Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: a systematic review and meta-analysis

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Research

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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 and meta-analysis of observational studies to compare oxygenation parameters in-hospital 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Results: A total of 46 published and 4 unpublished observational studies that included 2994 patients were included. APP was associated with significant improvement of various oxygenation parameters in 19 studies (n=381) that reported this outcome. The intubation rate was 27% (95%CI, 19 to 37%) in the 870 patients treated with APP, as compared to 30% (95%CI, 20 to 42%) in the 852 patients treated with usual care (p=0.71).

Conclusions: On the basis of the available evidence, it is not possible to demonstrate efficacy of APP for patients with COVID-19 acute respiratory failure, as assessed by the need for invasive ventilation. Routine implementation of APP outside of a clinical trial is not supported by current evidence. Randomized controlled clinical studies are urgently needed to definitively assess the utility of APP in these patients.

Registered on PROSPERO on August 3d, 2020, CRD42020201947.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to a sudden surge of hospital admissions for acute hypoxemic respiratory failure (AHRF). 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.

In the United Kingdom, among patients who were admitted to the intensive care unit (ICU), 72.1% received advanced respiratory support, defined as mechanical ventilation (MV), or extracorporeal membrane oxygenation (ECMO), or endotracheal intubation[2], during their stay, with a median duration of MV of 13 days, and mortality rate of 48%. Similar outcomes were reported elsewhere[3–5].

This surge of severely ill patients, who required high levels of care for protracted periods of time, threatened to overwhelm healthcare systems worldwide, especially in those regions with lower ICU capacity[6]. It is in this unusual setting in which both ICU beds and ventilators were in short supply, that clinicians turned to awake prone positioning (APP) as a means of avoiding – or, at least, delaying – endotracheal intubation, and thus lessening the pressure on the overburdened ICUs[7–14].

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[15,16]. 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 parenchyma[17].

Prior to the pandemic, two small studies (combined n=35) explored the feasibility of APP of spontaneously breathing non-intubated patients[18,19]. In one study, eleven of 20 patients with moderate to severe ARDS were able to avoid intubation with the use of APP combined with either high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV)[19]. Both studies demonstrated improvement of oxygenation, as measured by the ratio of arterial oxygen partial pressure (PaO₂ in mmHg) to the fraction of inspired oxygen(FiO₂)[18,19].

The first report of APP in patients with COVID-19 came from a Chinese retrospective study of 631 patients (10% of them critically ill). A multi-pronged intervention that included early and aggressive use of HFNC combined with APP resulted in lower overall mortality (3.33%, as compared to 4.34% in a nearby province). A very low percentage of patients required mechanical ventilation (<1%), as compared to the national average of 2.3%[7].

Since then, groups worldwide have reported on the use of APP in AHRF due to COVID-19, and showed improvement of oxygenation, and reduction of respiratory rate in populations with various disease severity[8–14]. However, whether improvement of surrogate physiological endpoints translates into better clinical outcomes, such as reduced incidence of intubation, or reduced mortality, remains unknown. Moreover, APP was variously combined with either conventional oxygen therapy, HFNC, or NIV, and for various periods of time. It is presently unknown whether the type of respiratory support impacts on the effects of APP.

The aim of this systematic review and meta-analysis was to investigate the hypothesis that APP of non-intubated patients with AHRF due to COVID-19 led sustained improvement of oxygenation, resulting in reduced intubation rate. The impact of APP on 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 AHRF, the type of respiratory support (conventional oxygen therapy, HFNC, or 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 guidelines[20].

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/CPAP 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, 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 main outcomes are and the proportion of physiological "responders" to APP and the in-hospital intubation rate. In conformity with established custom in the ARDS literature, responders were defined by an increase of $\text{PaO}_2/\text{FiO}_2$ ratio $\geq 20\%$ [21]. When the $\text{PaO}_2/\text{FiO}_2$ was not reported, an increase of $\text{SpO}_2/\text{FiO}_2$ ratio $\geq 20\%$ was considered as a response, given the linear relationship between the two ratios[22,23]. In-hospital mortality rate is a complex outcome that is modulated by multiple individual and population-level confounders, and is the reported as an exploratory secondary outcome.

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 I^2 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 $\text{PaO}_2/\text{FiO}_2$ 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 restrained the analysis to the studies with $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg vs. ≥ 150 mmHg and according to respiratory support devices (HFNC vs. CPAP/NIV). The cut-off value of $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg was based on the previously described signal of survival benefit when these patients are managed with early intubation, as compared to a non-invasive strategy[24]. The third subgroup analysis was restrained to studies in the group of APP, in which we analyzed the relationship between APP duration and the probability of intubation and mortality. For multiple comparisons, the Bonferroni correction was used to establish the threshold of statistical significance, thus all p-values were compared to the threshold of 0.0125. We also performed a sensitivity analysis by excluding all data obtained from unpublished sources.

