REVIEW

Prone position in COVID 19-associated acute respiratory failure

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Purpose of review

Prone position has been widely used in the COVID-19 pandemic, with an extension of its use in patients with spontaneous breathing ('awake prone'). We herein propose a review of the current literature on prone position in mechanical ventilation and while spontaneous breathing in patients with COVID-19 pneumonia or COVID-19 ARDS.

Recent findings

A literature search retrieved 70 studies separating whether patient was intubated (24 studies) or nonintubated (46 studies). The outcomes analyzed were intubation rate, mortality and respiratory response to prone. In nonintubated patient receiving prone position, the main finding was mortality reduction in ICU and outside ICU setting.

Summary

The final results of the several randomized control trials completed or ongoing are needed to confirm the trend of these results. In intubated patients, observational studies showed that responders to prone in terms of oxygenation had a better survival than nonresponders.

Keywords

acute respiratory distress syndrome, awake prone position, coronavirus disease 2019, mechanical ventilation, prone position

INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, the use of prone position has been exponential. A rate of use of prone as high as 70% or more has been reported in large prospective cohorts [1▪,2▪,3▪▪], to be compared with less than 20% before the pandemic [4,5]. This finding was observed even though the level of evidence and the strength of recommendation had not changed [6]. With the COVID-19 pandemic, prone position has reached its true significance. Furthermore, proning was offered to patients not intubated. Even though this option started before the COVID-19, its use in nonintubated COVID-19 patients also increased dramatically and a new terminology was created: awake prone position (aPP) or self-proning. Moreover, it was carried out in the non-ICU environment. The rationale of using pronation in intubated and nonintubated patients differ. In the former, the benefits of prone position are oxygenation improvement, drainage of respiratory secretions, stabilization/improvement of hemodynamics and prevention of ventilator-induced lung injury, all these are mechanisms by which proning can improve survival [7]. In the nonintubated patients, the expected benefit is to improve oxygenation and hence to avoid intubation, and therefore, prevent the ICU resources from overcrowding. It is speculated that aPP could prevent self-induced lung injury by decreasing the swing of respiratory muscle pressure during inspiration. Although we are awaiting for the publication of several trials on pronation in nonintubated patients (NCT04325906, NCT04347941, NCT04358939, NCT04395144, NCT04391140, and NCT04477655), prospective studies have shown that this strategy was feasible and tolerated in most of the cases in a non-ICU environment [8▪▪,9▪▪] with seldom adverse effects described.

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KEY POINTS

- Prone position in COVID-19 patients has been widely used.
- No new trial has been performed in intubated patients. Responders to prone in terms of oxygenation have a better outcome.
- In nonintubated awake patients, prone position has been largely used and has shown improvement on mortality. More complete results should be published very soon and confirm this trend.

Furthermore, these studies confirm that prone position can improve oxygenation in these patients.

The goal of the present study is to review the available literature on prone position in patients with COVID-19. Nonintubated and intubated patients were analyzed separately. For the nonintubated patients, the primary end-points are intubation and mortality outcomes, and hence we used the articles, which provided a control group in the supine position. For the intubated patients, the main end-point is the patient mortality and the secondary end-point the physiological response to prone. We, therefore, used articles, which provided a control group in the supine position to address the main end-point, and the articles, which analyzed responders and non-responders in the prone position. We also considered articles, which compared COVID and non-COVID patients in whom prone position was used. Indeed, it has been claimed that the pathophysiology of COVID-19-related acute respiratory syndrome (ARDS) may be different from the classic ARDS [10▪,11,12▪▪], casting some doubt about the usefulness of prone position in patients without severe impairment of respiratory system compliance [10▪].

METHODS

PICOS

The medical question according to the PICOS method involved the following:

(1) Patients: patients with COVID-19 hospitalized for acute respiratory failure.
(2) Intervention: intervention is the prone position whether the patient is intubated or not.
(3) Comparison: comparison is the supine position or the non-COVID patients.
(4) Outcomes: in nonintubated patients the outcomes are intubation, mortality (at ICU, hospital discharge or at the latest time point reported), and physiological response of proning on oxygenation and respiratory mechanics. In intubated patients, the outcomes are mortality (at ICU, hospital discharge, or at the latest time point reported) and physiological response of proning on oxygenation and respiratory mechanics.
(5) Study design includes prospective or retrospective, observational or randomized or quasi-randomized controlled trials.

