

Prone Positioning of Nonintubated Patients With Coronavirus Disease 2019—A Systematic Review and Meta-Analysis

OBJECTIVES: Several studies have reported prone positioning of non-intubated patients with coronavirus diseases 2019–related hypoxemic respiratory failure. This systematic review and meta-analysis evaluated the impact of prone positioning on oxygenation and clinical outcomes.

DESIGN AND SETTING: We searched PubMed, Embase, and the coronavirus diseases 2019 living systematic review from December 1, 2019, to November 9, 2020.

SUBJECTS AND INTERVENTION: Studies reporting prone positioning in hypoxemic, nonintubated adult patients with coronavirus diseases 2019 were included.

MEASUREMENTS AND MAIN RESULTS: Data on prone positioning location (ICU vs non-ICU), prone positioning dose (total minutes/d), frequency (sessions/d), respiratory supports during prone positioning, relative changes in oxygenation variables (peripheral oxygen saturation, Pao₂, and ratio of Pao₂ to the Fio₂), respiratory rate pre and post prone positioning, intubation rate, and mortality were extracted. Twenty-five observational studies reporting prone positioning in 758 patients were included. There was substantial heterogeneity in prone positioning location, dose and frequency, and respiratory supports provided. Significant improvements were seen in ratio of Pao₂ to the Fio₂ (mean difference, 39; 95% CI, 25–54), Pao₂ (mean difference, 20 mm Hg; 95% CI, 14–25), and peripheral oxygen saturation (mean difference, 4.74%; 95% CI, 3–6%). Respiratory rate decreased post prone positioning (mean difference, –3.2 breaths/min; 95% CI, –4.6 to –1.9). Intubation and mortality rates were 24% (95% CI, 17–32%) and 13% (95% CI, 6–19%), respectively. There was no difference in intubation rate in those receiving prone positioning within and outside ICU (32% [69/214] vs 33% [107/320]; *p* = 0.84). No major adverse events were recorded in small subset of studies that reported them.

CONCLUSIONS: Despite the significant variability in frequency and duration of prone positioning and respiratory supports applied, prone positioning was associated with improvement in oxygenation variables without any reported serious adverse events. The results are limited by a lack of controls and adjustments for confounders. Whether this improvement in oxygenation results in meaningful patient-centered outcomes such as reduced intubation or mortality rates requires testing in well-designed randomized clinical trials.

KEY WORDS: awake proning; coronavirus disease 2019; hypoxemic respiratory failure; positioning; prone endotracheal intubation; severe acute respiratory syndrome coronavirus 2

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2, mainly affects the respiratory system and can cause acute hypoxemic respiratory failure. About a third of these patients require admission to ICUs for advanced respiratory support (1–4). A surge in critically ill patients with respiratory failure has overwhelmed ICU capacity in many healthcare systems across the world (3, 4). Studies published during the early phase of the pandemic showed poor outcomes in patients with COVID-19 requiring invasive mechanical ventilation (IMV) with a recent systematic review estimated the reported mortality rate to be 45%, which was significantly higher with increasing age (5). Given the guarded prognosis and significant resource constraints, less invasive and innovative approaches such as prone positioning (PP) of nonintubated patients with hypoxemic respiratory failure have been considered. They were initiated in emergency departments (EDs), hospital wards, or in ICUs as an adjunct to conventional oxygen therapies, high-flow nasal cannula (HFNC), and noninvasive ventilation (NIV) (6, 7).

The potential efficacy of PP with hypoxemic respiratory failure is yet to be meaningfully tested in well-designed clinical trials. Limited data suggest that PP in nonintubated patients is feasible and is associated with an improvement in oxygenation in patients with respiratory failure (8). There have been case reports and cohort studies that report the use of PP of nonintubated patients with COVID-19 during the pandemic (2, 9–11). Conceptually, awake PP is relatively less time and resource consuming as compared to PP in intubated patients. Theoretically, it may decrease the risks of adverse events seen in intubated prone patients.

Deteriorating oxygenation despite optimal less-invasive respiratory support (12) is one of the common triggers for IMV. PP improves oxygenation by increasing ventilation-perfusion matching by the recruitment of the larger number of alveolar units located in dorsal areas of the lungs (13–15). The weight of the heart, dorsal lung, and abdominal viscera increases the dorsal pleural pressure and reduces the transpulmonary pressures in dorsal regions, thus generating a ventral-dorsal pleural pressure gradient. In patients with acute respiratory distress syndrome (ARDS), this gradient is further amplified due to the increased mass of the edematous lung that causes a collapse of the dependent dorsal regions. The gravitational gradient increases perfusion in these zones resulting in a region of low ventilation and high perfusion,

thereby causing hypoxemia. PP improves this pleural pressure gradient across the dorsal and ventral regions thereby decreasing ventilation-perfusion mismatch (15). Furthermore, in patients with COVID-19, PP may also enable gravity-assisted diversion of pulmonary blood flow to dorsal regions in the setting of pulmonary vascular dysregulation and loss of hypoxic pulmonary vasoconstriction response in selected patients (16). Thus, the success of PP largely hinges on its ability to reliably and predictably improve oxygenation, which may then subsequently improve the respiratory drive, thereby decreasing the risk of patient self-inflicted lung injury or respiratory fatigue.

Little is known about the magnitude of the effect of PP on oxygenation and its ability to improve patient-centered outcomes in nonintubated COVID-19 patients. Therefore, we performed this systematic review and meta-analysis to evaluate the effect of PP on oxygenation variables (ratio of P_{aO_2} to the F_{iO_2} [P_{aO_2}/F_{iO_2}], P_{aO_2} , or peripheral oxygen saturation [SpO_2]). Secondary analyses included rates of endotracheal intubation, in-hospital mortality, and adverse events.

METHODS

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42020194080). The study was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (17). Ethics approval was not pursued as the included studies had preexisting ethics approvals.

