Awake prone positioning in non-intubated patients for the management of hypoxemia in COVID-19: A systematic review and meta-analysis

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Abstract

Coronavirus disease-2019 (COVID-19) may lead to hypoxemia, requiring intensive care in many patients. Awake prone positioning (PP) is reported to improve oxygenation and is a relatively safe modality. We performed a systematic review of the literature to evaluate the available evidence and performed meta-analysis of the effect of awake PP in non-intubated patients on improvement in oxygenation and reducing the need for intubation. We searched the PubMed and EMBASE databases to identify studies using awake PP as a therapeutic strategy in the management of COVID-19. Studies were included if they reported respiratory outcomes and included five or more subjects. The quality of individual studies was assessed by the Qualsyst tool. A meta-analysis was performed to estimate the proportion of patients requiring intubation. The degree of improvement in oxygenation parameters (PaO_2: FiO_2 or PaO_2 or SpO_2) was also calculated. Sixteen studies (seven prospective trials, three before-after studies, six retrospective series) were selected for review. The pooled proportion of patients who required mechanical ventilation was 0.25 (95% confidence interval (CI) 0.16-0.34). There was a significant improvement in PaO_2: FiO_2 ratio, PaO_2, and SpO_2 during awake PP. To conclude, there is limited evidence to support the efficacy of awake PP for the management of hypoxemia in COVID-19. Further RCTs are required to study the impact of awake PP on key parameters like avoidance of mechanical ventilation, length of stay, and mortality.

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Authors' contributions: SPB, data extraction and manuscript preparation; SM, study concept, studies search, data extraction, statistical analysis, manuscript writing; KM, data extraction, manuscript revision; AM, PT, VH, RG, manuscript revision; RMP, statistical analysis. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author on reasonable request.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Key words: Awake proning; COVID-19; prone positioning; SARS-CoV-2.

Received for publication: 26 September 2020.
Accepted for publication: 28 January 2021.

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Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2021; 91:1623
doi: 10.4081/monaldi.2021.1623

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Introduction

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) emerged in China and spread globally, creating a pandemic. The disease results in a significant number of critically ill patients with the requirement of intensive unit care (ICU) admission and invasive mechanical ventilation (IMV) [1]. Among patients who need IMV, reported mortality is high varying from 49%- 88% [1,2]. Among hospitalized patients of COVID-19, the incidence of acute respiratory distress syndrome (ARDS) is reported to be about 33% and sometimes as high as 68% [3]. In intubated patients with moderate to severe ARDS, prolonged prone positioning has been shown to improve oxygenation, and reduce mortality [4]. Prone positioning (PP) improves oxygenation by multiple mechanisms, such as redistribution of blood flow and edema fluid to the ventral side with gravity and reopening of atelectatic alveoli, which causes improvement in ventilation-perfusion mismatch [5,6]. However, PP requires the initiation of deep sedation as well as neuromuscular blocking agents and may be associated with complications in the form of obstruction and displacement of the endotracheal tube (ET) or venous catheter [5]. Awake PP may have similar advantages in improving oxygenation and possibly reduce the need for IMV without the associated problems of deeper sedation and ET displacement [7]. Before the pandemic, awake PP was used sparingly and has shown to improve oxygenation and reduce intubation rates in hypoxic respiratory failure [8,9]. An intervention that may reduce mortality, especially one that can be easily implemented at little additional cost, requires adequate data to support its

benefits and possible harms. There is emerging data on the use of awake prone positioning to manage COVID-19 related hypoxemic respiratory failure [10,11]. This systematic review and meta-analysis aim to summarize the current evidence of awake PP in COVID-19 hypoxemic respiratory failure in non-intubated patients.

Methods

The report of this systematic review was made according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12].

Eligibility criteria

We included studies on adults (at least five patients) with COVID-19 and hypoxemic respiratory failure, not requiring IMV, and employing awake PP as a therapeutic strategy. We excluded small patient series (less than five) as they are highly likely to present a biased outcome in the form of only favorable outcome reporting [13]. We excluded studies on PP during IMV as well as studies not reporting respiratory outcomes. There was no comparator group.

Search strategy and initial review

A systematic search was performed in the PubMed and EMBASE databases to look for studies concerning awake PP in COVID-19 till July 26th, 2020. The following search terms were used: ("prone" OR "proning" OR "prone positioning") AND ("COVID-19" OR "SARS CoV-2" OR " SARS CoV 2"). Only English language studies were included. All the retrieved citations were imported into reference management software (EndNote) by two authors independently (SM and SP). The duplicate references were removed, and all references were screened through titles and abstracts. The reference lists of the extracted studies were also reviewed to look for relevant articles.

Study selection

Two review authors (SM and SP) independently screened and classified all citations as potential case-control studies, review articles, case series, or others for inclusion. We included all prospective, retrospective as well as randomized controlled studies reporting respiratory outcomes following awake PP in COVID-19 related hypoxemic respiratory failure. We defined COVID-19 hypoxemic respiratory failure as patients with confirmed COVID-19 infection requiring oxygen supplementation or with room air saturation less than 94%. Awake PP was defined as usage of prone positioning in a conscious alert patient, not on IMV, irrespective of the duration of proning. The primary outcome was the need for endotracheal intubation and IMV. Other outcomes included indices of oxygenation, mortality, and length of stay.