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 studies[25].

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 reported the p-value associated with the test for subgroup differences between group 1 and group 3. We also performed sensitivity analyses including group 2 as a separate subgroup in the analyses. While some patients were treated with conventional oxygen therapy in the "APP" group, only HFNC, CPAP and NIV were used in the "no APP". We therefore performed a sensitivity analysis by excluding patients treated with conventional oxygen therapy. We elected not to exclude these patients from our primary analysis, as the use of HFNC and CPAP or NIV was often prohibited early in the pandemic due to disease transmission considerations, and patients treated with conventional oxygen only were not necessarily less sick than those treated with other modalities. Finally, in order to test for geographical variation of care, we performed sensitivity analyses with restriction to high- or low-GDP countries.

All analyses were performed in R version 3.6.3[26], with the help of meta package[27].

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[8–10,12,14,28–68] 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[8–10,28,30,33–35,40–43,45].

Ten studies (n=198) reported on changes in the PaO₂/FiO₂ ratio[10,12,14,29,37,38,42,43,45,46], of them nine (n=192) reported significant improvement in PaO₂/FiO₂ ratios with APP[10,12,14,37,38,42,43,45,46]. 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[14,37,38,42,43,45,46]. In three studies (n=72), the improvement of the PaO₂/FiO₂ ratio was sustained even after the patients returned to the supine position[42,45,46]; one study (n=46) demonstrated sustained improvement in only 50% of patients[14], and in another report (n=26), improvement of PaO₂/FiO₂ was lost after returning to supine position[43].

Reduction of respiratory rate with APP was demonstrated in five studies (n=90)[10,28,36,40,41], but not in two other studies (n=34)[33,45]. Finally, significantly reduced PaCO₂ was demonstrated only in a single small study (n=9)[35], while no changes in PaCO₂ were observed in a larger report (n=46)[14].

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 ≥ 4 h daily), the device (HFNC vs CPAP vs NIV), and the severity of the ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg vs $\text{PaO}_2/\text{FiO}_2 \geq 150$ mmHg) did not demonstrate any significant difference in intubation rate between patients who were treated with APP and those who were not (Figure 3).

There was a very high level of heterogeneity across all studies. Sensitivity analyses with the inclusion of the subgroup of patients with some exposure to APP, and with exclusion of unpublished data demonstrated a similar lack of benefit (Figures E3 through E11), as did the analyses according to country GDP (Figures E23 and E24).

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. Sensitivity analyses with the inclusion of patients with partial exposure to APP, with exclusion of unpublished data, and with exclusion of patients treated with conventional oxygen therapy demonstrated a similar lack of mortality benefit (Figures E12 through E22). No statistically significant signal was seen in analyses restricted to high- or low-GDP countries (Figures E25 and E26).

Tolerability and comfort of awake prone positioning

Fifteen studies reported patients' tolerability to APP, varying from 47% to 100%[9,10,12,14,28–30,32,33,35,36,40,43,45,46]. Eight papers reported on patient's discomfort while in prone position[9,12,14,32,36,40,43,45], including back pain, dyspnea, and general discomfort. The daily duration of APP was reported in 17 papers ($n=366$)[8–10,12,14,28,29,31,34,36,38,40,41,45–47]. In 9 papers ($n=201$), patients tolerated APP for less than 4 hours daily[8–10,14,28,31,38,40,41]. A single paper reported on a cohort of 55 patients who were able to achieve APP for more than 16 hours daily[47].

Discussion

Our systematic review and meta-analysis demonstrated that APP improved oxygenation but did not change the frequency of intubation or mortality in patients with AHRF secondary to COVID-19. The main strength of our study was the large sample size, with a total of 921 patients treated with APP. However, given the observational nature of included studies, high heterogeneity, and broad confidence intervals, our results should be interpreted as demonstrating absence of evidence, rather than high quality evidence of an absence of benefit.

We found that APP improved oxygenation parameters, and this improvement was sustained even after the patients returned to the supine position in three studies[42,45,46]. 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 mismatch[11], better lung recruitment, and reduction of

alveolar strain[17]. 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 positioning[69]. 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[19,34], 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[8,55,70–72]. 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 (PaO₂/FiO₂ ratio >150mmHg) may be better tolerated, result in better oxygenation, and protect patients from self-induced lung injury (SILI), and thus prevent further disease progression[73,74]. However, in our meta-analysis, we did not detect a signal of benefit of APP in the subgroup of patients with PaO₂/FiO₂ ratio >150mmHg. 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 >16h[12,47]. 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”[46]. However, this finding has not been replicated in other retrospective studies[14], 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 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.

