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Prone Positioning in Patients With COVID-19: Analysis of Multicenter Registry Data and Meta-analysis of Aggregate Data

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Abstract. *Background/Aim: Evidence suggests a beneficial effect of prone positioning (PP) in COVID-19. Materials and Methods: Meta-analysis of individual (7 investigators' groups) and aggregate data (PubMed/EMBASE) regarding the impact of PP on the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PO_2/FiO_2) in patients with COVID-19. Results: Among 121 patients (mean age±SD 59.1±10.7 years, 55% males, 57% intubated) the mean post- versus pre- PP PO_2/FiO_2 difference was: (i) 50.4±64.3 mmHg, $p<0.01$, (ii) similar in awake (58.7±72.1 mmHg) versus intubated patients (44.1±57.5 mmHg, p=NS), (iii) inversely correlated with body mass index ($r=-0.43$, $p<0.01$). Meta-analysis of 23 studies (n=547, weighted age 58.3±4.1, 73% males, 59% intubated) showed a pooled PO_2/FiO_2 difference of 61.8 [95% confidence intervals=49.9-73.6] mmHg. Meta-regression analysis revealed no associations with baseline demographics, the time in PP before assessment, and the risk of bias of the studies. Conclusion: PP seems to improve oxygenation of patients with COVID-19.*

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Prone positioning has been shown to improve oxygenation in patients with acute respiratory distress syndrome (ARDS) through effects on the mechanics and physiology of gas exchange (1-3). The available evidence suggests a survival benefit in selected patients mainly with early application of prolonged prone-positioning sessions (2, 3).

Severe coronavirus disease 2019 (COVID-19) can lead to ARDS, which is characterized by high mortality (4). Preliminary evidence suggests that prone positioning might benefit oxygenation of awake patients with severe COVID-19 (5, 6). However, the effect of prone positioning in COVID-19-related ARDS is still unclear. This study aimed to characterize the effect of prone positioning on oxygenation in patients with COVID-19 and ARDS, including patients in the awake status, as well as mechanically ventilated, by meta-analyzing individual and aggregate data.

Materials and Methods

Analysis of raw data. Seven groups of investigators (PROne Positioning in COvid-19 Research Consortium-7) provided raw data regarding the effect of prone positioning on the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PO_2/FiO_2) values in hospitalized patients with COVID-19 (7-12). The summary characteristics and methodology of these studies are shown in Table I. Four studies included awake patients with COVID-19 (present study, 8,11,12). In case of multiple sessions of prone positioning per patient and respective comparisons of PO_2/FiO_2 values, the average PO_2/FiO_2 difference per patient was used in the main analysis. All studies were approved by Scientific and Ethics Committees with details included in the respective publications (7-12). The current study was approved by the Ethics Committee of the Sotiria Hospital, Athens, Greece.

Table I. *Main characteristics of the crossover studies examining the effect of prone positioning on PO_2/FiO_2 ratio (gray-highlighted the ones that contributed to the PROne Positioning in COvid-19 Research Consortium-7)*