Two review authors (SM and SP) examined all potential studies and decided whether they should be included in the review. Any disagreement was resolved by further discussion with a third author (KM).

Articles identified by the search were assessed for suitability. The primary outcome analyzed was the need for IMV. Other secondary outcomes included change in oxygenation status as assessed by pulse oxygen saturation (SpO_2), pulse oxygen saturation and the fraction of inspired oxygen ratio (SpO_2: FiO_2), the partial pressure of oxygen and fraction of inspired oxygen ratio (PaO_2: FiO_2), respiratory rate, mortality, length of stay, and adverse events of awake PP. In the case of non-intubated patients, the expected concerns with prone positioning include worsening of respiratory failure due to non-tolerance, pressure sores, back pain, vomiting, and issues of venous access.

Data abstraction

Two review authors (SM and SP) extracted and reviewed the data. Data from the finally selected studies were extracted on a data extraction form. By thorough review of the article, the following information was retrieved – (a) author, (b) year, (c) number of patients, (d) country, (e) inclusion criteria, (f) study design, (e) age, (f) gender, (g) intervention, (h) outcome measures including the number of patients requiring intubation, pre- and post-intervention oxygenation indices and respiratory rate, mortality, length of stay (i) strengths, and (j) limitations of the study.

Data, if not reported as mean and standard deviation, were derived from individual patient data given in the original papers or supplementary data using Stata software. In one study with a control group, we included data only from the group undergoing awake PP [6].

Assessment of study quality

The Qualsyst tool for quantitative studies was used to assess the quality of studies [14,15]. Two authors (S.M. and S.P.B.) evaluated the quality of the selected studies for meta-analysis. The definition of the quality of a paper was defined as: strong (summary score of >0.80), good (summary score of 0.71-0.79), adequate (summary score of 0.50-0.70), and limited (summary score of <0.50) [14].

Statistical analysis

Statistical analyses were performed using the STATA statistical analysis software (StataCorp. 2017. Stata Statistical Software: Release 15. StataCorp LLC., College Station, TX, USA) The Proportional meta-analysis was performed using the random-effects model for the primary outcome (*i.e.*,. the need for intubation). This data was extracted from the studies as the number of patients having the outcome of interest divided by the total number of patients. The forest plots were generated using Stata software for proportional meta-analysis.

When the same measure of oxygenation was reported in studies, the pooled effect of change in each oxygenation parameter (SpO_2, PaO_2, PaO_2: FiO2) and respiratory rate were presented as a weighted mean difference with corresponding 95% confidence intervals. The analyses for these outcomes were conducted using the means and standard deviations provided in the articles. These forest plots were generated using Revman 5 software. When dif-

ferent measures of oxygenation such as PaO_2: FiO_2, PaO_2, SpO_2 were reported, we estimated the pooled effect using standardized mean difference (SMD) with 95% confidence intervals by inverse variance statistical method. If a study reported more than one oxygenation parameter, we preferred PaO_2: FiO_2 and PaO_2 change over SpO_2 for the estimation of SMD. A qualitative synthesis of data was performed in case the data for meta-analysis was not available.

Heterogeneity and publication bias assessment

The impact of heterogeneity on the pooled estimates of the outcome was assessed using the Cochran Q statistic and I^2 test (measures the extent of inconsistency among the results of the studies) [16]. The presence of publication bias assessment was done using the funnel plot, which is a measure of the proportion (in the X-axis) against the standard error of the proportion (in the Y-axis). The minimum number of studies required for a funnel plot is usually 10 and Begg's test was used for publication bias assessment.

Results

The search yielded 221 citations out of which we accessed 57 full-text articles (Figure 1). A total of 16 articles (six prospective cohort studies [6,11,17-20], four before-after studies [10,21-23], and six retrospective cohort studies [24-29]) including a cumulative 316 patients with COVID-19 acute hypoxic respiratory failure undergoing awake PP were included for final review. No randomized controlled trials or systematic reviews were available.

Study characteristics

The basic details of the 16 included studies are summarized in Table 1. Female patients comprised 32.1% of the total population (89/ 277 patients, 14 studies). The interfaces used for oxygen therapy varied from conventional oxygen therapy with nasal cannula, face mask or non-rebreather mask [6,11,17,18,22,26,27,29], high flow nasal cannula [11,20,26,28,29], continuous airway positive pressure (CPAP) [17,19,25], and non-invasive ventilation (NIV) [10,21] including helmet NIV/ CPAP [19,21]. The same study had applied multiple methods of oxygen delivery as per the requirement of the patients. Among the 262 patients for whom interface data was available, 108 (41.2%) were on positive airway pressure therapy by CPAP or NIV. The severity of hypoxia in the included studies indicates a moderate ARDS, with a mean PaO_2: FiO_2 ratio of 161.7 from seven studies that reported the PaO2: FiO2 ratio before awake PP. The proning protocol used in studies also varied widely, with studies reporting the mean duration of awake PP per day from 2 hours to 9 hours [20,21]. In another study, 63% of the patients enrolled were able to continue awake PP for more than 3 hours per day [17]. One study also employed lateral positioning depending upon the radiological distribution of infiltrates, with prone positioning used in bilateral disease and lateral position with healthy lung down in case of unilateral infiltrates [19].