Literature search

The literature search was performed in PubMed by entering the following words: (((((Prone) OR (Prone position) OR (prone positioning) OR (pronation)) AND COVID-19) to any field. The literature search was done from inception to 10 April 2021. To be selected, the articles had to meet all the following inclusion criteria: being an original research, being a prospective or a retrospective study, being an observational or a randomized or a quasi-randomized controlled trial, dealing with prone position in intubated or in nonintubated patients, having included adult patients with a suspected or confirmed COVID-19 pneumonia, and written in English. Articles were excluded for any of the following noninclusion criteria: case reports (five or less), narrative or systematic reviews or meta-analysis, articles not specifically dedicated to prone position, that is, reporting on the overall rate of proning in a cohort of patients, or on prone position during patient transport, or during cardiac arrest, or during ECMO, or dealing with the feasibility of echocardiography in prone position or with the correct position of EKG leads, editorial or view point or expert(s) opinion papers, articles without abstract, not written in English in the main text. A snowball strategy was also applied to the retrieved articles by reading the references.

The retrieved articles were further excluded first by reading the title (level 1), then by reading the abstract and the whole text (level 2).

Case record form

A specific case record form was set up and included for each included article the following information: first author name, journal name, year of publication, kind of patients (mild, moderate or severe COVID-19), ARDS (Berlin definition), location of prone position delivery (ICU or outside); Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS), Acute Physiology and Chronic Health Evaluation (APACHE), at time of ICU admission; baseline characteristics (before proning): length of COVD-19 before admission, age, sex, BMI; kind of respiratory support [intubation, oxygen, high-flow oxygen nasal cannula, noninvasive ventilation

(NIV), continuous positive airway pressure (CPAP)], ventilator settings [tidal volume, respiratory rate, positive-end expiratory pressure (PEEP), FIO_2]; respiratory rate, F_IO_2, PaO_2/F_IO_2 measured at baseline, before proning, during proning and after proning; characteristics of proning: mean duration of proning sessions, number of proning sessions; date and status (intubation or not in patients nonintubated, alive or dead) at ICU, hospital discharge and at specific time points (longest reported follow-up, which varied from D14 to D90). If not available, SpO_2/F_IO_2 was computed as equal to $64 + 0.84 \times PaO_2/F_IO_2$ according to Rice *et al.* [13].

Data analysis

The continuous variables were expressed as mean values. If the original article provided the median, we used published equations to translate it into mean. When the continuous data were not available as numbers in the main text or in tables but available as points in figures, we extracted them by using the WebPlotDigitizer 4.4 version free software.

The pooled data were expressed as mean difference [95% confidence intervals (CI)] for the continuous variables and odds ratio (OR) (95% CI) for the binary variables. A random effects model was used. The heterogeneity was assessed by using I^2 statistic. The overall effect was tested with the z score. The data were displayed as Forrest plots. For the primary outcomes (intubation and mortality), contour-enhanced funnel plots were used to detect publication bias and to assess causes of funnel plot asymmetry. Subgroup analysis were performed: we compared the ICU versus the non-ICU application of prone position for the nonintubated patients. A P value less than 0.05 was deemed as statistically significant. The analysis was performed by using the *meta* package of the R software version 4.0.3.

RESULTS

The literature search retrieved 947 articles of which 717 were excluded after reading the title (Figure 1 Supplemental Material, http://links.lww.com/COCC/A40). Among the remaining 230, 164 were further excluded after reading the abstract and the manuscript. Therefore, 70 articles were analyzed, 24 in intubated and 46 in nonintubated patients, that is, nearly twice higher number of articles were dedicated to nonintubated than to intubated patients, which is worth mentioning (Figure 1 Supplemental Material, http://links.lww.com/COCC/A40) and reflects the current trend of using prone position outside ICU. All data retrieved from the studies included were reviewed by authors (A.K., C.G.) and differences were discussed during several distant meetings and a consensus made. The quality of the observational articles was evaluated based on QUIPS criteria [14]. Overall, the studies had a moderate-to-high risk of bias (Table 1 Supplemental Material, http://links.lww.com/COCC/A38).

