JL) searched the MEDLINE, EMBASE, and PubMed, Web of Science, Scopus, MedRixv, BioRixv, ClinicalTrials.gov, and Wanfang databases for studies published from January 1st 2020 to August 15th 2020, with restrictions to English and Chinese languages. The keywords of (“prone position*” OR “Pron*”) AND (“COVID-19” OR “SARS” OR “coronavirus”) AND (“awake” OR “non-intubated” OR “conscious”) were utilized to search literature evaluating APP for patients with COVID-19. This enabled the identification of cohorts of patients treated with APP. The keywords of (“nasal high-flow” OR “HFNC” OR “high-flow nasal cannula” OR “noninvasive ventilation” OR “NIV” OR “continuous positive airway pressure” OR “CPAP”) AND (“COVID-19” OR “SARS” OR “coronavirus”) were used to identify reports of patients treated with either HFNC or NIV/CPAP, without the use of APP, to be included as a control cohort. Equivalent keywords were used for searches in Chinese. Searches were supplemented with examination of reference lists in identified studies, and verbal communication with experts.

Studies were included if they met the following criteria: (1) original research reports of COVID-19 patients, (2) patients were treated with APP and/or HFNC or NIV or conventional oxygen

therapy. The exclusion criteria were: (1) languages other than English or Chinese, (2) study protocols, review articles, abstracts, editorials, (3) research on newborns or animals, (4) reports of fewer than 3 cases.

The investigators then independently parsed through the titles and abstracts of all identified articles and produced a list of potentially relevant papers. The full texts of these papers were then reviewed, and a final list of studies to be included in the meta-analysis was produced. Any disagreements were resolved by consensus.

Data from the articles were extracted by two independent teams (HH and JL, BM and YP) using a standardized data extraction form. Extracted data included the authors, year of study, country, patient characteristics, the type of respiratory support, the details of APP intervention, tolerability and outcomes. Any disagreements were resolved by consensus in the presence of all four investigators.

If the outcomes of intubation rate and mortality were not reported, or if it was not clear whether the patients received APP and for what duration, the corresponding authors were contacted for clarifications.

To enlarge the sample size, and to assess for the possibility of publication bias, unpublished data provided by the investigators' institutions (BM, JJ, WZ, DR) was also included in the meta-analysis. Ethical approval was obtained at each institution prior to data collection.

Pre-planned statistical analyses

The primary outcome was the in-hospital intubation rate. The proportion of physiological "responders" to APP and the in-hospital mortality were reported as secondary outcomes. In

conformity with established custom in the ARDS literature, responders were defined by an increase of PaO₂/FiO₂ ratio $\geq 20\%$ ¹³. When the PaO₂/FiO₂ was not reported, an increase of SpO₂/FiO₂ ratio $\geq 20\%$ was considered as a response, given the linear relationship between the two ratios^{14, 15}. In-hospital mortality was reported as an exploratory secondary outcome, as it is a complex outcome that is modulated by multiple individual and population-level confounders.

For dichotomous outcomes, we pooled proportions using a logit transformation with 95% confidence intervals (CI). We assessed statistical heterogeneity by visual inspection of the forest plots and by calculating the Q and I² statistics, which were interpreted according to conventional thresholds. For all analyses, we implemented random-effects models with inverse variance weighting, providing that at least three studies were available.

Potential sources of heterogeneity or inconsistency include baseline disease severity in terms of PaO₂/FiO₂ at the initiation of therapy, duration of APP, the timing of APP initiation, and the type of respiratory support (conventional oxygen therapy, HFNC, NIV). We investigated the distributions of these characteristics across groups and studies.

We pre-specified 3 characteristics in the protocol to be subject to subgroup analyses on the probability of intubation and mortality. When the information was available we limited the analysis to the studies with PaO₂/FiO₂<150 mmHg vs. ≥ 150 mmHg and according to respiratory support devices (HFNC vs. CPAP/NIV). The cut-off value of PaO₂/FiO₂<150 mmHg was based on the previously described survival benefit when these patients are managed with intubation, as compared to a non-invasive strategy with a high chance of failure¹⁶. The third subgroup analysis was limited to studies in the group of APP, in which we analyzed the relationship between APP

duration and the probability of intubation and mortality. Up to 0.6 statistically significant interaction tests ($p < 0.05$) would be expected on the basis of chance alone.

We did not formally assess bias of included studies, as all of them were observational, and inherently highly biased. We did not produce a funnel plot, as this method is inaccurate for meta-analyses of proportion studies¹⁷.