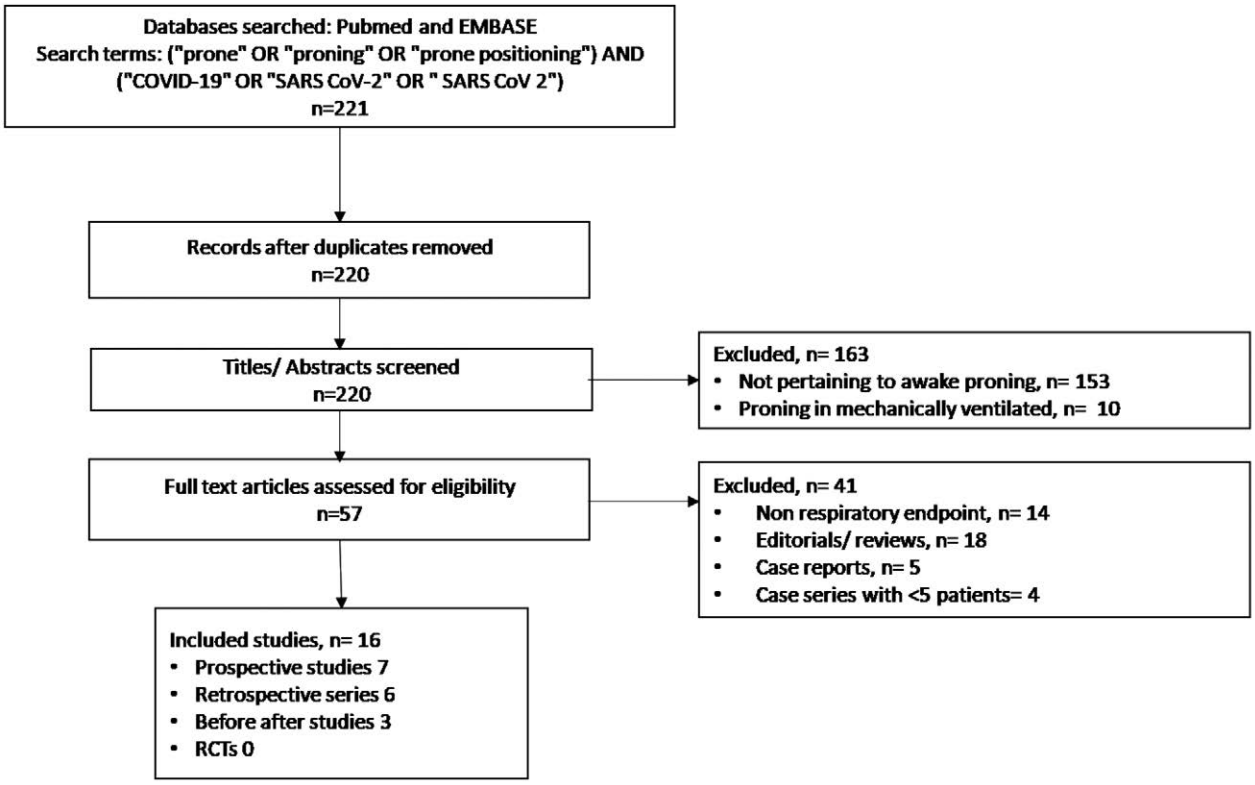

Figure 1. The flow-diagram for studies included in the systematic review and meta-analysis.

Table 1. Characteristics of the studies included in the systematic review.

No.	Authors	Number of patients	Intervention	Setting	Outcomes	Characteristics of included patients Mean age Female, n (%)	Interface	Prone duration	Key results*	Remarks
1	Caputo *et al.* [18]	50	Awake PP	New York Prospective cohort study Patients with hypoxia on arrival in Emergency Department	SpO_2 before and five minutes after PP	59 years 20 (40%)	NRBM 38, NC 12	NA	Median (IQR) SpO2 improved from 84 (75-90) to 94% (90-95) Intubation rate: 24% at 24 hours, 18/ 50 overall Death: NA	Large sample size No defined standard of care Excluded patients on NIV
2	Coppo *et al.* [17]	56	Awake PP for ≥3 h	Italy Prospective cohort study 56 patients on supplemental oxygen/CPAP	Variation in oxygenation PaO_2: FiO_2 between baseline and after 1 hour of resupination, as an index of pulmonary recruitment	57.4 years 12 (26.1%)	CPAP (4) Reservoir mask (9) Venturi mask (3)	3.5 hours/day	PaO_2: FiO_2 ratio 180.5 mm Hg in supine *vs* 285.5 mm Hg in prone position (p<0.0001) Improvement was maintained in half patients after 1h resupination (responders) Awake PP feasible (≥3 h) in 47 (83·9%) Intubation rate: 13/46 Death: 5/46	Largest cohort study Done in various settings (ED/ward) Low duration of PP (mean 3.5 h per day) No use of HFNC Majority were on CPAP so effect of PAP may cause bias
3	Damarla *et al*. [29]	10	Two hours alternating prone and supine	USA Retrospective cohort study Single center ICU, non-intubated hypoxic patients	Change in Spo_2 and RR after one hour of PP	56.6 years 4 (40%)	1 RA, HFNC 4, NC 5	NA	SpO_2 change 94% [IQR, 91-95%] to 98% [IQR,97-99%] Respiratory rate change 31 [IQR, 28 to 39] to 22 [IQR, 18 to 25] per minute Intubation rate: 2/10 Death: 0/ 10	No control group. Small sample size
4	Sartini *et al.* [10]	15	One hour awake PP. Continued if improvement in oxygenation in 1 hour	Milan, Italy Before-after study Outside ICU Inclusion criteria: Poor response to NIV in supine at FiO2 0.6, CPAP 10 cm H2O	Spo_2, derived Pao_2:Fio_2, respiratory rate, and patient's comfort using a numerical rating scale (0, totally uncomfortable, to 10, fully comfortable) measured before NIV, during NIV in pronation (60 minutes after start), and 60 minutes after NIV end	59 years 2 (13.3)	NIV	3 hours/day	Oxygenation values not available. All patients had improvement in RR, SpO_2, and PaO_2:FiO_2 11 (73.3%) had an improvement in comfort during pronation. 14 day follow up- 3 continued PP Intubation rate: 1/15 Death: 1/ 15	14 day follow up reported Mean duration of prone position is 3 hours. Short duration of NIV Lack of control group