Eligibility Criteria

Studies on laboratory-confirmed severe acute respiratory syndrome coronavirus 2 hypoxemic adult patients (≥ 18 yr) requiring supplemental oxygen who received PP and reported on oxygenation variables (P_{aO_2}/F_{iO_2} , P_{aO_2} , or SpO_2) were included. Studies were excluded if they were narrative reviews, they did not report on oxygenation variables, or they were case reports or case series with fewer than five patients. Corresponding authors of selected studies were contacted for additional information.

Search Strategy, Information Sources, and Study Selection

Two authors (M.P.R., A.Z.) independently searched on PubMed, Embase, Cochrane, Scopus, and the

COVID-19 living systematic review from December 1, 2019, to November 9, 2020. The validated COVID-19 living systematic review has a daily-updated list of preprint and published articles relating to COVID-19 obtained from PubMed, EMBASE, medRxiv, and bioRxiv (18–20). Search terms were “Prone,” or “Prone Position*,” or “Prone Positioning” along with “COVID-19”-related terms were used within the title and abstract columns of the systematic review list. Our search strategy was further supported by an independent medical librarian search. A detailed search terms and tools are summarized in **Supplementary Table 1** (<http://links.lww.com/CCM/G408>). No language restrictions were applied.

Quality Assessment and Risk of Bias in Individual Studies

The Newcastle-Ottawa Scale (21) was used to assess the quality of cohort studies, whereas Joanna Briggs Institute Critical Appraisal Checklist (22) was used to evaluate case series. Using relevant appraisal tools, each study was objectively evaluated by two reviewers independently (M.P.R., Z.J.L.). Any discrepancies in the approval scores were reviewed and resolved by an additional reviewer (A.S.) (**Supplementary Table 2**, <http://links.lww.com/CCM/G409>).

Study Outcomes

The primary outcome was the change in oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio, PaO_2 , and SpO_2) following PP. Different measures, such as the SpO_2 , PaO_2 , and $\text{PaO}_2/\text{FiO}_2$, were used in the reported studies. We derived the PaO_2 from SpO_2 and vice versa if they were not reported in studies using the accepted conversion formulae for consistency to analyze the data (**Supplementary Table 3**, <http://links.lww.com/CCM/G410>) (23). For a small number of studies, an estimation formula was used to convert median to mean values (**Supplementary Table 4**, <http://links.lww.com/CCM/G411>) (24). Sensitivity analyses for physiologic variables were performed by restricting studies with sample sizes greater than or equal to 20.

Secondary outcomes included endotracheal intubation and mortality rates, analyzing changes in the primary outcome between patients with pre-PP $\text{PaO}_2/\text{FiO}_2$ greater than 150 and $\text{PaO}_2/\text{FiO}_2$ less than or equal to 150, and the effect of PP on respiratory rate (RR). We further analyzed the primary and secondary outcomes in patients depending on the location within the hospital where PP was

initiated, within ICU versus outside ICU (ED, respiratory wards, high-dependency units [HDUs]). We also performed an exploratory analysis on the changes in patients' RR after PP. Major adverse events were defined as cardiac arrest, clinically significant hemodynamic instability, or accidental dislodgment of an IV line following PP. Post hoc analyses were performed on PP dose (minutes spent in PP/d), frequency (PP sessions/d), and respiratory supports during PP. Given the significant heterogeneity in reported doses of PP, a cut off of 180 minutes was arbitrarily chosen to analyze the dose-response relationship and its effect on study outcomes.

Data Analysis

Statistical analyses were performed using the statistical software package Stata-Version 16 (StataCorp, College Station, TX). Mean (SD) or median (interquartile range [IQR]) was used for continuous data and proportion for categorical data. We report weighted mean difference (MD) with 95% CIs for physiologic variables and event rates using a random-effects model to account for both within-study and between-study variances (25). Results were presented in Forest plots. Heterogeneity was tested using the chi-square test on Cochran's Q statistic, which was calculated using H and I^2 indices. The I^2 index estimates the percentage of total variation across studies based on true between-study differences rather than on chance. Conventionally, I^2 values of 0–25% indicate low heterogeneity, 26–75% indicate moderate heterogeneity, and 76–100% indicate substantial heterogeneity (26). We carried out two subgroup analyses on oxygenation and clinical outcomes: ICU versus non-ICU and baseline $\text{PaO}_2/\text{FiO}_2$ ratio ($\text{PaO}_2/\text{FiO}_2 \leq 150$ and >150). A post hoc subgroup analysis using different sample sizes was carried out to identify the possible causes of substantial heterogeneity. The symmetry of the funnel plots was evaluated, and Egger's regression test was used to examine for publication bias (27). A p value less than 0.05 was considered significant.

RESULTS

From 816 studies, we included 25 eligible studies (2, 10, 11, 28–49), and a total of 758 patients were included in the final analysis (**Table 1**). These studies originated from nine countries (Brazil, Canada, China, France, Iran, Italy, Spain, the United States, and the United Kingdom). Four-hundred ninety-eight patients were