Prone position in nonintubated patients

Seventeen studies (12 observational, 9 retrospective [15–23] and 3 prospective [24–26], and 5 RCTs [27–31]) met our inclusion criteria (Table 1). Six studies were done in the ICU and 11 outside the ICU (Table 1). The baseline respiratory support was mixed. At baseline, supine and prone groups were similar except for age and SpO_2/F_IO_2 ratio, the patients in the prone group being younger and more hypoxemic than those in the supine group (Table 2 Supplemental Material, http://links.lww.com/COCC/A39). The pooled analysis found that the intubation rate was not different between supine and prone groups, overall (OR 0.74 [0.49–1.12]) (Fig. 1). However, when prone position was applied outside the ICU, the intubation rate was significantly lower than in the supine group (Fig. 1). In nonintubated patients, the mean number and duration of proning sessions were 3 and 14 h, respectively.

By contrast, the mortality measured at the latest time recorded was significantly lower in the prone than in the supine group [OR 0.44 (0.35–0.55)], the benefit being observed in the patients managed in the ICU but not outside (Fig. 2). The funnel plots were asymmetrical, which suggested a publication bias for both intubation and mortality outcomes (Fig. 3). In particular, the funnel plot in Fig. 3 suggests missing publications that would have been favoring the effect of prone for preventing intubation risk (superior quadrant). Clearly, there is strong need to acknowledge the results of the RCT previously mentioned.

No severe adverse complication was reported.

There was only three studies that categorized prone position effect as responders and nonresponders [8▪▪,9▪▪,32]. The definition of responders was variable, such as prepost prone lung ultrasound (LUS) score reduction, PaO_2 increase and SpO_2/FiO_2 increase.

In responders vs. nonresponders, intubation rate was of 0% (0/16) and 50% (3/6), respectively in Avdeev *et al.* [32], and 30% (7/23) and 26% (6/23) in Coppo *et al.* [8▪▪].

Prone position in intubated patients

As discussed above, all the studies on prone position in intubated COVID-19 are observational.

Table 1. Studies of prone position in nonintubated patients

Study rank, first author	Country	Kind of study	Inclusion	Location	Oxygen	HFNC	NIV	CPAP	Other	Criteria to prone	Planned proning session duration	*N* prone	*N* supine
1. Barker	UK	O,R	March–June 2020	S, ICU	4	0	16	0	0	Not defined	As long as possible	10	10
2. Ferrando	Spain	O,P	March–June 2020	M, ICU	0	199	0	0	0	Not defined	16 h	55	144
3. Jagan	USA	O,R	March–May 2020	S, Other	NA	NA	NA	NA	NA	Not defined	NA	40	65
4. Jayakumar	India	RCT	NA	M, Other	56	1	2	0	1	$SpO_2 \geq 92\%$ $O_2 > 4$ l/min or PaO_2/F_IO_2 100–300 mmHg	6 h	30	30
5. Johnson	USA	RCT	April–August 2020	S, Other	11	0	0	0	0	Not defined	2 h	15	15
6. Jouffroy	France	O,R	February–April 2020	M, ICU	2	37	0	1	0	Clinican discretion	3 h	40	339
7. Kharat	Switzerland	RCT	April 2020	M, Acute Care	27	0	0	0	0	SpO_2 90–92% O_2 1–6 l/min	As long as possible	10	17
8. Liu	China	O,R	January–March 2020	S, Other	NA	NA	NA	NA	NA	Not defined	10–14 h	13	16
9. Padrao	Brazil	O,R	March–April 2020	S, ER	93	72	0	0	0	Not defined	4 h	57	109
10. Prudhomme	France	O,R	March–April 2020	M, ER	NA	NA	NA	NA	NA	Not defined	3 h	48	48
11. Perez	Mexico/ Ecuador	O,R	May–June 2020	M, ER &ICU	744	83	0	0	0	Clinican discretion	2 h	505	322
12. Rosen	Sweden	RCT	October 2020–February 2021	M, Other	0	60	15	0	0	$PaO_2/F_IO_2 \leq 50$ mmHg	16 h	36	39
13. Simioli	Italy	O,R	March–April 2020	S, Step Down	0	6	0	23	0	Not defined	10 h	18	11
14. Sryma	India	O,P	NA	ICU	42	1	2	0	0	Not defined	8 h	30	15
15. Taylor	USA	RCT	June–August 2020	M, Other	38	0	1	0	0	$SpO_2 < 93\%$ or $O_2 > 3$ l/min	As long as possible	27	13
16. Tonelli	Italy	O,R	March–June 2020	M, ICU	0	69	19	25	0	Not defined	3 h	38	76
17. Zang	China	O,P	February–April 2020	S, ICU	0	15	15	0	0	Not defined	3–8 h	23	37