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Table 1. Continued from previous page.

No.	Authors	Number of patients	Intervention	Setting	Outcomes	Characteristics of included patients Mean age Female, n (%)	Interface	Prone duration	Key results*	Remarks
5	Elharrar *et al.* [11]	24	Awake PP as tolerated	France Prospective cohort study Single center Requiring oxygen and CT showing posterior lesions	Proportion of responders i.e. PaO_2 increase ≥20% between before and during PP. Tolerance of prone positioning as on Visual Analogue Scale	66.1 years 8 (33.3)	COT (<4l/min)-16, HFNC or >4l/min - 8	63% more than 3 h/day	No significant difference between PaO_2 before PP and PaO_2 after resupination 25% responders 63% able to tolerate PP for ≥3h Intubation rate: 5/24 Death: NA	Reported patient tolerance to PP Small study Single episode of PP was evaluated
6	Moghadam *et al.* [23]	10	Awake PP	Iran Before-after study COVID-19 ward	SpO_2 before and after prone positioning	41 years 3 (30%)	NA	NA	Mean (SD) SpO_2 improved from 85.6 (0.69) % to 95.9 (2.2) %. Feeling of dyspnea decreased to 40% Intubation: 0 Death: 0	Duration of PP not available No control group
7	Golestaniera ghi *et al.* [21]	10	Awake PP in 2 h cycles or as per tolerability	Iran Before-after study PaO_2: FiO_2 <150 on helmet NIV	Oxygenation before and after proning	NA	Helmet NIV	9 hours/ day	Sustained improvement (>12 mm Hg) in oxygenation in 60% cases No adverse events Intubation: 2/ 10 Death: 2/ 10	Higher mean duration of PP No control group
8	Ng *et al.* [22]	10	Awake PP 1 hour each session, five sessions a day, three hours apart	Singapore Before after study General ward COVID-19 related hypoxia with FiO_2 < 50%	Descriptive study	60.6 years 2 (20%)	NC	Cumulative median 21 h over median 8 days	Oxygenation improvement: 70% Intubation: 1/10 Death: 1/ 10	Protocolized proning done Detailed oxygenation parameters not reported
9	Xu *et al.* [28]	10	Awake PP with target prone 16 h/day	China Retrospective cohort study Early awake PP combined with HFNC	Oxygenation improvement Survival	50.2 5 (50%)	HFNC	NA	Significant improvement in median PaO_2:FiO_2 (exact numbers not available) Median (IQR) $PaCO_2$ increased slightly [32.3(29.3-34.0) *vs* 29.7 (28.0-32.0), p<0.001] Intubation:0 Death: 0	Larger target mean duration of PP Exact PP duration not reported

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No.	Authors	Number of patients	Intervention	Setting	Outcomes	Characteristics of included patients Mean age Female, n (%)	Interface	Prone duration	Key results*	Remarks
10	Thompson *et al.* [27]	25	Awake PP as long as tolerated up to 24 hours a day	USA Retrospective cohort study Severe hypoxemia (respiratory rate of 30 breaths/min or greater and Spo_2 of 93% or less while receiving supplemental oxygen 6 L/min via nasal cannula and 15 L/min *via* non-rebreather face mask)	Change in Spo_2 before and 1 hour after initiation of the prone position	66 years 7 (28%)	NC and NRBM	5 hours/day	Median (SE) increase in SpO_2 7% (1.2%) Range of improvement in Spo_2 1% to 34% Intubation rate: 12/25 Death: 3/ 25	Reported intubation rate difference as per demographic characteristics Lack of control group Small Sample size
11	Despres *et al.* [26]	6	Awake PP duration 1-16 hours	France Retrospective case series HFNO or conventional oxygen therapy $SpO_2 \leq 92\%$ at oxygen ≥ 5 l/min	Change in P/F ratio	60 years All male	HFNC 3, COT 3	3 hours/day	PaO_2: FiO_2 ratio improved in 4 out of 6 cases after PP Intubation rate: 3/6 Death: Not available	No control group Small sample size
12	Tu *et al.* [20]	9	Awake PP	China Prospective cohort study HFNC for >2 days, and PaO_2: FiO_2 <150	PaO_2, SpO_2 and $PaCO_2$ before and after PP	51 years 5 (55.6%)	HFNC	2 hours/day	Mean (SD) improvement in SpO_2 from 90 (2) to 96 (3)% ($p<0.001$) Mean (SD)improvement in PaO_2 from 9 (10) to 108 (14) mmHg ($P<0.001$) Decrease in mean (SD) $PaCO_2$ from 47 (7) to 39 (5) mmHg ($P=0.007$) Intubation: 2/9 Death: Not available	Low median duration of awake PP, awake PP used as salvage therapy

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Table 1. Continued from previous page.