TABLE 1.
Twenty-Five Studies Included in the Systematic Review and Meta-Analysis

References	n ^a	Settings	Patient Location of PP	Supplemental O ₂ and Noninvasive Respiratory support	No. of Episode and Duration of PP (hr)	Mean Duration of PP When Respiratory Variables Were Assessed (min)	Respiratory Physiology Variables Reported Pre and Post PP			Other Outcome Variables Reported	
							Ratio of Pao ₂ to the Fio ₂	Pao ₂	Peripheral O ₂ Saturation	Hospital Mortality	Patients Requiring Intubation
Burton-Papp et al (49)	20	Single center, Southampton, United Kingdom	ICU	NIV	2 (2–4)	180	+	N	N	+	+
Caputo et al (2)	50	Single center, NY	ED	NRB and NC	1 (NR)	5	D	D	+	NR	+
Coppo et al (28)	46	Single center, Monza, Italy	ED, respiratory HDU	NIV, VM, and NRB	1–3 (3.5hr)	10	+	+	+	+	+
Damarla et al (29)	10	Single center, Baltimore, MD	ICU ^b	HFNC and NC	Multiple (2hr)	60	D	D	+	0	+
Despres et al (11)	6	Single center, Besancon, France	ICU	HFNC or VM	Multiple (1–7hr)	180	+	N	D	NR	+
Dong et al (39)	25	Single center, Wuhan, China	ICU	HFNC, VM, NC, and NIV	Daily (4.9)	294	+	N	N	0	0
Elharrar et al (38)	24	Single center, France	NR	NC and HFNC	< 1, 1–3, > 3 hr	90	D	+	D	NR	+
Ferrando et al (48)	55	Multicenter, Spain	ICU	HFNC	NR	NR	+	D	+	+	+
Golestani-Eraghi et al (37)	10	Single center, Teheran, Iran	ICU	NIV	NR/multiple (14 hr)	NR	+	+	D	+	+
Kelly et al (47)	17	Single center, London, United Kingdom	ICU/ward	NR	2 (4)	100		D	N	+	+
Lawton et al (30)	165	Single center, Bradford, United Kingdom	Ward, ED	NIV	2 times/d	30	+	N	+	+	+
Moghadam et al (36)	10	Single center, Qom, Iran	ICU	NR	NR	NR	N	D	+	NR	0
Padrão et al (46)	57	Single center, CT	ED/ward	NP	NR	NR	D	D	+	+	+
Paternoster et al (45)	11	Single center, Potenza, Italy	HDU	Helmet CPAP	1–6 (6–13)	780	+	D	+	+	+
Ramirez et al (44)	45	Single center, Milan, Italy	Ward	NIV	NR	NR	+	+	+	NR	NR
Ripoll-Gallardo et al (43)	13	Single center, Piedmont, Italy	Ward	NIV	NR	NR	+	D	D	+	+

(Continued)

TABLE 1. (Continued).
Twenty-Five Studies Included in the Systematic Review and Meta-Analysis

References	n ^a	Settings	Patient Location of PP	Supplemental O ₂ and Noninvasive Respiratory support	No. of Episode and Duration of PP (hr)	Mean Duration of PP When Respiratory Variables Were Assessed (min)	Respiratory Physiology Variables Reported Pre and Post PP			Other Outcome Variables Reported	
							Ratio of Pao ₂ to the Fio ₂	Pao ₂	Peripheral O ₂ Saturation	Hospital Mortality	Patients Requiring Intubation
Retucci et al (35)	26	Single center, Milan, Italy	Respiratory HDU	NIV	29 (1 hr)	60	+	+	+	+	+
Sartini et al (34)	15	Single center, Milan, Italy	ICU/medical ward	NIV	1–3 (1–6hr)	60	+	N	+	+	+
Solverson et al (42)	17	Single center, Calgary, Canada	ICU/ward	NP	2 (0.5–8)	75	D	D	+	+	+
Taboada et al (41)	50	Single center, Galicia, Spain	Ward	HFNC/NIV	3 (0.5–1)	30	+	D	+	+	+
Thompson et al (33)	29	Single center, NY	HDU	NRB and NC	1 hr	60	+	D	+	+	+
Tu et al (32)	9	Single center, Shanghai, China	ICU	HFNC and NIV	3–8 (1–4hr)	120	+	+	+	+	+
Winearls et al (40)	24	Single center, Bristol, United Kingdom	ICU	NIV	1 (6)	480	+	D	+	+	+
Xu et al (31)	10	Single center, Anhui, China.	ICU	HFNC	3 (16hr)	300	+	N	+	0	0
Zang et al (10)	23	Single center, Beijing, China	ICU	HFNC	13.43 (8.04hr)	30	D	D	+	+	+

D = the variable was derived from other reported values, ED = emergency department, HDU = high-dependency unit, HFNC = high-flow nasal cannula, N = the variable not reported and unable to derive, NC = nasal cannula, NIV = noninvasive ventilation, NP = nasal prongs, NR = the variable was not reported in the study, NRB = nonbreather mask, PP = prone positioning, R = the variable was reported, VM = venturi mask/Hudson mask, 0 = no events.

^aNumber of awake prone positioned patients in the study.

^bPP in one of the 10 patients happened in medical ward following ICU consultation and supervision.

Preferred reporting items for systematic reviews and meta-analyses checklist: flowchart of study inclusions and exclusions.

Addition symbol indicates variable reported in the study.

men (66%) with a mean age (SD) of 58 (± 8) years. The PP dose varied (median, 120 min; IQR, 23–221 min) with a frequency of one to three times/d during their hospital stay or until intubation, if it occurred. Data on oxygen therapy provided during PP were reported in 642 patients. Fifty-eight percent (369/642) received NIV, 16.7% (107/642) on HFNC, 10% (65/642) received oxygen via face mask, and 16% (101/642) via low-flow nasal cannula. Forty-six percent of them (225/493) received Fio₂ less than 50%, 38% (189/493) were on Fio₂ between 50 and 70%, and 16% of them (79/493) received Fio₂ greater than 70% (**Supplementary Table 5**, <http://links.lww.com/CCM/G412>).

Primary Outcome

The improvements in physiologic variables (Pao₂/Fio₂, Pao₂, Spo₂) pre and post PP are presented in **Figure 1** (Figs. 1 and 2) (**Supplementary Fig. 1**, <http://links.lww.com/CCM/G413>; **Supplementary Fig. 2**, <http://links.lww.com/CCM/G414>; **Supplementary Fig. 3**, <http://links.lww.com/CCM/G415>; and **Supplementary Fig. 4**, <http://links.lww.com/CCM/G416>).