The use of APP has been widely promoted as the new standard of care, and even included as such clinical care guidelines[76], on the basis of physiological plausibility and low quality evidence from case reports. It has been suggested that studies of this intervention are not warranted and that investigators lack equipoise. Our meta-analysis of available low quality data does not support this unbridled enthusiasm, and we strongly caution against uncritical inclusion of unproven therapies in routine patient care. The critical care literature is replete with examples of interventions that improved surrogate outcomes, yet ultimately failed to improve clinical outcomes in randomized controlled trials[77–79]. Implementing an ineffective therapy is not benign, as, at best, this diverts finite clinical resources and attention. At worst, it could result in unnecessarily delayed intubations in difficult conditions, self-induced lung injury, and potentially higher mortality[80]. Unfortunately, there are numerous precedents of physiologically sound therapies that unexpectedly resulted in higher mortality, such as aggressive fluid resuscitation[81] or liberal red-cell transfusions[82].

Limitations

Our study has several significant 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 ARDS[75]. 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 cohorts[2,4,5], which suggests selection and publications bias, which would be expected to be in favor of APP. Sixth, we were not able to control for the use of evidence-based treatments such as corticosteroids. However, all included reports finished enrolment before the benefit of corticosteroid was demonstrated [83] 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. Lastly, data for other important outcomes, such the number of ventilator-free days or the length of ICU stay, were not available for analysis.

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. 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.

List Of Abbreviations

Awake prone positioning (APP); coronavirus disease 2019 (COVID-19); acute hypoxemic respiratory failure (AHRF); acute respiratory distress syndrome (ARDS); intensive care unit (ICU); mechanical ventilation (MV); extracorporeal membrane oxygenation (ECMO); high-flow nasal cannula (HFNC); non-invasive ventilation (NIV); Continuous positive airway pressure (CPAP); arterial oxygen partial pressure (PaO_2); fraction of inspired oxygen(FiO_2); confidence interval (CI); Peripheral oxygen saturation (SpO_2); self-induced lung injury (SILI).

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable

Availability of data and materials

Not applicable

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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OR provides consultancy to Hamilton Medical. All fees were received by his Institution of Research. He also received speaker fees by Air Liquide.

JGL has received research grant and consulting fees from Baxter Healthcare.

SE received unrestricted research grants, travel fee reimbursements and speaker fees from Fisher & Paykel Healthcare, consulting fees from La Diffusion Technique Française, consulting fees and unrestricted research grants from Aerogen Ltd., and an unrestricted research grant from Hamilton medical.

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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Authors' contributions

BL, HH, IP, JL, and YP extracted and summarized data from individual papers.

ET performed the statistical analyses

IP, HH, JL drafted the manuscript

All authors provided critical feedback and reviewed the manuscript.

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Table

Due to technical limitations, table 1 xlsx is only available as a download in the Supplemental Files section.

Table 1. Summary of included studies of patients severe COVID treating with, and without the use of awake prone positioning.

Abbreviations, in order of appearance: P/F, $\text{PaO}_2/\text{FiO}_2$, i.e., the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2); PaCO_2 , arterial carbon dioxide partial pressure; SpO_2 , peripheral oxygen saturation; ED, emergency department; IMCU, intermediate care unit; ICU, intensive care unit; CPAP, Continuous positive airway pressure; COT, conventional oxygen therapy; NIV, non-invasive ventilation; APP, awake prone positioning.

The data on the prevalence and the duration of APP included unpublished data obtained by personal communication with principal investigators of included studies. Continuous variables are reported as means or medians. Missing variables are marked with a dash. Whenever possible, mortality is reported only for the subset of patients discharged from the ICU at the moment of each study publication. Outcomes are reported stratified by the type of respiratory support device.

^a The papers by Retucci et al., and Burton-Papp et al., report on the subset populations of patients from larger cohorts

described by Aliberti et al., and Sivaloganathan et al., respectively. In order to avoid counting single patients twice, we report data from the two larger cohorts with the exclusion of outcomes of patients managed with APP.

^b Burns et al. report on a cohort comprised exclusively by patients with do-not-intubate orders, which was not included in the meta-analysis of the intubation rate.

Figures

Figure 1

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

Figure 2

Association between awake prone positioning and intubation, in each report, and overall

Figure 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.

Figure 4

Association between awake prone positioning and mortality, in each report, and overall.

Figure 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.

Supplementary Files

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