No.	Authors	Number of patients	Intervention	Setting	Outcomes	Characteristics of included patients Mean age Female, n (%)	Interface	Prone duration	Key results*	Remarks
13	Retucci *et al.* [19]	26	Awake PP in bilateral disease Lateral positionin g in unilateral disease	Italy Prospective cohort study PaO_2:FIO_2 during helmet CPAP <250 after at least 48 hours	Primary outcome was the success of the prone/lateral positioning trial, defined as the occurrence of all of the following criteria at T1 in comparison with T0: (1) a decrease of A-aO_2 of at least 20%, (2) equal or reduced respiratory rate, (3) equal or reduced Dyspnea BORG scale), (4) SBP >90 mm Hg.	62 years 9 (34.6%)	Helmet CPAP	NA	15.4% successful with a decrease of A-aO_2 of 20%or more during the trial in comparison with baseline. Seventeen trials (46.1%) showed a decrease of <20% ofA-aO_2 25% (awake PP) and 40% (lateral positioning failed Intubation: 7/ 26 Death: 2/ 26	Lateral positioning employed Excluded SpO_2 <90% at FIO_2 >0.8.
14	Zang *et al.* [6]	60	23 Awake PP 37 controls	China Prospective cohort study 86% ≤ SpO_2 ≤93% on NRBM 10 l/min	SpO_2, RR, ROX index at 10 min and 30 min of PP 90 d mortality	62.7 years 10 (16.7%)	NRBM	9 hours cumulati ve	Significant improvement in SpO_2, RR, ROX index at 10 min and 30 min of awake PP. 90 days of follow-up, 10 (43.5%) died in the awake PP group, 28 (75.7%) in non-prone position group Intubation rate: 8/ 23 Death: 10/ 23	90d mortality assessed Presence of control group Non randomized
15	Ripoll-Gallardo *et al.* [25]	13	Awake PP	Italy Retrospecti ve cohort study CPAP with 0.6 FiO_2 and 10 CMH20 PEEP and pronated if PaO_2: FiO_2 <150 mmHg	12/ 13 improved oxygenation	66.3 years 2 (15.3%)	CPAP	2.4 hours/ day	PaO_2: FiO_2 improved from 115.2 ± 13.3 to 166.4 ± 70 Intubation rate: 9/ 13 Death: 7/ 13	Sicker cohort
16	Huang *et al.* [24]	29	Awake PP	China Retrospecti ve cohort study Series of 60 patients of severe COVID-19	No mortality	NA	NA	NA	PaO_2: FiO_2 improved from 158.7 to 237.3 Intubation rate: not available Death: None	Awake PP data not separately provided

*Numerical values for oxygenation parameters are provided for studies reporting the same in their original publication or calculated from the individual patient values provided in original publication or supplementary data; NRBM, non rebreather mask; NC, nasal cannula; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; PEEP, positive end expiratory pressure; PP, prone positioning; RR, respiratory rate; ROX, SpO_2/ FiO_2/RR; NIV, non-invasive ventilation.

Quality assessment

Eight studies were classified as limited quality, while four strong, one good, and three were adjudged of adequate quality. The mean (SD) score on Qualsys was 0.58 (0.22) (Supplementary Table 1). Only one study had included a control group; however, the method of group allocation was not clear [6]. The study flow diagram is shown in Figure 1.

Intubation rate

Among the 316 patients included in the review, the incidence of intubation was reported in all except one study. Out of the 287 patients for whom intubation outcome was available, 83 patients (28.9%) required IMV. The overall pooled proportion of patients who required IMV was 0.25 (95% confidence interval 0.16-0.34) (Figure 2). There was significant heterogeneity among studies reporting intubation rate (I^2=62.5%) and there was no publication bias as assessed by funnel plot (Supplementary Figure 1).

Oxygenation indices

Most of the studies report a significant improvement in oxygenation status as measured by PaO2: FiO2 ratio, PaO2, pulse oxygen saturation, and respiratory rate. The percentage of patients who exhibit improvement in oxygenation status after awake PP varied widely from 25% to 100%, as varying criteria were used for defining improvement Prone positioning yielded a significant medium effect size for overall oxygenation improvement measured by any of the parameters (SMD 1.72, 95% CI 1.01-2.43) as depicted in Figure 3. In the two studies which reported oxygenation parameters after re-supination, the improvement in oxygenation was not sustained [17,19].

PaO_2: FiO_2

The PaO_2: FiO_2 ratio was compared before and during PP in five studies [17,19,24–26]. Cumulatively, the weighted mean difference in PaO_2: FiO_2 ratio after and before prone positioning was 51.29 mmHg (95% CI 13.91-88.67) in four studies with complete data (Figure 4a). There was significant heterogeneity among the studies reporting a change in PaO_2: FiO_2 ratio (I2=72.4%).

Partial pressure of oxygen in arterial blood (PaO_2)

The partial pressure of oxygen in arterial blood (PaO_2) before and during awake PP was reported in five studies [10,11,18,20,23]. The cumulative mean improvement (WMD) in PaO_2 during prone positioning was 27.94 mm Hg (95% CI 15.20-40.69) (Figure 4b).