Pao₂/Fio₂ Post PP. This was reported in 22 studies (2, 7, 10–14, 27, 29–35, 37, 39, 40, 47, 50). The Pao₂/Fio₂ improved post PP (MD, 39.5; 95% CI, 24.85–54.1; $p = 0.001$). Heterogeneity persisted despite analyzing

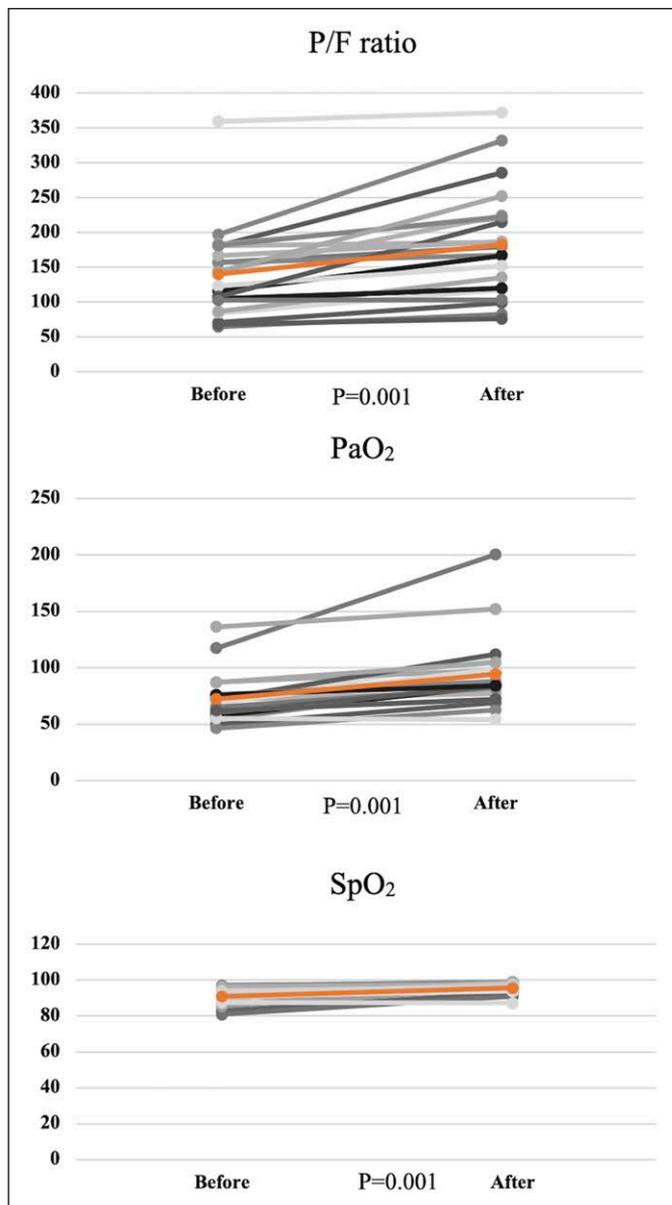


Figure 1. Graphical representation of mean improvements in physiologic variables post prone positioning. P/F = ratio of P_{aO_2} to the F_{iO_2} , SpO_2 = peripheral oxygen saturation.

studies with a sample size of greater than 20 patients (10 studies [2, 10, 30, 35, 40, 41, 44, 46, 48]; $I^2 = 99.81\%$; $p = 0.001$). However, the Egger’s regression test ruled out publication bias ($p = 0.38$).

P_{aO_2} Post PP. P_{aO_2} was reported or derived from SpO_2 in 21 studies (2, 6, 10, 11, 18, 24, 28–38, 43, 45). An improvement in P_{aO_2} was demonstrated post PP (MD, 19.7 mm Hg; 95% CI, 14.2–25.2; $p = 0.001$). The heterogeneity was high ($I^2 = 99.5\%$; $p = 0.001$). Egger’s regression test ($p < 0.001$) suggests presence of a publication bias. The heterogeneity continued to be high ($I^2 = 99.4\%$; $p = 0.001$) when 12 studies with greater than 20 patients were analyzed (2, 10, 28, 30, 33, 35, 38, 40, 41, 44, 46, 48).

SpO_2 Post PP. SpO_2 was reported in 21 studies (2, 10, 29–38, 40, 41, 43–46, 48). Improvement in SpO_2 (MD 4.7%; 95% CI, 3.3–6.2; $p = 0.001$) was seen across all studies where SpO_2 was obtained. However, there was high heterogeneity ($I^2 = 96.3\%$; $p = 0.001$), and Egger’s regression test ruled out publication bias ($p = 0.82$). The heterogeneity continued to be high when only studies with greater than 20 patients (12 studies [2, 10, 30, 33, 35, 38, 40, 41, 44, 46, 48]; $I^2 = 97.2\%$; $p = 0.001$).

Secondary Outcomes

Intubation after a trial of PP was reported in 23 studies (2, 11, 28–43, 45–49), and its prevalence was 24% (95% CI, 17–32; $p = 0.001$). Despite substantial heterogeneity ($I^2 = 85.8\%$), there was no publication bias (Egger’s regression test $p = 0.14$) (Supplementary Fig. 5, <http://links.lww.com/CCM/G417>; Supplementary Fig. 6, <http://links.lww.com/CCM/G418>; Supplementary Fig. 7, <http://links.lww.com/CCM/G419>; and Supplementary Fig. 8, a and b, <http://links.lww.com/CCM/G420>; and Supplementary Fig. 8c, <http://links.lww.com/CCM/G421>).

Mortality in patients who underwent awake PP was reported in 22 studies (10, 11, 28–31, 33–43, 45–49). The overall mortality rate was 13% (95% CI, 6–19; $p = 0.001$). Despite the high heterogeneity ($I^2 = 83.3\%$), there was no publication bias (Egger’s regression test $p = 0.32$).

There were no reported life-threatening or major adverse events post PP. Among the nine studies (36%) that have reported on adverse events, none of them described life-threatening or major adverse events following PP. Five studies (34 patients) reported minor events including pain in the back, sternum, or scrotum; general discomfort, dyspnea, and coughing and confusion in a small number of patients (28, 38–40, 49). Four studies reported no major or minor events.

Oxygenation outcomes were analyzed based on the mean pre-PP P_{aO_2}/F_{iO_2} less than or equal to 150 (13 studies [11, 30, 31, 35, 39, 43, 45, 49]) or greater than 150 (9 studies [2, 10, 29, 32, 34, 37, 41, 47, 49]). Patients with a Pre-PP P_{aO_2}/F_{iO_2} greater than 150 had higher improvement in oxygenation (P_{aO_2}/F_{iO_2}) post PP when compared with those with a pre-PP P_{aO_2}/F_{iO_2} less than or equal to 150 (MD = 41.3 [95% CI, 13.9–68.6; $p = 0.001$] vs MD = 38.6 [95% CI, 20.8–56.4; $p = 0.001$] (Fig. 3).