Post hoc comparator groups

While collecting data, and before carrying out any analyses, we realized that only a minority of identified papers reported on “pure” populations in which either all patients were subjected to APP, or none were. We therefore decided to group patients into three groups a priori: (1) “APP” when all patients were prone, (2) “some APP” when some (at least 10%) but not all patients were prone, and (3) “no APP” when no patients were prone (less than 10%). Papers that focused on APP were classified as APP, regardless of the number or proportion of patients that were able to remain in PP. We compared patients treated with APP (group 1) with those not treated with APP (group 3), and we finally reported the p-value associated with the test for subgroup differences between group 1 and group 3.

All analyses were performed in R version 3.6.3, with the help of meta package.

Results

Our search strategy identified 173 publications on the subject of APP (Figure E1 in the online supplement), and 271 papers on the subject of non-invasive oxygenation modalities (Figure E2 in the online supplement) in severe COVID-19. Thus, a total of 444 potentially relevant publications were identified, and 440 were screened for inclusion after removal of duplicates (Figure 1). After full-text review, 46 published studies^{5-7, 9, 11, 18-57} and data from 4 unpublished datasets were included in the final review, with a combined 2994 subjects: 921 patients treated with APP, 870 patients treated without APP, and a group of 1203 patients in whom a significant proportion were treated with APP (Figure 1, Table 1, and Tables E1 and E2 in the online supplement). Clarifications and supplemental data were obtained from 18 corresponding authors.

Physiological response to awake prone positioning.

Nineteen studies (n=381) reported on the physiological responses to APP. APP resulted in improved SpO₂ or PaO₂ in all 13 studies (n=271) that reported on changes in oxygenation.

Ten studies (n=198) reported on changes in the PaO₂/FiO₂ ratio, of them nine (n=192) reported significant improvement in PaO₂/FiO₂ ratios with APP. Mean improvement was greater than our predefined threshold of $\geq 20\%$ in all seven studies in which changes of PaO₂/FiO₂ ratios were reported in sufficient detail. In three studies (n=72), the improvement of the PaO₂/FiO₂ ratio was sustained even after the patients returned to the supine position^{31, 34, 35}; one study (n=46) demonstrated sustained improvement in only 50% of patients¹¹, and in another report (n=26), improvement of PaO₂/FiO₂ was lost after returning to supine position³².

Reduction of respiratory rate with APP was demonstrated in five studies (n=90)^{7, 18, 29, 30}, but not in two other studies (n=34)^{23, 34}. Finally, significantly reduced PaCO₂ was demonstrated only in a single small study (n=9)²⁵, while no changes in PaCO₂ were observed in a larger report (n=46)¹¹.

Probability of intubation with awake prone positioning

Data on intubation rate were available for 870 patients treated with APP (23 published studies, n=717; 2 unpublished studies, n=153), and for 852 patients treated with HFNC, or CPAP, or NIV, without APP (16 published studies, n=645; 2 unpublished studies, n=207). In the APP group, 27% (95%CI, 19 to 37%) required intubation and mechanical ventilation, as compared to 30% (95%CI, 20 to 42%) in the control group (Figure 2). This difference was not statistically significant (p=0.71).

Subgroup analyses, with stratification according to the duration of APP (<4h daily vs ≥4h daily), the device (HFNC vs CPAP vs NIV), and the severity of the ARDS (PaO₂/FiO₂<150 mmHg vs PaO₂/FiO₂≥150 mmHg) did not demonstrate any significant difference in intubation rate between patients who were treated with APP and those who were not (Figure 3).

Probability of death with awake prone positioning

Mortality data were available for 767 patients treated with APP (18 published studies, n=614; 2 unpublished studies, n=153) and for 761 patients treated with HFNC, or CPAP, or NIV, without APP (12 published studies, n=554 ;2 unpublished studies, n=207). The mortality rate was 11% (95%CI, 6 to 20%) in patients treated with APP, as compared to 22% (95%CI, 13 to 36%) in patients treated with usual care (Figure 4). This difference was not statistically significant (p=0.10).

Outcomes were highly heterogeneous between studies, and subgroup analyses did not demonstrate any significant differences in mortality across predetermined subgroups (Figure 5), and did not identify a subgroup in which APP was associated with statistically significant reduction of mortality.

Tolerability and comfort of awake prone positioning

Fifteen studies reported patients' tolerability to APP, varying from 47% to 100%. Eight papers reported on patient's discomfort while in prone position, including back pain, dyspnea, and general discomfort. The daily duration of APP was reported in 17 papers (n=366). In 9 papers (n=201), patients tolerated APP for less than 4 hours daily. A single paper reported on a cohort of 55 patients who were able to achieve APP for more than 16 hours daily³⁶.

Discussion

Our systematic review of proportional outcomes from observational studies demonstrated that APP improved oxygenation but did not show benefit for the frequency of intubation or mortality in patients with acute hypoxemic respiratory failure secondary to COVID-19. The main strength of our study was that it was the first report focused on effect of APP on intubation rate with a comparison with the data from population treated with usual care during the similar time period within the first wave of pandemic. Our study also had a large sample size, with a total of 921 subjects treated with APP.