Study	Setting, Country	N	ICU (%)	Age, years (mean±SD)	Oxygen delivery mode	Time of prone positioning session before assessment (min)	Post minus pre prone PO_2/FiO_2 difference (mean±SD)
Present study	GW, Greece	14	0	57±8	Supplemental oxygen	283	112±122
Avdeev *et al*. (21)	CCU, Russia	22	0	50±18	Supplemental oxygen, NIMV	180	37±21
Astua *et al*. (7)	ICU, USA	29	100	59±9	Endotracheal intubation	900	31±55
Clarke *et al*. (22)	ICU, Ireland	20	100	53±12	Endotracheal intubation	NR	151±102
Khullar *et al*. (23)	ICU, USA	23	100	54±13	Endotracheal intubation	NR	118±75
Perier *et al*. (24)	ICU, France	14	100	NR	Endotracheal intubation	NR	53±41
Singh *et al*. (8)	HDU, India	15	0	52±12	Supplemental oxygen, NIMV	NR	33±21
Gleissman *et al*. (25)	ICU, Sweden	44	100	61±13	Endotracheal intubation	910	55±70
Boselli *et al*. (9)	ICU, France	15	100	62±10	Endotracheal intubation	NR	94±58
Weiss *et al*. (26)	ICU, USA	42	100	60±13	Endotracheal intubation	60	77±73
Bagate *et al*. (27)	ICU, France	10	100	61±7	Endotracheal intubation	NR	49±49
Abou-Arab *et al*. (10)	ICU, France	25	100	61±6	Endotracheal intubation	960	31±53
Burton-Papp *et al*. (28)	ICU, UK	20	100	53±8	NIMV	NR	29±23
Paternoster *et al*. (29)	HDU, Italy	11	0	62±10	NIMV, helmet CPAP	NR	137±95
Berrill *et al*. (30)	ICU, UK	34	100	59±11	Endotracheal intubation	90	44±55
Winearls *et al*. (31)	HDU, UK	24	0	62±13	NIMV	15	51±71
Taboada *et al*. (32)	GW, Spain	29	0	64±12	Supplemental oxygen	60	46±85
Solverson *et al*. (33)	GW, ICU, Canada	17	71	55±13	Supplemental oxygen, HFNC	NR	27±23
Ripoll-Gallardo *et al*. (11)	GW, Italy	13	0	66±8	NIMV, helmet CPAP	NR	51±59
Coppo *et al*. (34)	ER, GW, HDU, Italy	56	0	57±7	Supplemental oxygen, NIMV	10	105±118
Golestani-Eraghi *et al*. (35)	ICU, Iran	10	100	NR	NIMV	NR	21±4
Lemyze *et al*. (36)	ICU, France	33	100	NR	Endotracheal intubation	NR	162±68
Xu *et al*. (12)	Hospitalized, China	10	100	50±9	HFNC	300	34±16
Ziehr *et al*. (37)	ICU, USA	31	100	NR	Endotracheal intubation	NR	84±82

CCU: COVID-19 care unit; COVID-19: coronavirus disease 2019; CPAP, continuous positive airway pressure; ED: emergency department; GW: general ward; HDU, high dependency unit; HFNC: high flow nasal cannula; ICU: intensive care unit; NIMV: non-invasive mechanical ventilation; NR: not reported; PO_2/FiO_2: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

Meta-analysis of aggregate data.

Search strategy. A systematic review and meta-analysis was performed according to PRISMA Guidelines (13). A systematic search at PubMed and EMBASE databases was performed to identify eligible articles until January 26, 2021 using the following algorithm: ("coronavirus 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR COVID OR COVID19) AND ("prone position*" OR "proning"). Articles were also identified from reference lists of relevant papers and handsearch. The study selection was performed independently by three investigators (KGK, VR, IPT). Disagreements were resolved by consensus with a senior author (AK).

Selection criteria and data extraction. Eligible studies were full-text peer-reviewed articles in English that included at least 10 hospitalized patients with COVID-19 and reported results regarding the effect of prone positioning on oxygenation and outcome. The primary endpoint included the difference in PO_2/FiO_2 values derived from crossover studies (same patients pre- and post- prone positioning). The secondary outcome included the adjusted odds/hazard ratio for intubation or death derived from parallel arm studies.

Data extraction and risk of bias assessment. Authors of the included studies were contacted by email to obtain additional details not reported in the published paper (*i.e.*, mean and SD of difference regarding the variable of interest). Three investigators (KGK, VR, IPT) extracted independently data concerning study design, main characteristics of included populations, and data regarding primary endpoint from included studies where available. The risk of bias was assessed in terms of patients' selection (selection bias), methodology, analysis and confounders, using a combination of questions from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) and Critical Appraisal Skills Programme (CASP) checklists for assessing cohort studies (14, 15). Studies fulfilling ≥6 of the quality domains were deemed as high quality (low risk of bias).