CPAP, continuous positive airway pressure; ER, emergency room; HFNC, high flow nasal cannula; M, multicenter; NA, not available; NIV, noninvasive ventilation; O, observational; P, prospective; R, retrospective; RCT, randomized controlled trial; S, single center.

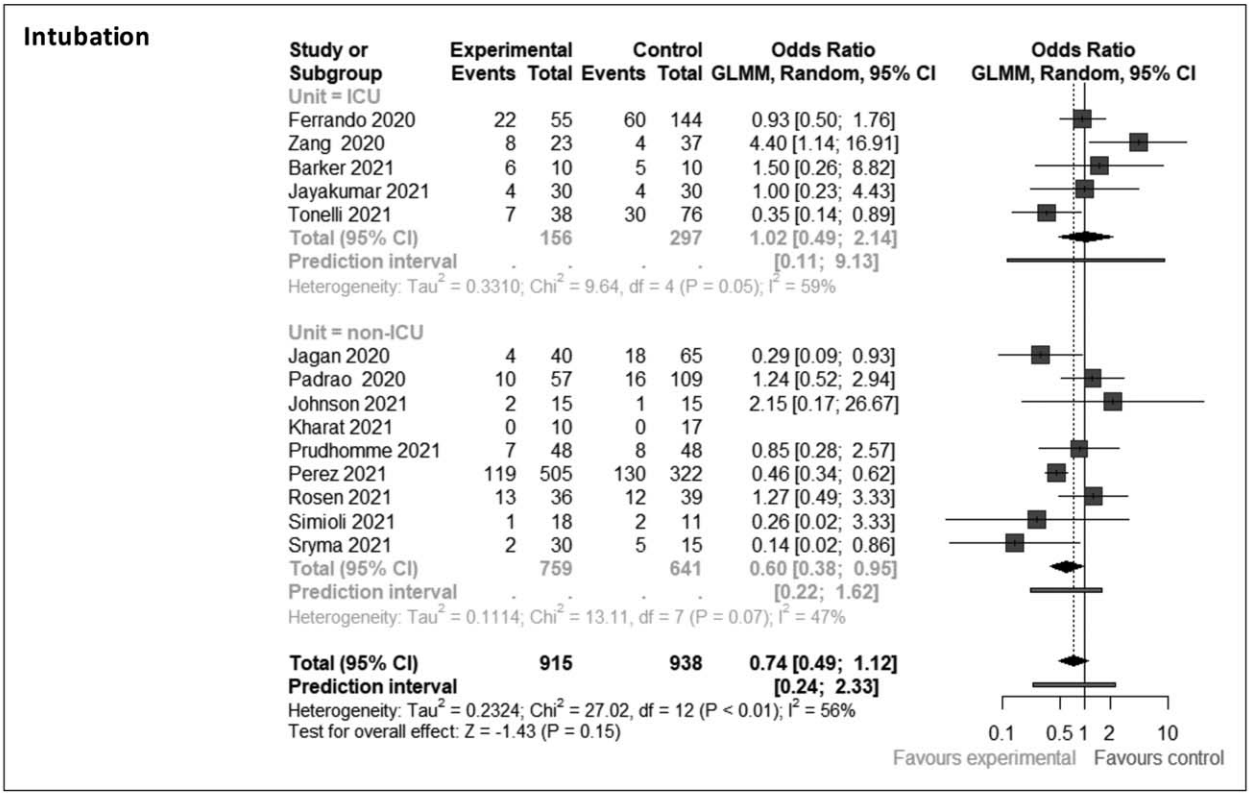

FIGURE 1. Forrest plot for intubation at the latest recording time. CI, confidence interval; GLMM, general linear mixed model.