We found that APP improved oxygenation parameters, and this improvement was sustained even after the patients returned to the supine position in three studies^{31, 34, 35}. APP was also associated with reduced respiratory rate, and good tolerability was reported with the use of various modalities of respiratory support, including conventional oxygen therapy, HFNC, and CPAP or and NIV that was delivered through either a helmet or full face mask. Improvement in oxygenation with APP can be explained by the correction of ventilation/perfusion mismatch⁸, better lung recruitment, and reduction of alveolar strain⁴. However, improvements in oxygenation do not guarantee better clinical outcomes. For instance, improvements of PaO₂/FiO₂ ratio do not correlate with mortality in intubated patients subjected to prone positioning⁵⁸. More physiological and clinical studies are needed to delineate the relationship between improvement of oxygenation parameters and clinical outcomes in patients with COVID-19.

Contrary to previous reports^{24, 59}, we did not find that APP reduced intubation rates. Several reasons can be advanced to explain this lack of efficacy. First, intubation criteria were not uniformly defined across studies, and involved the treating physician's subjective judgment. During the pandemic, the recommended respiratory support strategies evolved from early aggressive intubation to strategies of respiratory support designed to prevent intubation^{5, 44, 60-62}. Second, the timing of APP initiation, either as an "adjunctive" (early) or "salvage" (late) therapy may influence intubation rate. The use of APP at an early stage ($\text{PaO}_2/\text{FiO}_2$ ratio $>150\text{mmHg}$) may be better tolerated, result in better oxygenation, and protect patients from self-induced lung injury (SILI), and thus prevent further disease progression^{63, 64}. However, in our meta-analysis of proportions, we did not detect a signal of benefit of APP in the subgroup of patients with $\text{PaO}_2/\text{FiO}_2$ ratio $>150\text{mmHg}$. Third, the duration of APP might have a dose-response relationship, and it is possible that a reduction in the rate of intubations could be seen only in patients who were subjected to longer periods of APP. Our subgroup analyses did not demonstrate significantly lower intubation rates for patients who remained in PP for longer periods of time, but it could be argued that our analysis was underpowered, as only two studies ($n=65$) reported daily APP periods $>16\text{h}$ ^{9, 36}. Fourth, intubation might be inevitable as the disease progresses, despite initial and sustained improvement in oxygenation. It has been argued that intubation rates are lower in patients who experience sustained improvement in oxygenation after APP, the so-called "responders"³⁵. However, this finding has not been replicated in other retrospective studies¹¹, and could be the result of simple reverse causality, with patients "responding" to APP because of their already favorable clinical course. Finally, an unknown proportion of patients with do-not-intubate orders were included in both groups, which could have diluted any possible benefit of APP.

We did not demonstrate a signal of reduced mortality with APP. Given the complex relationship between disease severity, individual co-morbidities, socio-economic status, and variable access to quality care during a pandemic, this finding should be interpreted as exploratory. Due to the retrospective nature of included studies, selection biases are very likely. The type of respiratory support (conventional oxygen therapy, HFNC, CPAP/NIV delivered through a conventional mask vs a helmet) was not balanced between patients treated with APP and those who were not. Analyses with stratification by the type of respiratory support device did not demonstrate significant subgroup differences in mortality. These subgroup analyses were severely limited by the fact that we only included observational studies in our analysis, had access only to overall group statistics, not individual patient data, and a proportion of patients were treated with various devices through the course of their disease.

Our study has several limitations. First, data were available only from a group of relatively heterogeneous observational studies. Significant levels of inclusion bias are also likely to be present. Without individual patient data, we could not account for the many uncontrolled differences between patients treated with APP, and those who received usual care. Some patients were subjected to APP in extremis after failing usual care, and could have been sicker than patients included in cohorts without APP. Conversely, in other reports, only patients who could self-prone were treated with APP, and these were likely less sick than those in the control group. Second, a variety of respiratory support devices, including helmet CPAPs, were used in both groups. It is not known whether the choice of the device has an impact on outcomes in patients with severe COVID-19. Third, outcomes were highly heterogeneous, which likely reflects populations with various disease severities, various co-morbid conditions, as well as geographical variations of care for patients with ARDS⁶⁵. Fourth, we included unpublished, non