Statistical analysis. For the analysis of the raw data, the Kolmogorov-Smirnov test was used to check the normal distribution of the study variables. Wilcoxon signed-rank test was used to compare PO_2/FiO_2 values before and after prone positioning. Mann-Whitney test was used for comparison between groups *i.e.,* males *vs*. females, awake *vs*. intubated patients. Spearman correlations coefficients (r) were determined for assessing the associations of the

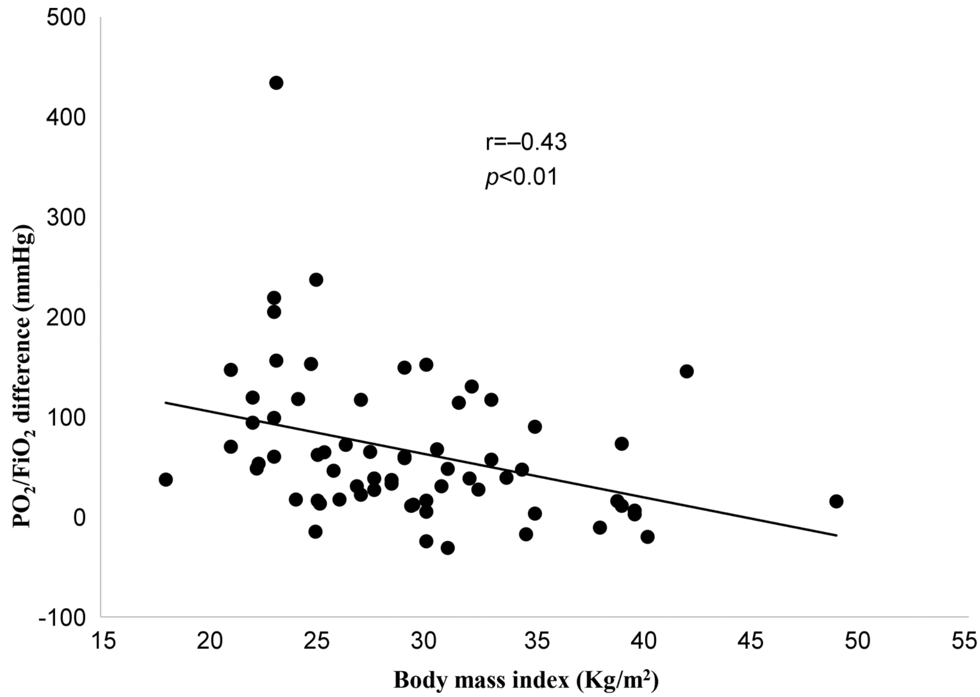

Figure 1. *Correlation between post- minus pre-prone PO_2/FiO_2 difference and body mass index.*

PO_2/FiO_2 values. Repeated measures analysis of variance with Bonferroni correction was performed for comparison of PO_2/FiO_2 values at different time points in the subgroup with 2 different sessions of pre- *versus* post-prone assessment. The IBM SPSS Statistics 21 (SPSS Inc., Chicago, IL, USA) statistical package was used. Results are expressed as mean±SD.

Random-effects meta-analysis was performed using the Stata/SE 11 (Texas) software. Sensitivity analyses were performed to compensate for the observed methodological heterogeneity among the included studies. Meta-regression analysis was performed for assessing associations of the difference in PO_2/FiO_2 values with gender, age, body mass index (BMI), duration of prone positioning and baseline PO_2/FiO_2 values. Mean values of subgroups were combined where feasible (16). Median (interquartile range) values were converted to mean values (SD) using appropriate formulas (17). In the case of missing values regarding the mean (SD) of difference in the outcome of interest between the examined groups, these were calculated from the groups' mean values using an appropriate formula for the calculation of the SD of difference as follows:

$$\text{SD of difference} = \sqrt{SD_1^2 + SD_2^2 + 2rSD_1SD_2}$$

SD_1, SD of pre-prone positioning PO_2/FiO_2; SD_2, SD of post-prone positioning PO_2/FiO_2; r, correlation coefficient between pre-prone and post-prone positioning PO_2/FiO_2 as calculated from the raw database (18). Heterogeneity was tested using I^2 statistics. Publication bias was assessed by inspecting funnel plots, as well as Egger's test (linear regression method) and Begg's test (rank correlation method) (19, 20). Two-sided *p*-values of <0.05 were considered statistically significant.