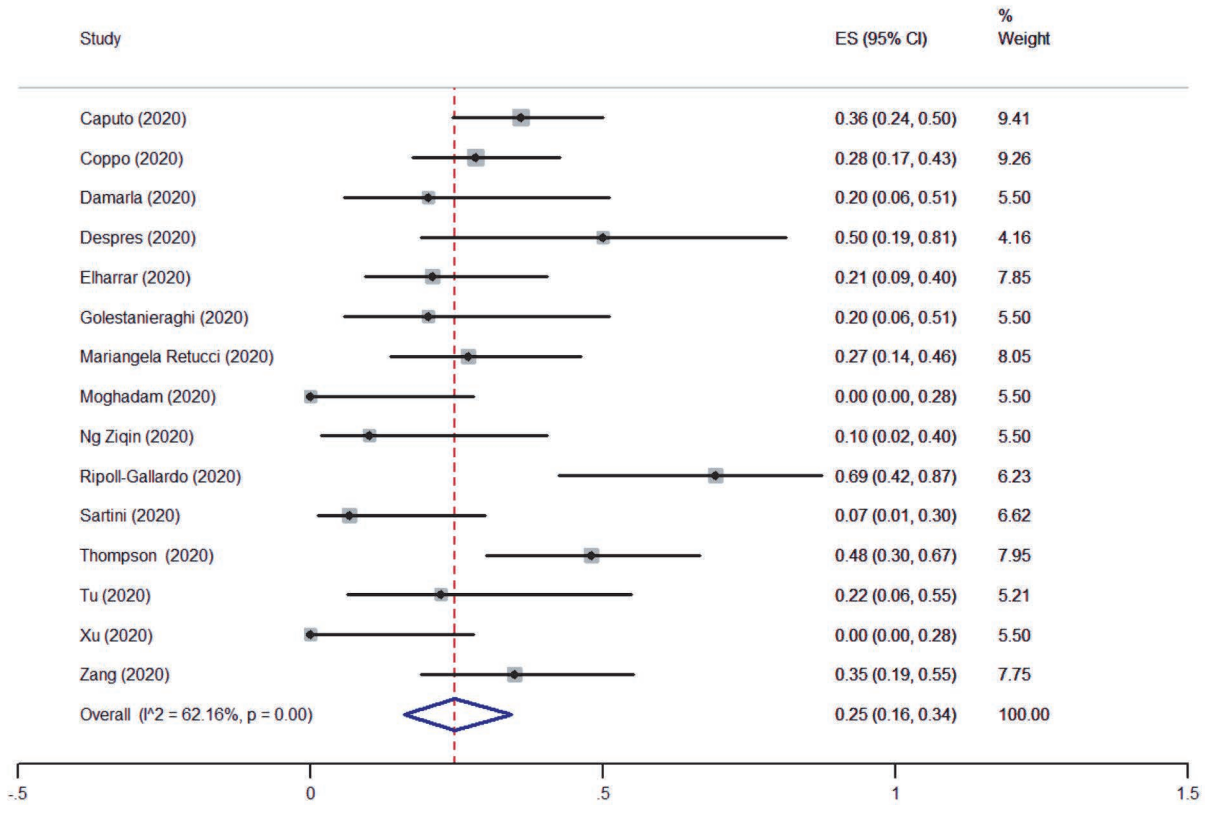

Figure 2. The forest plot depicting pooled proportion of patients requiring intubation and mechanical ventilation.

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Pulse oxygen saturation (SpO_2)

Pulse oxygen saturation (SpO_2) before and during awake PP was described in seven studies [6,17,18,20,23,27,29]. The pooled effect, *i.e.* the mean difference in SpO_2 after awake PP, from four studies providing mean and SD, was 5.39 % (95% CI 1.53-9.25) (Figure 4c) [6,17,20,23].

Respiratory rate

Respiratory rate change with awake PP was reported in six studies, and complete data were available for five of them. The mean change in RR following awake PP was -0.83 (95% CI -3.02 to 1.37) (Figure 4d).

ROX index

ROX index (SpO_2/FiO_2 (%)/ Respiratory rate) was reported in one study [6]. ROX index increased from 3.35±0.46 to 3.96±0.45 after 30 min of prone positioning ($p<0.01$).

Mortality and length of stay

Only one study with a control group reported the 90-day mortality [6]. A total of 10 (43.5%) patients died in the awake PP group, compared with 28 (75.7%) patients in the non-prone position group [6]. Twelve studies reported the number of deaths in the observational cohort, yielding a cumulative 31 deaths out of 227 patients (13.7%). Length of stay was reported in four studies, yielding a median (IQR) of 12.9 (5.6- 25.4) days.

Timing of awake PP initiation

The time from hospitalization to awake PP was significantly different in responders and non-responders in one study (2.7d *vs* 4.6 d) suggesting the role of employing awake PP early in the disease course [17].