peer-reviewed data. However, our findings remained robust with the exclusion of unpublished data. Fifth, the mortality rate in our studies is lower than reported in other large cohorts⁶⁶⁻⁶⁸, which suggests selection and publication bias, which would be expected to be in favour of APP. Sixth, we were not able to control for the use of evidence-based treatments such as corticosteroids. However, all included reports finished enrollment before the benefit of corticosteroid was demonstrated⁶⁹ and when their use was indeed actively discouraged. Seventh, only a minority of patients were able to tolerate longer periods of APP, and it can be argued that the duration of APP was not sufficient to generate a clinically meaningful change in outcomes. However, a physiologically effective, but clinically intolerable intervention would remain ineffective overall. Eighth, data for other important outcomes, such as the number of ventilator-free days or the length of ICU stay, were not available for analysis. Finally, all included studies were performed during the initial months of the pandemic. At that time, most group were not experienced with APP. We may imagine that APP would be more effective after the learning period when patient selection, positioning, monitoring, and duration of session is more established. Most of these patients were affected with the initial virus. The efficacy of APP may be different in variants, and the effect of APP may be higher as clinicians gain experience with this technique.

Conclusions

In summary, available evidence from observational studies suggests that awake prone positioning improves oxygenation, but these improvements do not appear to translate into reduced rates of intubation at the first wave of pandemic real-world practice. We did not find any obvious signals of harm, and we did not see any worrisome signal in mortality.

The high selectivity of patients, the inconsistency in the application of prone positioning in published reports and the heterogeneity of outcomes emphasizes the need for randomized controlled trials, as a clinically significant benefit cannot be excluded based on available low-quality data. Given the promising benefit of APP on the intubation, trials should endeavor to include patients with different disease severity, managed with a uniform strategy of respiratory support, and with clear criteria for intubation.

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Ethics approval and consent to participate

All published and unpublished reports included in the meta-analysis of proportions have undergone appropriate ethical approval.

Competing interests

JL has received research support from Fisher & Paykel Healthcare Ltd, Aerogen Ltd, and Rice Foundation, and lecture honorarium from AARC and Fisher & Paykel Healthcare Ltd outside the submitted work.

IP received a research grant and speaker fees from Fisher & Paykel Healthcare.

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JAJ and MWT received speaker fees from Fisher & Paykel Healthcare

DR is the president of DRDR Mobile Health, a company that creates mobile applications for healthcare, including functional capacity assessment applications. He has engaged in consulting for mobile applications as well. He has not taken any salary or money from the company.

DLV reports consulting for Ohio Medical, speaking for Theravance Biopharma, and research funding from Teleflex Medical, Inc. and Rice Foundation.

Other authors have no conflict of interest to declare.

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Figure titles and legends

Fig. 1 Flow diagram showing identification of eligible studies included in the meta-analysis of proportions.

aOne paper reported on both sub-groups, and is thus counted twice.

Fig. 2 Association between awake prone positioning and intubation, in each report, and overall. A meta-analysis of pooled proportion demonstrating the intubation rate for studies describing patients who did or did not undergo prone positioning.

Fig. 3 Association between awake prone positioning and intubation, within subgroups defined by the duration of proning, the type of respiratory support device, and the PaO₂/FiO₂ ratio at enrolment. A meta-analysis of pooled proportion of intubation for studies reporting time spent in prone position (< or > 4 hours), oxygen delivery device (HFNC, CPAP) and degree of hypoxemia (P/F < or > 150 mmHg) for studies describing patients who did not undergo prone positioning and studies that reported in patients that underwent prone positioning. HFNC -high flow nasal cannula, PP- prone position, CPAP continuous positive airway pressure, P/F- PaO₂ to FiO₂ ratio.

Fig. 4 Association between awake prone positioning and mortality, in each report, and overall. A meta-analysis of pooled proportion demonstrating the intubation rate for studies describing patients who did or did not undergo prone positioning.

Fig. 5 Association between awake prone positioning and mortality, within subgroups defined by the duration of proning, the type of respiratory support device, and the PaO₂/FiO₂ at enrolment. A meta-analysis of pooled proportion of mortality for studies reporting time spent in prone position (< or > 4 hours), oxygen delivery device (HFNC, CPAP) and degree of hypoxemia (P/F < or > 150 mmHg) for studies describing patients who did not undergo prone positioning and studies that reported in patients that underwent prone positioning. HFNC -high flow nasal cannula, PP- prone position, CPAP continuous positive airway pressure, P/F- PaO₂ to FiO₂ ratio.

Table caption and legend

Table 1. Basic characteristics and main results for studies with awake prone positioning

Abbreviations: APP, awake prone positioning; UR, unreported; PaO₂, partial pressure of oxygen; SpO₂, pulse oximetry; PFR, the ratio of partial pressure of oxygen to the fraction of inspired oxygen.

Table 2. Detailed information about the studies that implemented awake prone positioning

Abbreviations: APP, awake prone positioning; UR, unreported; ICU, intensive care unit; ED, emergency department; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; NC, nasal cannula; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; IQR, interquartile range.