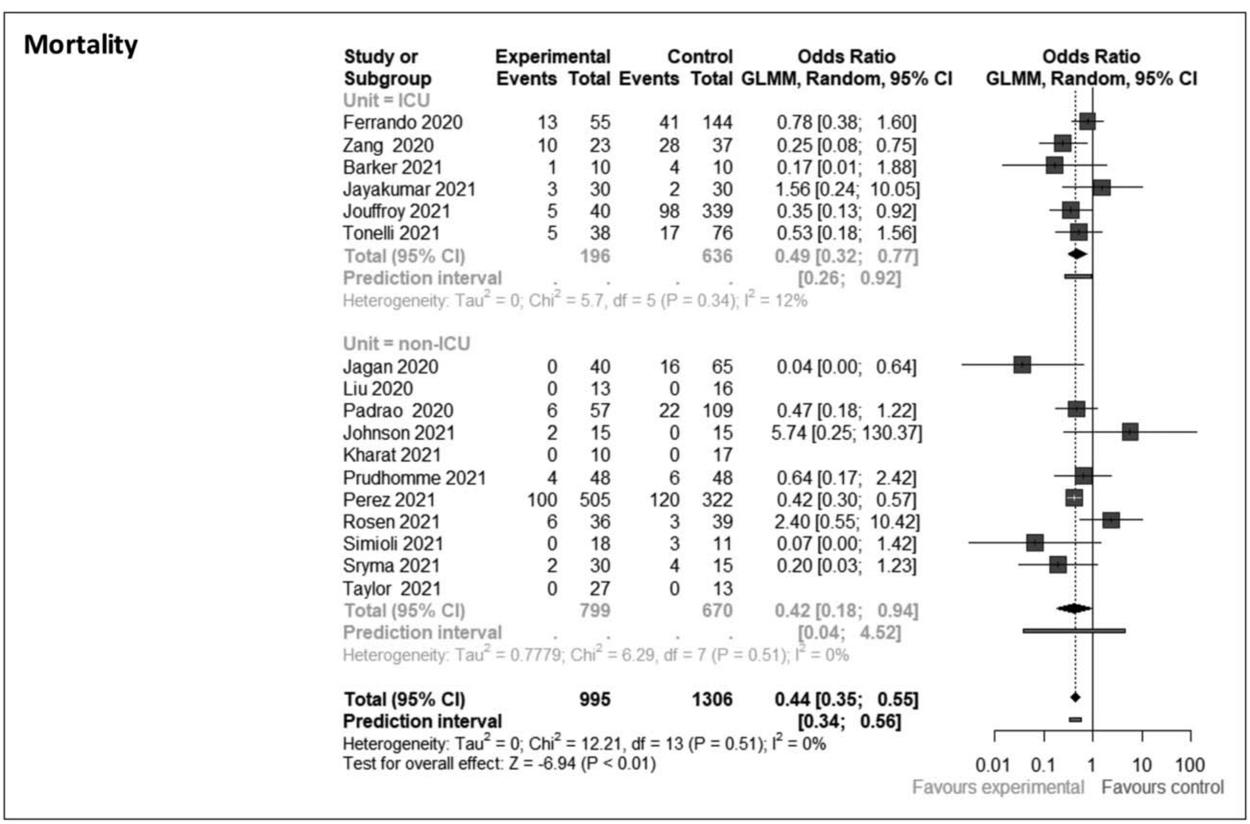

FIGURE 2. Forrest plot for mortality at the latest recording time. CI, confidence interval; GLMM, general linear mixed model.