Safety

Most safety data were of low quality from single-group studies. In the study by Elharrar *et al*., 63% of patients were able to tolerate awake PP for ≥3 hours, while another study showed feasibility in up to 83.9% [11,17]. Back pain was reported in 42% during awake PP [11]. Episodes of hypotension or desaturation were not observed in any of the studies. One series reported half the patients showing a decrease in PaO_2: FiO_2 ratio when awake PP was used in severe COVID-19 patients [26]. One study analyzed comfort and dyspnea before and during awake PP by visual analog scale (VAS) and reported an improvement from 3 to 2 in dyspnea and an increase in discomfort from 0 to 4 median [11]. Failure of awake PP in terms of increased respiratory rate or elevation of the alveolar-arterial gradient happened in 25% in prone positioning to 40% in the lateral position [19]. No studies reported any pressure sores.

Discussion

Evidence from the available studies indicates that awake PP used along with non-invasive oxygen delivery devices improves oxygenation in patients with COVID-19 related acute hypoxemic respiratory failure. The intubation rate in this pooled cohort was 28.9%. As per a recent review, among COVID-19 patients admitted to ICU, 35.4-100% require invasive mechanical ventilation [30]. This difference in intubation rate can not be directly attributed to awake PP, but it does suggest a lack of harm as there was no increase in the intubation rate in the patients undergoing awake PP. When added to high-flow nasal cannula (HFNC) or NIV, early prone positioning has been shown to avoid the need for intubation in almost half of the patients with moderate to severe ARDS, even in non-COVID-19 patients [8]. Improvement in oxygenation alone may not lead to improved clinical outcomes as demonstrated in previous trials of inhaled nitric oxide, surfactant therapy, and higher tidal volumes which improved oxygenation but did not produce

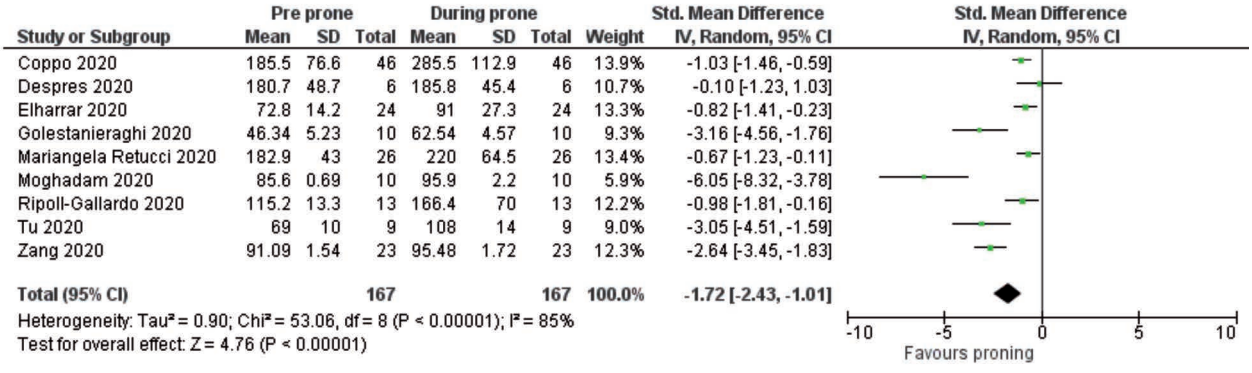

Figure 3. The first plot depicting pooled difference in any of the oxygenation parameter as measured by standardized mean difference during awake PP. Four studies (Coppo, Despres, Mariangela Retucci and Ripoll-Gallardo) reported PaO_2:FiO_2, three studies (Elharrar, Golestanieraghi and Tu) reported PaO_2 and two studies (Moghandam and Zang) reported SpO_2.

any clinically relevant outcomes in larger trials [31]. A critical finding from this meta-analysis is improved oxygenation by awake PP; however, no conclusion regarding other clinically relevant outcomes such as the need for IMV or length of stay could be withdrawn. The effect of awake PP on these outcomes needs further studies with a comparison group, ideally in a randomized fashion.

There remains a concern whether awake PP may delay intubation and cause harm which can not be concluded from the available evidence. There was a wide variation in the severity of hypoxemia in the included studies, leading to a variable rate of intubation.

No conclusion can be drawn about the minimum duration of awake PP required for clinical improvement as no study compared varying durations of awake PP and included studies had heterogeneity in the durations employed. We initially planned analysis to assess the effect of the duration of awake PP on oxygenation and avoidance of intubation; however, this was not possible due to lack of required data of duration of awake PP. The subset of patients who will benefit from awake PP is also hard to conclude, but there is an indication that early awake PP may have better results [17]. All studies have excluded patients requiring emergent intubation. The effect of concomitant drug therapy on the clinical outcomes studied could not be estimated because of the data's non-availability. We could not assess the effect of the application of CPAP over the conventional mode of oxygenation. As CPAP might correct hypoxemia more than standard oxygen delivery, it remains known whether patients receiving CPAP therapy had greater oxygenation improvement [32,33]. The study by Sartini *et al*. [10] described the combined effect of NIV and prone positioning; thus, it was not possible to separate the effect of NIV from the awake PP.

The pre-requisite for awake PP is an alert and conscious patient who can cooperate with position changes. Contraindications for awake PP include the requirement of urgent intubation, agitation or altered mental status, unstable spine or thoracic injury, recent abdominal surgery, and morbid obesity [34]. Hemodynamic instability is an absolute contraindication as a cardiac arrest without a definitive airway in the prone position may prove difficult for resuscitation as the patient will have to be supinated for securing the airway. Second or third-trimester pregnancy is a relative contraindication for awake PP, though case reports of the same have been published [35]. Tolerance is a concern with some studies reporting an inability to tolerate awake PP in a significant proportion. Awake PP requires close monitoring from the nursing staff to ensure it is successful and tolerated, especially during the initial sessions.