Table 1. Basic characteristics and main results for studies with awake prone positioning

Data	Authors, year of publication	Type of study	Number of patients included	country	Gender (Male, %)	Age	starting oxygenation status (Reported type)	starting oxygenation status	oxygenation status during APP	Starting respiratory rate	respiratory rate during APP	Improvement of SpO ₂ /PO ₂ /PFR after APP (% of number of patients with improvement)	Improvement of Oxygenation after supine (% of Persistent Responders)	intubation rate	mortality	
1	Coppo et al, 2020	Prospective	56	Italy	79%	57.4	PFR PO2	180.5 117.1	285.5 200.4	24.5	24.5	50%	50%	32%	10.8%	
2	Caputo et al, 2020	Prospective	50	USA	60%	59	SPO2	84%	94	UR	UR	74%	UR	36%	UR	
3	Damarla et al, 2020	Retrospective	10	USA	70%	56	SPO2	94%	98	31	22	UR	UR	20%	0%	
4	Despres et al, 2020	Retrospective	6	France	100%	60.5	PFR	180.6	UR	UR	UR	44%	UR	50%	UR	
5	Elharrar et al, 2020	Prospective	24	France	67%	66.1	PO2	72.8	91	18	UR	25%	12.5%	20.8%	UR	
6	Golestani-raghi et al, 2020	Prospective	10	Iran	UR	UR	PO2	46.34	UR	UR	UR	60%	NA	20%	20%	
7	Huang et al, 2020	Case reports	3	Singapore	67%	59	PFR	101.8	UR	UR	UR	UR	UR	33%	UR	
8	Ng et al, 2020	Prospective	10	Singapore	80%	60	SPO2	91.5%	UR	UR	UR	UR	UR	10%	10%	
9	Moghadam et al, 2020	Prospective	10	Iran	70%	41	SPO2	85.6%	95.9	21	22	UR	UR	0%	0%	
10	Sartini et al, 2020	Prospective	15	Italy	87%	59	PFR	157	UR	UR	UR	80%	80%	7%	7%	
11	Thompson et al, 2020	Prospective	29	USA	72%	67	SPO2	88%	95	UR	UR	76%	UR	48%	12%	
12	Tu et al, 2020	Prospective	9	China	44%	51	SPO2 PO2	90% 69	96 108	UR	UR	UR	UR	22%	UR	
13	Xu et al, 2020	Retrospective	10	China	50%	51	PFR	157	UR	UR	UR	UR	UR	0%	0%	
14	Retucci et al, 2020	Prospective	12	Italy	67%	62	PFR SPO2 A-aDO2 PO2	168.7 95% 219.3 83.6	227.7 98 193.1 112.3	23.5	UR	UR	UR	UR	26.9%	77%
15	Dong et al, 2020(Preprint)	Retrospective	25	China	64%	59.5	PFR	UR	331	28.4	21.3	UR	UR	0%	0%	
16	Bastoni et al, 2020	Prospective	10	Italy	80%	73	PFR	68	97	UR	UR	UR	UR	100%	UR	
17	Ripoll-Gallardo	Retrospective	13	Italy	UR	66.3	PFR	115	166	31.4	UR	UR	UR	69.2%	53.8%	

18	et al. 2020 Villarreal-Fernandez et al. 2020	Prospective	10	USA	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	33.3%	0%
19	Solverson et al. 2020	Retrospective	17	Canada	71%	53	SPO2	91%	98	28	22	UR	UR	41.1%	11.7%	
20	Zang et al. 2020	Prospective	23	China	56%	63	SPO2	91%	95.5%	UR	UR	UR	UR	UR	UR	
21	Taboada et al. 2020	Prospective	29	Spain	78%	64	SPO2 PFR	93.6% 196	95.8% 242	28	25	UR	UR	UR	UR	
22	Hallifax et al. 2020	Retrospective	48	United Kingdom	67%	69	UR	UR	UR	UR	UR	UR	UR	22.9%	60.4%	
23	Winearls et al. 2020	Retrospective	24	United Kingdom	63%	62	PFR SpO2	143 94%	252 96%	27	24	UR	UR	4.5%	18.2%	
24	Burton-Papp et al. 2020	Retrospective	20	United Kingdom	55%	53.4	PFR	UR	UR	UR	UR	UR	UR	35%	0%	
25	Calligaro et al. 2020	Prospective	293	South Africa	56%	52	PFR	68	UR	UR	UR	UR	UR	37.9%	48.3%	
Summary	Prospective:14 Retrospective 7 Case report: 1	Total 429	Italy 5 USA 4 UK 3 France 2 Iran 2 Singapore 2 China 4 Canada 1 Spain 1 South Africa 1	Mean 69%	Mean 59.8	SPO2 11 PO2 5 PFR 10	SPO2 91% PO2 77 PFR 147	SPO2 96% PO2 128 PFR 225	26	23	58%	47%	29.6%	18.8%		

APP, awake prone positioning; UR, unreported; PaO₂, partial pressure of oxygen; SpO₂, pulse oximetry; PFR, the ratio of partial pressure of oxygen to the fraction of inspired oxygen.