Sixteen studies (2, 10, 28–38, 40, 42–48) reported changes in RR upon PP. There was a significant reduction

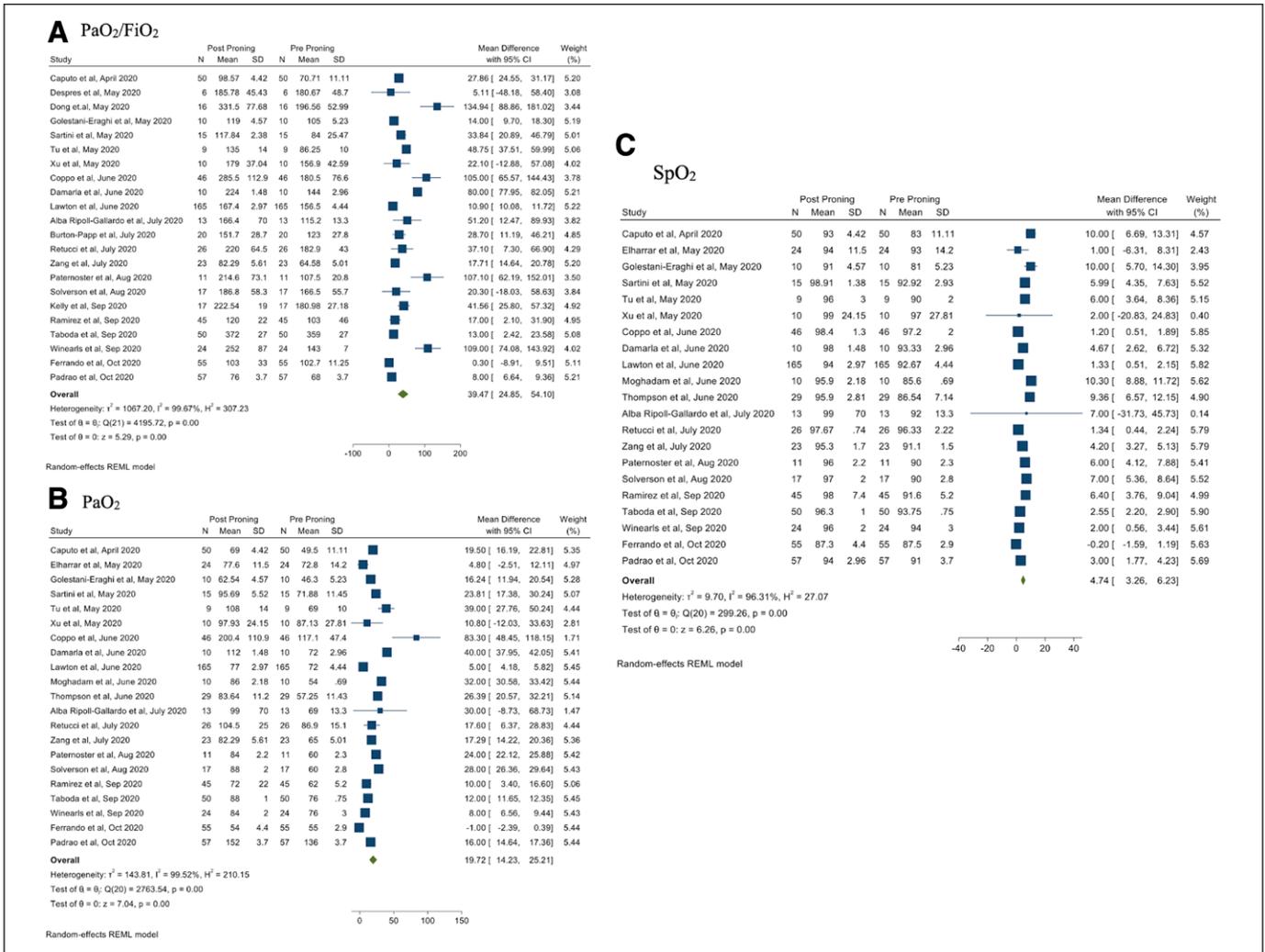


Figure 2. Primary outcome demonstrating the physiologic variables post prone positioning (PaO₂/FiO₂ ratio [A], PaO₂ [B], and peripheral oxygen saturation [SpO₂] [C]). H₂ = homogeneity test, I₂ = heterogeneity measures such, Q = a test of between-group differences based on the Q statistic, REML = random effect mode, τ^2 = the variance of the effect size parameters across the studies.

in RR post PP (MD, -3.2 breaths/min; 95% CI, -4.6 to -1.9; $p = 0.001$). High heterogeneity was observed ($I^2 = 81.5\%$) (Fig. 4) which persisted despite exclusion of smaller sample studies (10, 16, 28, 30, 35, 40, 48, 49) ($I^2 = 70.8\%$; $p = 0.01$).

Forty percent patients (214/534) received PP in ICU, and 60% (320/534) outside ICU (respiratory wards, HDUs, or EDs). Of the 176 patients who were eventually intubated, there was no difference in the proportion of patients needing intubation either in ICU or outside ICU (32% [69/214] vs 33.4% [107/320]; $p = 0.84$). Mortality data were available in 22 studies (10, 11, 28–31, 33–36, 38–41, 43–49) where patients had PP either in ICU or outside ICU. A total of 14% patients (30/214) died in ICU compared with 10.2% (23/225) who died in non-ICU areas ($p = 0.49$).