The major limitation of this systematic review is that we also

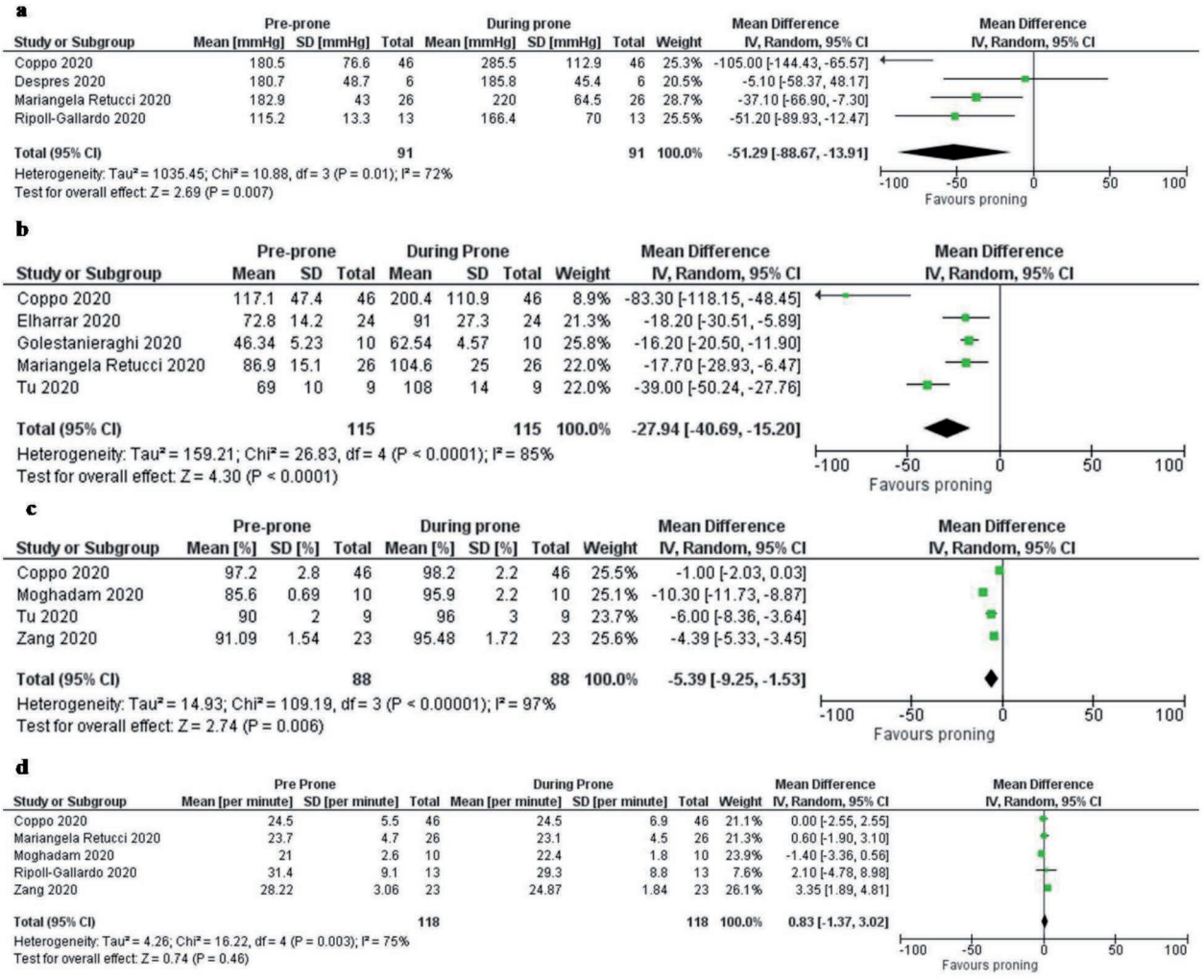

Figure 4. Forest plots depicting change in various parameters as weighted mean difference during awake PP. a) PaO_2: FiO_2 ratio. b) Partial pressure of oxygen (PaO_2). c) Pulse oxygen saturation (SpO_2). d) Respiratory rate.

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included studies with lower quality. As the evidence for awake PP is still sparse and emerging, we attempted to summarize the evidence rather than derive definite conclusions. As there was only one study with a control group, it was not possible to derive a conclusion regarding awake PP compared to patients who did not undergo awake PP. In the current scenario of the ongoing pandemic, further studies regarding awake PP will likely continue to be conducted, and RCTs are being conducted as well (NCT04395144). Another major limitation is the substantial heterogeneity found in the meta-analysis. It is likely due to variable inclusion criteria and the duration of proning in the studies included in this meta-analysis. Due to this heterogeneity, we need to use caution in interpreting these results. However, as all studies demonstrated improved oxygenation, it is likely real benefit though the degree of improvement may vary.

Conclusions

Awake PP in non-intubated patients with COVID-19 hypoxemic respiratory failure might be associated with a reduction in the need for intubation and improvement in oxygenation. However, its effect on reducing mortality is still unclear. Awake PP is one strategy that has been widely advertised as low risk and inexpensive. Though available evidence is supportive, more studies, especially randomized trials, are required before this can become a routine procedure in hypoxic respiratory failure.

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