Table 2. Detailed information about the studies that implemented awake prone positioning

Data	Authors, year of publication	Respiratory support methods (COT/HFNC/NIV)	Time from admission to start of APP (days after hospital / ICU/ ED admission)	Times of APP per day	Duration of each APP (hours) (Mean/Median)	total days for APP (Mean/Median)	total hours for APP (Mean/Median)	Tolerability (%)	Percentage of patients tolerated < 1 hour (%)	Discomfort (%)	Symptoms of discomfort
1	Coppo et al, 2020	COT-face mask 21% Helmet-CPAP 79%	3.5	UR	3	UR	UR	47/56(83.9%)	9	10.7	Discomfort: 5 cough:1
2	Caputo et al, 2020	NC 24% Non-rebreather Mask 76%	0	UR	2	UR	UR	UR	7	UR	UR
3	Damarla et al, 2020	HFNC 40% NC 50% Room air 10%	0.21	UR	2	UR	UR	10/10(100%)	0	UR	UR
4	Despres et al, 2020	COT 5/9(56%) HFNC 4/9(44%)	UR	UR	5.5	UR	8.3	6/6(100%)	3	UR	UR
5	Elharrar et al, 2020	COT 16/24(67%) HFNC 8/24(33%)	1	UR	3	UR	UR	15/24(63%)	4	42	Back pain: 10
6	Golestani-raghi et al, 2020	NIV 10/10(100%)	UR	UR	UR	UR	9	8/10(80%)	UR	UR	UR
7	Huang et al, 2020	HFNC 100%	7	4	2	4.33	104	UR	UR	UR	UR
8	Ng et al, 2020	NC n=6 Venturi n=2 HFNC n=2	9	5	UR	8	21	10/10(100%)	UR	UR	nausea musculoskeletal discomfort
9	Moghadam et al, 2020	UR	4.8	UR	UR	UR	UR	10/10(100%)	UR	UR	UR
10	Sartini et al, 2020	NIV 15/15(100%)	UR	2	3	UR	UR	15/15(100%)	UR	UR	UR
11	Thompson et al, 2020	NC Non-rebreather mask	3.25		5	2		UR	UR	UR	UR
12	Tu et al, 2020	HFNC50-60L/min:100%	UR	2	UR	UR	UR	9/9(100%)	UR	UR	UR
13	Xu et al, 2020	HFNC (100%)	UR	1	16	UR	UR	10/10(100%)	UR	UR	reported,

												anxiety number NA
14	Retucci et al, 2020	helmet CPAP 100%	4	UR	1	UR	UR	24/26(92.3%)	UR	17	2	
15	Dong et al. 2020(Preprint)	UR	UR	UR	6.4	UR	UR	21/25(64%)	6	36	dyspnea and pain	
16	Bastoni et al, 2020	helmet CPAP 100%	UR	UR	UR	UR	UR	UR	UR	UR	UR	
17	Ripoll-Gallardo et al. 2020	helmet CPAP 100%	3.1	2.5	2.4	UR	UR	UR	UR	UR	UR	
18	Villarreal-Fernandez et al. 2020	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	
19	Solverson et al. 2020	NC 16 HFNC 1	2	2	1.25	1	UR	8/17(47%)	8	35	2=pain 6=general discomfort 1=delirium	
20	Zang et al. 2020	COT 15(65.2%) HFNC 8(34.7%) NIV 7(30.4%)	UR	UR	2	5	13.4	UR	UR	UR	UR	
21	Taboada et al. 2020	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	
22	Hallifax et al. 2020	CPAP 100% CPAP transfer to HFNO 54.2%	UR	UR	2	UR	UR	UR	UR	UR	UR	
23	Winearls et al. 2020	CPAP 100%	1.25	8	UR	10	UR	22/24(91.6%)	UR	UR	1=pain	
24	Burton-Papp et al. 2020	CPAP/BiPAP 100%	UR	5	3	UR	UR	20/20(100%)	UR	UR	UR	
25	Calligaro et al. 2020	HFNO 100%	UR	UR	UR	UR	UR	UR	UR	UR	UR	
Mea dian +IQR			3.3 (1-4.8)	2 (2-4)	2.4 (2-5)	4.3 (1.5-6.5)	13.4 (8.7-62.5)	100% (72-100%)	6 (3-8)	35 (13.9-39%)		

APP, awake prone positioning; UR, unreported; ICU, intensive care unit; ED, emergency department; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; NC, nasal cannula; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; IQR, interquartile range.