Post Hoc Analysis

- 1) “PP Dose (minutes spent in PP/d)”: Ten studies had PP dose less than or equal to 180 minutes (2, 11, 28–30, 33, 34, 41, 47, 49), whereas eight studies reported PP dose greater than 180 minutes (10, 31, 36, 37, 39, 40, 45) (Supplementary Fig. 9, a and b, <http://links.lww.com/CCM/G422>; Supplementary Fig. 9, c and d, <http://links.lww.com/CCM/G423>; Supplementary Fig. 9, e and f, <http://links.lww.com/CCM/G424>; Supplementary Fig. 10, a and b, <http://links.lww.com/CCM/G425>; Supplementary Fig. 10, c and d, <http://links.lww.com/CCM/G426>; Supplementary Fig. 10, e and f, <http://links.lww.com/CCM/G427>; Supplementary Fig. 11, a and b, <http://links.lww.com/CCM/G428>; Supplementary Fig. 11, c and d, <http://links.lww.com/CCM/G429>;

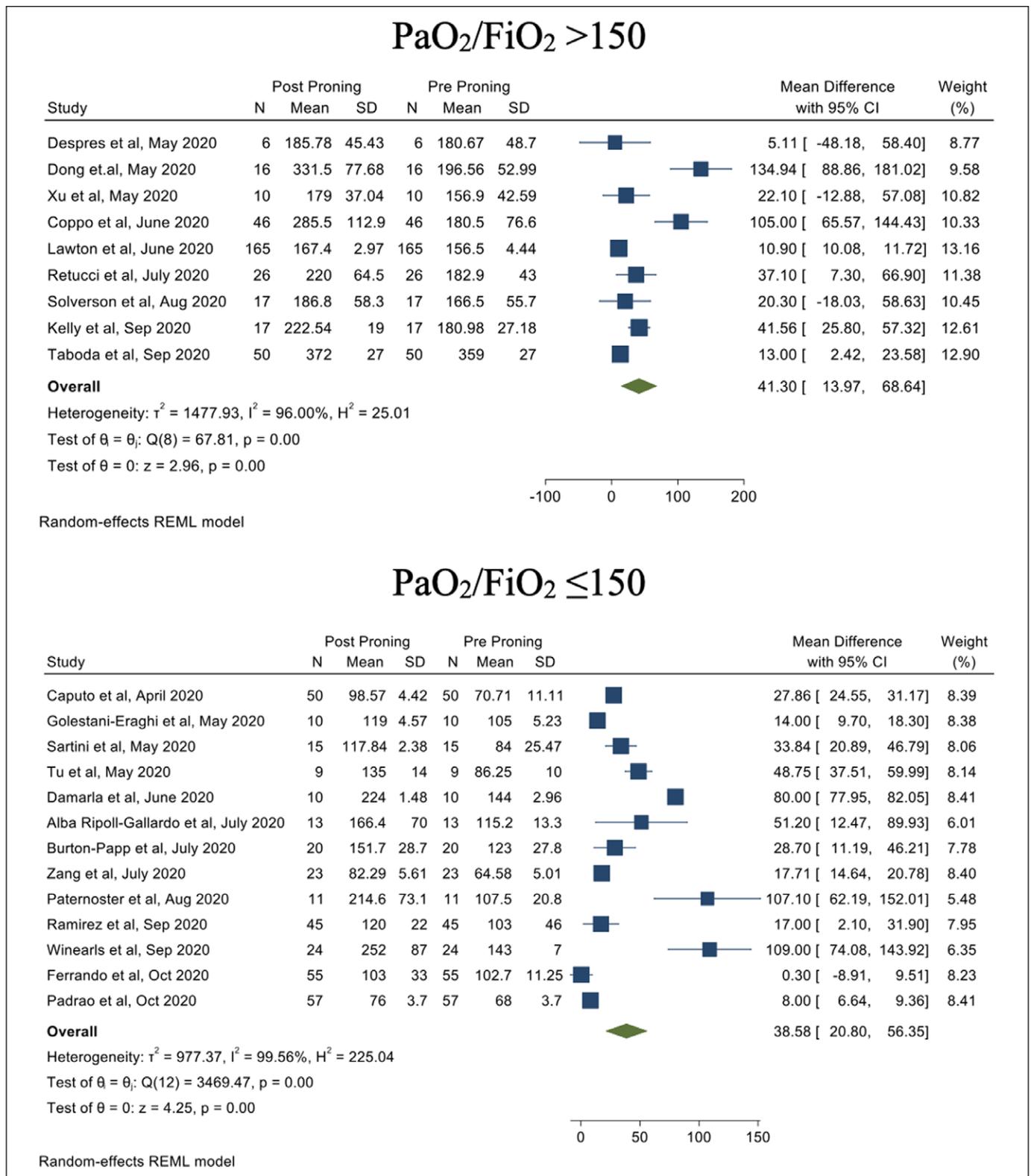
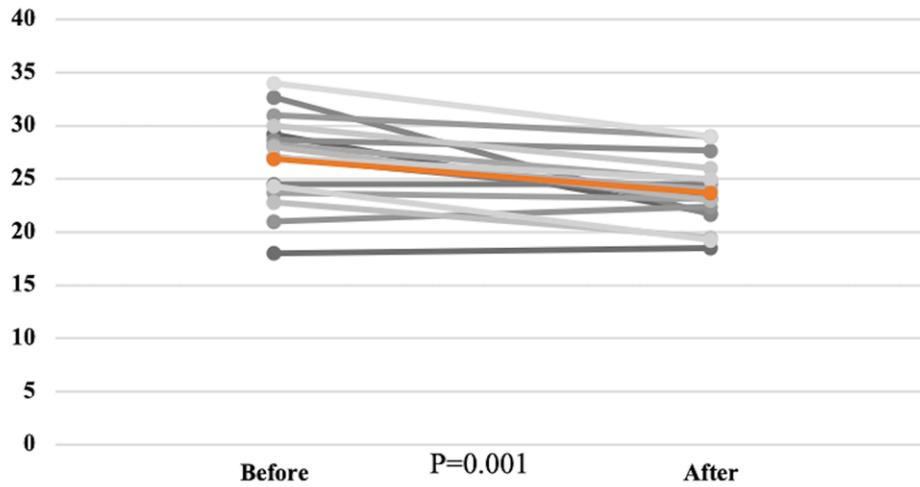


Figure 3. Secondary analysis based on ratio of PaO₂ to the FiO₂ (P/F) demonstrate that P/F less than or equal to 150 pre prone positioning had statistically significant improvements when compared with P/F greater than 150.