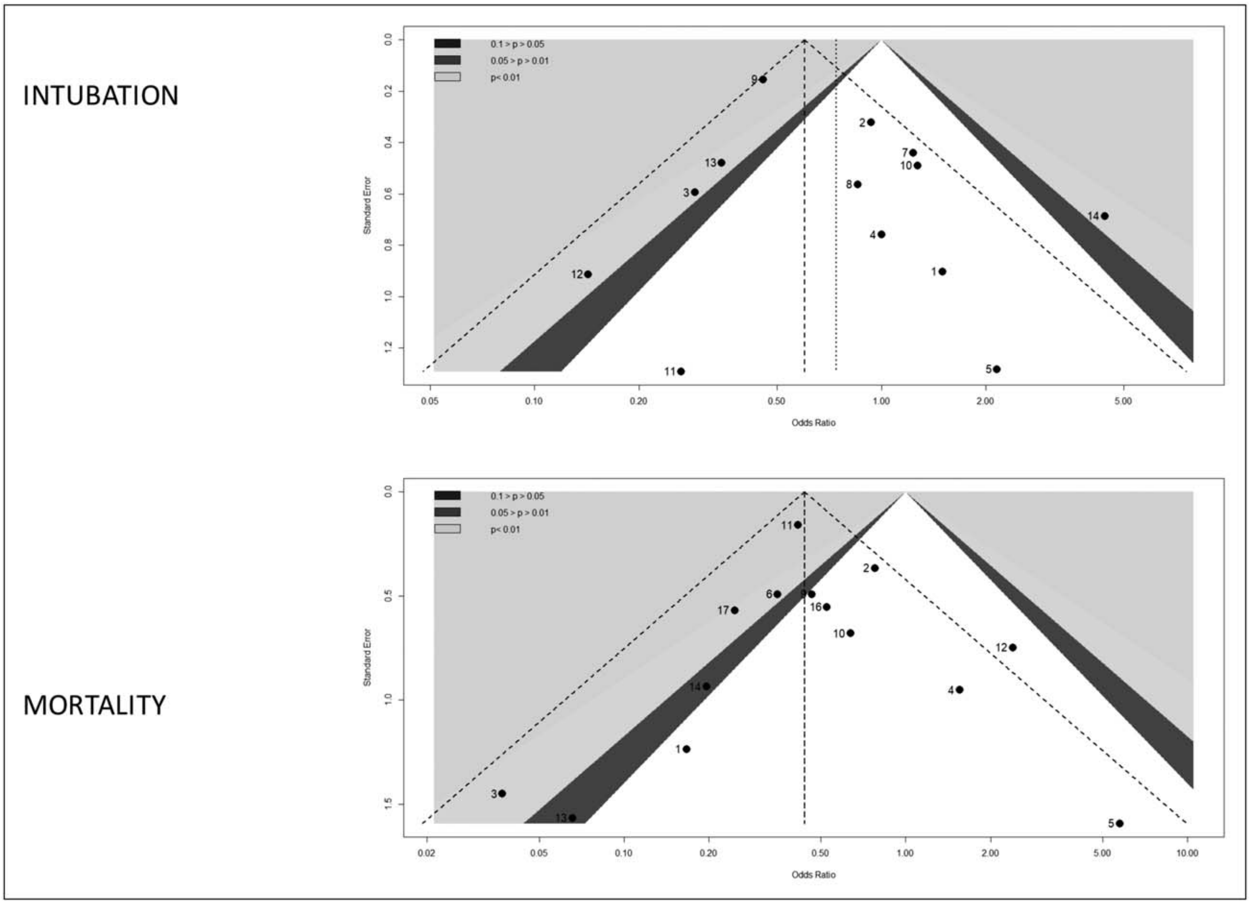

FIGURE 3. Contoured-Funnel plots displaying the relationship between the effect of size on the *x*-axis and the standard error on the *y*-axis for intubation and mortality at the latest recording time. Grey, dark grey, and light grey contours pertain to less than 0.1, less than 0.05, and less than 0.01 levels of significance, respectively. The favorable effect of the experimental group, that is, the prone position, is shown in the left hand side of the funnel plots.

Studies comparing prone to supine position in intubated coronavirus disease 2019 patients

Three studies compared COVID-19-related ARDS patients who were proned to patients who were not [3▪▪,33,34]. The mortality was not significantly different between groups [OR 0.45 (0.09–2.18)] but the heterogeneity was extremely high ($I^2 = 91\%$).

Physiological response to prone position in intubated coronavirus disease 2019 patients

On the basis of respiratory physiology and COVID-19 infection specificity, it is thought that not all patients respond in the same manner to prone positioning. Therefore, the aim to identify patient who will respond most positively to prone position is crucial. Fifteen studies had PaO_2/F_IO_2 data available before and during proning [3▪▪,35–48]. The ratio increased by 52 (38–66) mmHg ($P < 0.01$), when the heterogeneity was significant ($I^2 = 93\%$). Except in two studies only, the mean increase in PaO_2/F_IO_2 ratio in prone was more than 20 mmHg from its value before proning, a common threshold used to define responders. The rate of responders ranged from 9 to 77%. Seven studies provided data on static compliance of the respiratory system in supine pre-prone and in prone in intubated patients [3▪▪,35,37,42,45–48]. It significantly increased after a few hours in prone by 2 ml/cmH_2O on average ($z = -2.68$, $P < 0.01$) ($I^2 = 30\%$). Therefore, in present analysis, the short-term physiological response is consistent with what is known in the classic non-COVID-19 ARDS.