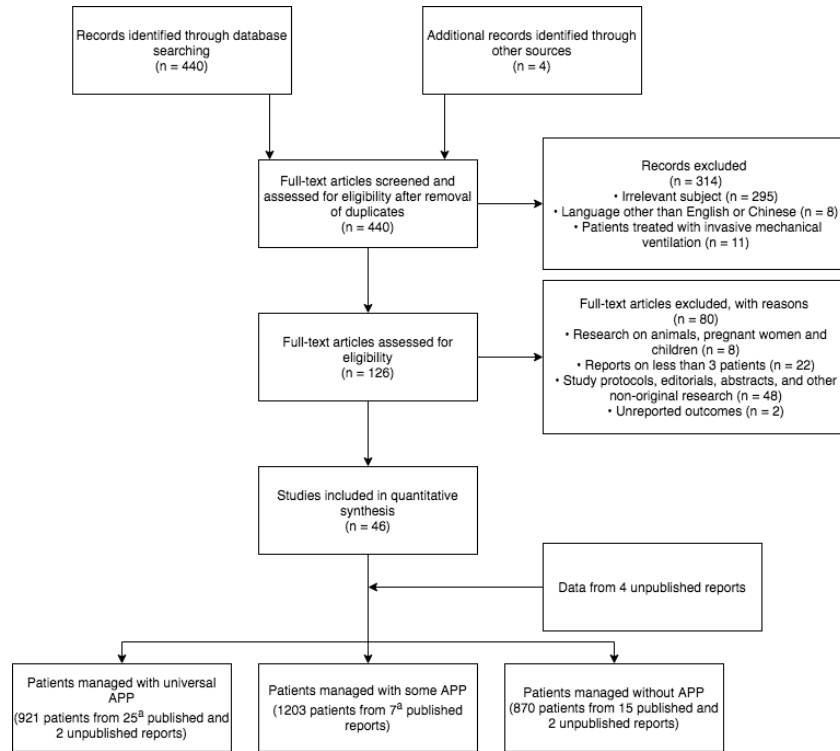


Fig. 1 Flow diagram showing identification of eligible studies included in the meta-analysis of proportions.
a One paper reported on both sub-groups, and is thus counted twice.

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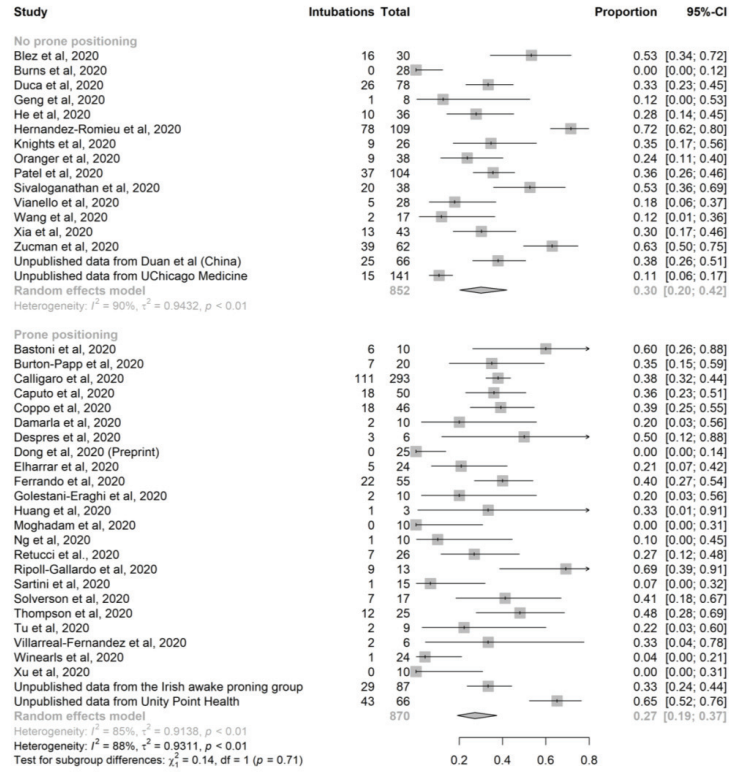


Fig. 2 Association between awake prone positioning and intubation, in each report, and overall. A meta-analysis of pooled proportions demonstrating the intubation rate for studies describing patients who did or did not undergo prone positioning.