A Graphical representation of mean improvements in respiratory rate



B Forest plots

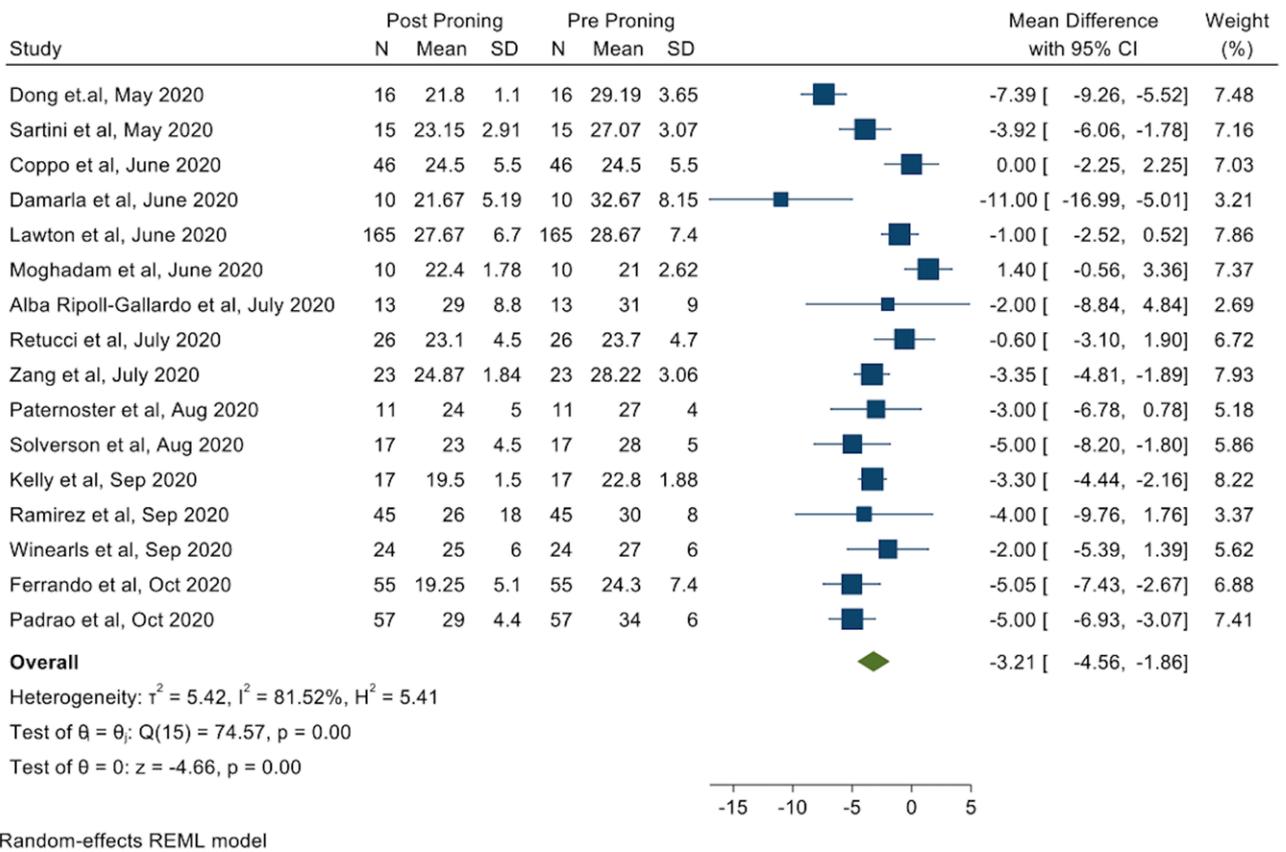


Figure 4. A and B, Secondary outcomes: Reduction in respiratory rate (RR) who underwent prone positioning (PP). Graphical representation of mean difference pre and post PP and Forest plot depicting the changes in RR post PP.

and **Supplementary Fig. 11, e and f**, <http://links.lww.com/CCM/G430>). There were no significant differences in $\text{Pao}_2/\text{Fio}_2$ (MD, 45.6; 95% CI, 26.3–64.9; $p = 0.30$), Pao_2 (MD, 22.0 mm Hg; 95% CI, 15.8–26.2; $p = 0.37$), Spo_2 (MD, 5.5%; 95% CI, 3.7–7.3%; $p = 0.51$), RR (MD, –3.1; 95% CI, –4.9 to –0.14; $p = 0.90$), or rates of intubation (19%; 95% CI, 11–26%; $p = 0.001$) and mortality (12%; 95% CI, 4–20%; $p = 0.62$) between the two groups.

- 2) “PP frequency (PP sessions/d)”: The outcomes were compared between patients who received at least one PP session per day (nine studies [2, 11, 28–30, 36–39]) with those who received multiple daily PP sessions (32, 41, 42, 49). There were no significant differences in $\text{Pao}_2/\text{Fio}_2$ (MD, 42.4; 95% CI, 19.5–65.4; $p = 0.26$), Pao_2 (MD, 24.7 mm Hg; 95% CI, 14.3–35.1; $p = 0.97$), Spo_2 (MD, 5.4%; 95% CI, 3.1–7.7%; $p = 0.82$), RR (MD, –3.4; 95% CI, –6.9 to –1.3; $p = 0.51$), or rates of intubation (19%; 95% CI, 11–26%; $p = 0.001$) and mortality (21%; 95% CI, 12–30%; $p = 0.72$) between the two groups.
- 3) “Respiratory support during PP”: The reported outcomes from nine studies (28, 30, 34, 37, 40, 43–45, 49) that reported PP in patients using NIV were compared with seven studies (2, 11, 29, 32, 38, 41, 48) that reported use of “other” oxygenation delivery modes (e.g., HFNC, nasal prongs, and Hudson mask) during PP. There were no significant differences in $\text{Pao}_2/\text{Fio}_2$ (MD, 40.9; 95% CI, 22.9–58.9; $p = 0.34$), Pao_2 (MD, 19.2 mm Hg; 95% CI, 10.9–27.4; $p = 0.99$), Spo_2 (MD, 4.2%; 95% CI, 2.5–5.9%; $p = 0.88$), RR (MD, –3.0; 95% CI –4.7 to –1.3; $p = 0.07$), or rates of intubation (25%; 95% CI, 16–34%; $p = 0.79$) and mortality (13%; 95% CI, 3–22%; $p = 0.09$) between the two groups.