Results

Analysis of raw data. The methodology and characteristics of the studies contributing to the raw database are shown in Table I (7-12). The database included 121 patients (mean age 59.1±10.7 years, 55% males, 57% intubated). The mean post-*versus* pre- prone positioning PO_2/FiO_2 difference±SD was 50.4±64.3 mmHg, $p<0.01$ and the mean % increase in PO_2/FiO_2 was 41.7±58.9%. The PO_2/FiO_2 absolute difference and % change in patients in the awake status (n=52) did not differ compared to that in the intubated patients (n=69): 58.7±72.1 *vs*. 44.1±57.5 mmHg and 46.2±72.0 *vs*. 38.4±47.1% respectively, *p*=NS for both comparisons. Among the 121 patients, a total of 11 (9%) did not present any increase in PO_2/FiO_2 with prone positioning and additional 11 (9%) showed <10% increase in PO_2/FiO_2.

The increase in PO_2/FiO_2 with prone positioning was inversely correlated with BMI (r=–0.43, $p<0.01$; n=66) (Figure 1), whereas there was no association with age (r=–0.07, *p*=NS). The increase in PO_2/FiO_2 with prone positioning tended to correlate with baseline pre-prone PO_2/FiO_2 values (r=0.17, $p=0.06$). There was no difference with respect to gender (55.5±71.3 *vs*. 60.2±50.3 mmHg in males *vs*. females respectively, *p*=NS). In 37 patients (24 in the awake status), there was assessment of the PO_2/FiO_2 difference in at least 2 separate subsequent sessions or at