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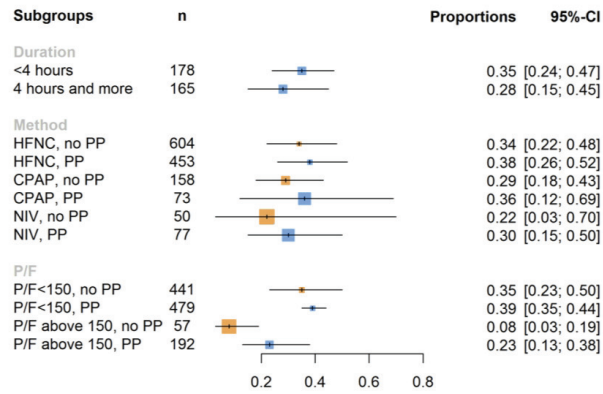


Fig. 3 Association between awake prone positioning and intubation, within subgroups defined by the duration of proning, the type of respiratory support device, and the PaO₂/FiO₂ ratio at enrolment. A meta-analysis of pooled proportions of intubation for studies reporting time spent in prone position (< or > 4 hours), oxygen delivery device (HFNC, CPAP) and degree of hypoxemia (P/F < or > 150 mmHg) for studies describing patients who did not undergo prone positioning and studies that reported in patients that underwent prone positioning. HFNC -high flow nasal cannula, PP- prone position, CPAP continuous positive airway pressure, P/F- PaO₂ to FiO₂ ratio.

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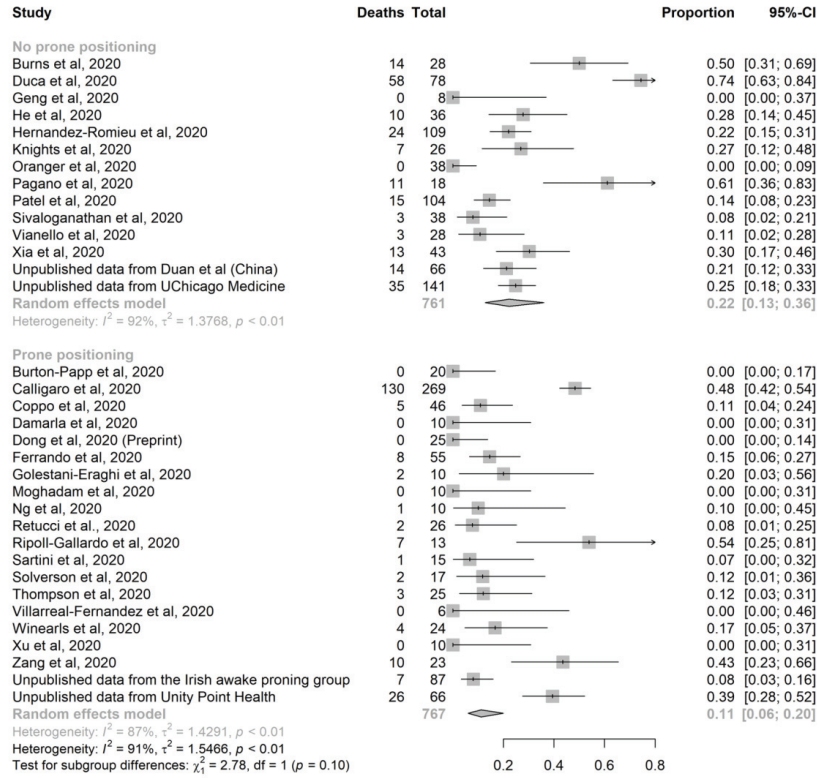


Fig. 4 Association between awake prone positioning and mortality, in each report, and overall. A meta-analysis of pooled proportions demonstrating the intubation rate for studies describing patients who did or did not undergo prone positioning.

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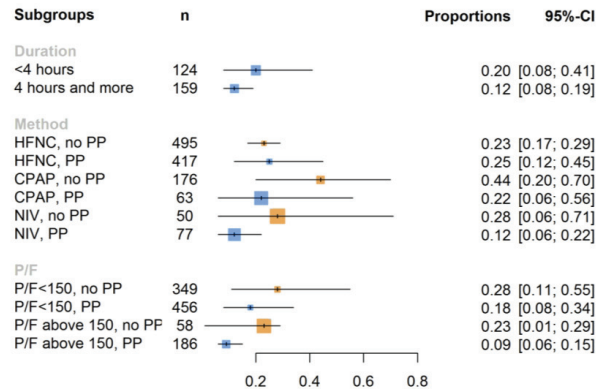


Fig. 5 Association between awake prone positioning and mortality, within subgroups defined by the duration of proning, the type of respiratory support device, and the PaO₂/FiO₂ at enrolment. A meta-analysis of pooled proportions of mortality for studies reporting time spent in prone position (< or > 4 hours), oxygen delivery device (HFNC, CPAP) and degree of hypoxemia (P/F < or > 150 mmHg) for studies describing patients who did not undergo prone positioning and studies that reported in patients that underwent prone positioning. HFNC -high flow nasal cannula, PP- prone position, CPAP continuous positive airway pressure, P/F- PaO₂ to FiO₂ ratio.

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