DISCUSSION

This systematic review examined the effect of PP of nonintubated patients on oxygenation variables in a heterogeneous group of adult patients with COVID-19-related hypoxemic respiratory failure. There was significant variability in PP dose and frequency of PP provided during their hospital stay. There was a significant improvement in oxygenation variables ($\text{Pao}_2/\text{Fio}_2$, Pao_2 , and Spo_2) and RR post PP. There was a consistent improvement in these variables across studies despite the significant variability in both practices of PP

and respiratory supports provided. Although patients with $\text{Pao}_2/\text{Fio}_2$ greater than 150 demonstrated a relatively greater improvement in oxygenation, the clinical significance of this finding is difficult to ascertain. This should be treated as exploratory and hypothesis generating.

There was also significant heterogeneity in oxygen therapies and other respiratory supports provided before and during PP. For example, the respiratory or oxygenation supports during PP included NIV (58%), HFNC (17%), Hudson mask (10%), and nasal cannula (16%). This may be reflective of real-world practice; however, these patient populations can be significantly different and may represent different stages of disease evolution. Treatment effects and expected outcomes of PP in each of these patient populations may also be variable, as the outcomes depend on the success of combinations of these therapies and timely escalation of respiratory support. In a recent network meta-analysis of trials of adult patients with acute hypoxemic respiratory failure (51) that predated COVID-19, treatment with NIV and HFNC was associated with a lower risk of death when compared with standard oxygen therapy. These are all important considerations for future clinical trials that aim to test the efficacy of PP in nonintubated patients.

In this selected group of patients who received PP, the overall pooled prevalence of intubation (24%) and mortality (13%). In the absence of appropriate controls who did not receive PP for comparison, it is unclear whether these physiologic improvements resulted in the reduced need for intubation or improved mortality. A noticeable oxygenation improvement was observed in patients who underwent PP in non-ICU areas as compared to those in the ICU; however, the rates of intubation and mortality amongst patients who had PP were similar. Placing critically ill, hypoxemic, nonintubated patients in a prone position outside closely monitored units without the ability to rapidly administer IMV is not without risks. Therefore, patients should preferably undergo PP in monitored environments, in the presence of trained staff. A recent cohort study did not show any reduction in intubation rates or 28-day mortality in COVID-19 patients who received awake PP as an adjunctive therapy to HFNC (48).

Also, the PP practices have evolved, and more recent studies report a variable combination of both lateral positioning and PP. Such variability in the practice

of PP is a concern when it comes to feasibility and generalizability of this practice outside of centers that have some experience in PP of awake patients. Therefore, the safety and efficacy of this intervention can only be tested in a well-designed randomized controlled trial, and they are ongoing (52, 53).

Selecting an appropriate patient would be quintessential for success in adopting PP. Recent studies suggest that patients with mild-moderate ARDS ($\text{PaO}_2/\text{FiO}_2$ between 100 and 300) and RR less than 40 breaths/min may be considered for PP (54, 55). Interestingly, the post hoc analysis did not show an improvement in outcomes when a higher dose or frequency of PP was administered. Similarly, there was no difference in studied outcomes in patients who received NIV and those who received other respiratory supports. Although it is not possible to draw any strong conclusions, these findings highlight the need to standardize PP practices for better comparison. It is possible that some patients may be able to self-prone, but whether their ability to remain in that position for prolonged periods is unclear. Equally, patients who can self-prone are likely to be younger, less frail, and require less assistance. All these factors introduce selection bias when interpreting the potential benefits of awake PP. Future studies need to adjust for these confounders in relation to patient selection.

Our study has some limitations, most notably the lack of comparator groups. Consequently, heterogeneity and all the antecedent biases associated with patient selection and reporting were expected. The heterogeneity persisted despite sensitivity analyzes. Given the inconsistent reporting of oxygenation variables, we had to derive some of the variables from other reported variables where possible. Furthermore, lack of reporting may not mean the nonoccurrence of adverse events. There could be an element of reporting bias that favors awake PP. Besides, strong conclusions cannot be reached due to several factors: first, the absence of tested, established triggers and a standardized process for initiating PP in nonintubated COVID-19 patients; second, the significant heterogeneity in the patient populations included and lack of granular data on cointerventions used (steroids, antiviral therapies, etc.); third, an absence of standardized intubation criteria; and, fourth, that the intervention was provided in some instances under pandemic stressors that affected resource availability.

CONCLUSIONS

Based on this review, PP appears feasible and safe when undertaken in appropriately monitored environments by trained staff. There was a variable but significant improvement in oxygenation variables with PP in nonintubated, adult patients with COVID-19-related hypoxemia. However, the data available for this review were not of sufficient quality to identify the precise population that may benefit. The absence of standardized intubation criteria, variable PP practices, and the provision of the intervention under pandemic stressors limit further interpretation. Future studies should rigorously evaluate any patient-centered benefits associated with the physiologic improvements seen with PP of nonintubated patients with COVID-19.

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All the data analyzed in this study are included in the main article and additional files. Extra information that was obtained from some of the studies after contacting the authors is available from the corresponding author on reasonable request.

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Drs. Subramaniam and Shekar conceived the study idea and coordinated the review process. Drs. Ponnappa Reddy, Subramaniam, Lim, Zubarev, and Shekar drafted the review protocol, conducted the systematic review, assisted with data analysis, and wrote the initial draft of the article. Drs. Ponnappa Reddy and Subramaniam contributed equally. Dr. Wong assisted with the literature search. Dr. Zubarev designed the summary tables. Drs. Afroz and Billah conducted the statistical analysis and wrote sections of the article. Dr. Fan made significant contributions to the analysis plan. Drs. Blecher, Tiruvoipati, Ramanathan, Brodie, and Fan critically evaluated the article and contributed to the writing of the article. All authors critically reviewed the article and approved the final version before submission.

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