An important finding came up regarding the mortality of patients based on their response to prone in terms of oxygenation, a question that was subjected to debate in the classic ARDS. Three studies in intubated COVID-19 patients found that the outcome was better in responders than in non-responders [OR 0.44 (0.27–0.71), $P < 0.01$] without any heterogeneity ($I^2 = 0\%$) [3▪▪,49,50▪▪]. One study compared prone position in intubated COVID-19 and non-COVID-19 patients [51]. This is the only study describing spontaneous breathing in intubated and mechanically ventilated patients. The authors conclude that the use of prone position in pressure support ventilation mode reduced the use of neuromuscular blockade agents.

DISCUSSION

During the current pandemic, prone position was widely used in patients admitted with COVID-19 pneumonia and ARDS. This was based on the known evidence that prone position reduces mortality in intubated patients with moderate-to-severe non-COVID-19 ARDS [7]. Nevertheless, while there is no strong medical evidence supporting the effect of prone position in mild-to-moderate intubated and in nonintubated patients, numerous studies were carried out on prone position in those specific settings during the ongoing COVID-19 pandemic.

Even though patients with COVID-19 present the same respiratory disorder, the severity of disease, the setting of management and the pathophysiology, were also a source of heterogeneity, as discussed previously.

In nonintubated patients, the pooled results in our present review do not show a beneficial effect of proning on intubation. The potential risk of broadened use of aPP is delaying intubation, therefore, invasive and protective mechanical ventilation. This aspect could potentially counter-balance the beneficial effect of prone position in ICU patient as suggested by the study of Ferrando *et al.* [24]. The fact that intubation would not be done in the appropriate time when needed could be a concern with the prone position applied outside the ICU. Whereas our results cannot answer this question, present findings do not support a harmful effect of prone position performed outside the ICU.

In our review, there is an effect on mortality of aPP whether it is performed in or outside ICU. This could be because of the fact that proning could avoid immediate mortality from severe hypoxemia. However, it should be pointed out that this result was obtained after merging RCTs and observational studies and that mortality was recorded at different times across the studies. An important meta-trial merging the above-mentioned RCTs is undergoing review for imminent publication to assess the effect of aPP on intubation rate and mortality. We are impatiently awaiting those results to establish more precisely the expected effect of this treatment.

In intubated patients, no new randomized control trial on prone position has been conducted and the outcome of physiological respiratory effect analyzed show a significant increase in the static respiratory compliance prepost proning. Our data show that the outcome in terms of survival was significantly better in responders than in nonresponders, which is an important new finding. The implication of this will be a better selection of patients and a better definition to stop the treatment. However, this could be because of a potential specificity of the COVID-19 phenotypes, and therefore, should not be extended to non-COVID-19 unless further studies are performed. These results were obtained during a unique context of pandemic with a large number of patients in a short timeframe, therefore, leaving out some confounders, such a heterogeneity in practice and management.

Limitations of our review are that most studies included are observational and retrospective, and that the definition of prone position ‘responder’ was not similar throughout the studies. There is also a heterogeneity in the studies regarding the criteria of proning, its definition and use.

Between submission and reviewing of this article, the above mentioned ongoing RCTs have been published as a meta-trial [52]. The conclusion of the authors is that aPP reduces the risk of intubation in patients with COVID-19 with no effect on the mortality.

CONCLUSION

Prone position and awake prone position are therapies developing rapidly in the management of COVID-19 pneumonia. This review of the available literature on the subject in intubated and nonintubated patient focuses on patient’s centered outcomes, such as intubation and death. The main finding is that the use of aPP might be associated with lower mortality. High-quality studies on aPP will be available very soon and should confirm beneficial effect of aPP on COVID-19 patient’s outcome.

In intubated patients, those who exhibited a positive response to prone in term of oxygenation had a lower mortality than those who did not.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest

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