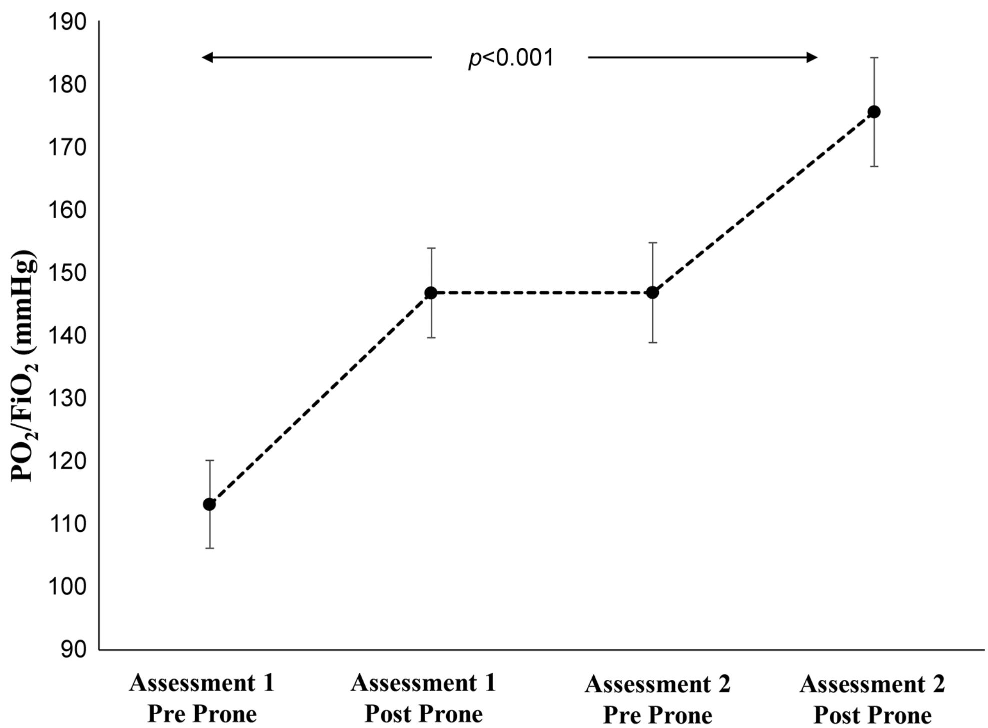

Figure 2. *Effect of repeated prone positioning sessions on PO_2/FiO_2 values.*

least 2 separate days. The effect of repeated prone positioning sessions on PO_2/FiO_2 values is shown in Figure 2.

Meta-analysis of aggregate data. Among 836 initially identified articles, 23 studies fulfilled the inclusion criteria and were included in the systematic review (flowchart shown in Figure 3) (7-12, 21-37). The main characteristics of these studies are shown in Table I. Only 10 out of 23 studies reported the time in prone position before PO_2/FiO_2 assessment (Table I), whereas the majority of the studies did not report details of the prone positioning protocol (number of cycles/day, hours per cycle, number of days).

Meta-analysis of 23 studies (n=547, weighted age 58.3±4.1, 59% intubated, 73% males) showed a pooled PO_2/FiO_2 difference of 61.8 [95% confidence intervals (CI)=49.9-73.6] mmHg (Figure 4).

Egger's test and Begg's funnel plot revealed a small study effect ($p<0.01$). Nine studies (33%) were deemed as low risk of bias (7, 10, 12, 22-24, 28, 29, 34).

Meta-regression analysis did not reveal any significant association of the PO_2/FiO_2 difference with mean age, mean BMI, prevalence of males, hypertension, diabetes across studies, the time in prone position before assessment, as well as the risk of bias score of the included studies (all p=NS). However, there was a trend towards higher PO_2/FiO_2 difference in patients with higher pre-prone baseline PO_2/FiO_2 values, but this did not reach statistical significance.

In sensitivity analysis including only studies in awake patients (11 studies; n=227), the pooled PO_2/FiO_2 difference was 40.0 (95%CI=30.5-49.5) mmHg, whereas the respective estimate in studies in intubated patients (12 studies; n=320) was 77.4 (95%CI=53.4-101.5) mmHg.

Regarding feasibility, the percentage of patients unable to retain the prone positioning sessions was reported to be from 0% to 16% (23, 29, 31, 33, 34). In terms of complications, a single study reported pressure ulcers (stage I or II) in 21% of intubated patients, which did not compromise further positional care, whereas there were no inadvertent extubations or disruptions of arterial lines, central venous catheters, chest tubes or dialysis catheters (7).

A total of five studies reported the adjusted risk (odds or hazard ratio) for intubation and/or mortality in patients subjected to prone positioning sessions *versus* those who were not (38-42) (Table II). Due to the heterogeneity in the assessment of the risk estimate and the outcome, as well as the restricted size of data, a meta-analysis was not feasible. However, a trend for a lower adjusted risk could be observed for adverse outcome with prone positioning.

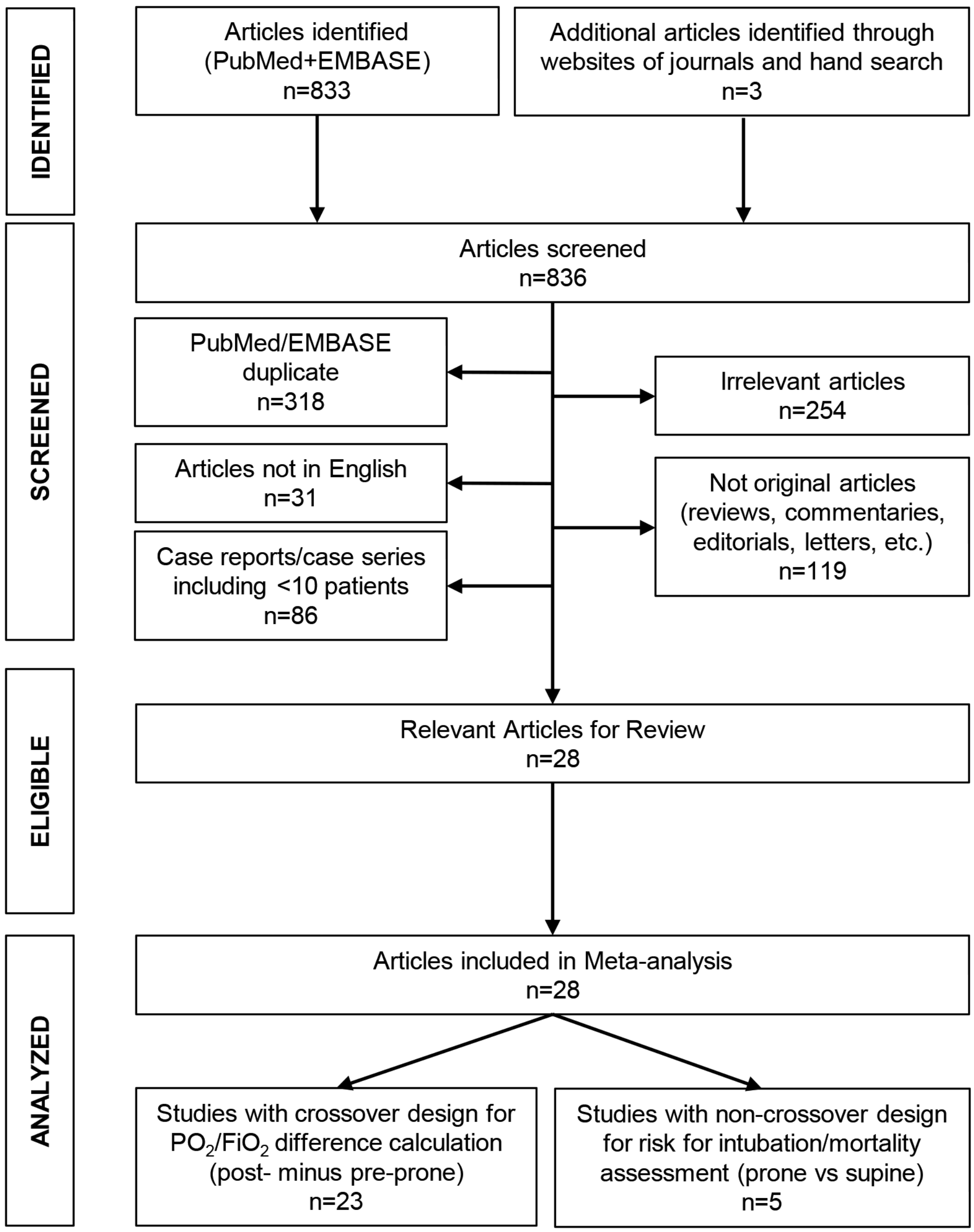

Figure 3. *Flow chart for the selection of included studies.*

Discussion

The main findings of the present study included the following: (i) there was a significant improvement in the PO_2/FiO_2 after proning in both the awake and intubated patients with COVID-19, consistently evident in the meta-analysis of raw individual data, as well as of aggregate data, (ii) the beneficial effect of prone positioning might be more evident with higher baseline pre-prone PO_2/FiO_2 values and lower BMI values, (iii) there was sustained beneficial effect on oxygenation with repeated sessions of prone positioning.

The present meta-analysis of both individual participants' data and aggregate data showed that prone positioning in patients with COVID-19 was associated with an increase in PO_2/FiO_2 in the range of 50-60 mmHg. The latter regarded patients in the awake status receiving heterogeneous types of oxygen supplementation, as well as mechanically ventilated patients in the Intensive Care Unit. The consistency of the

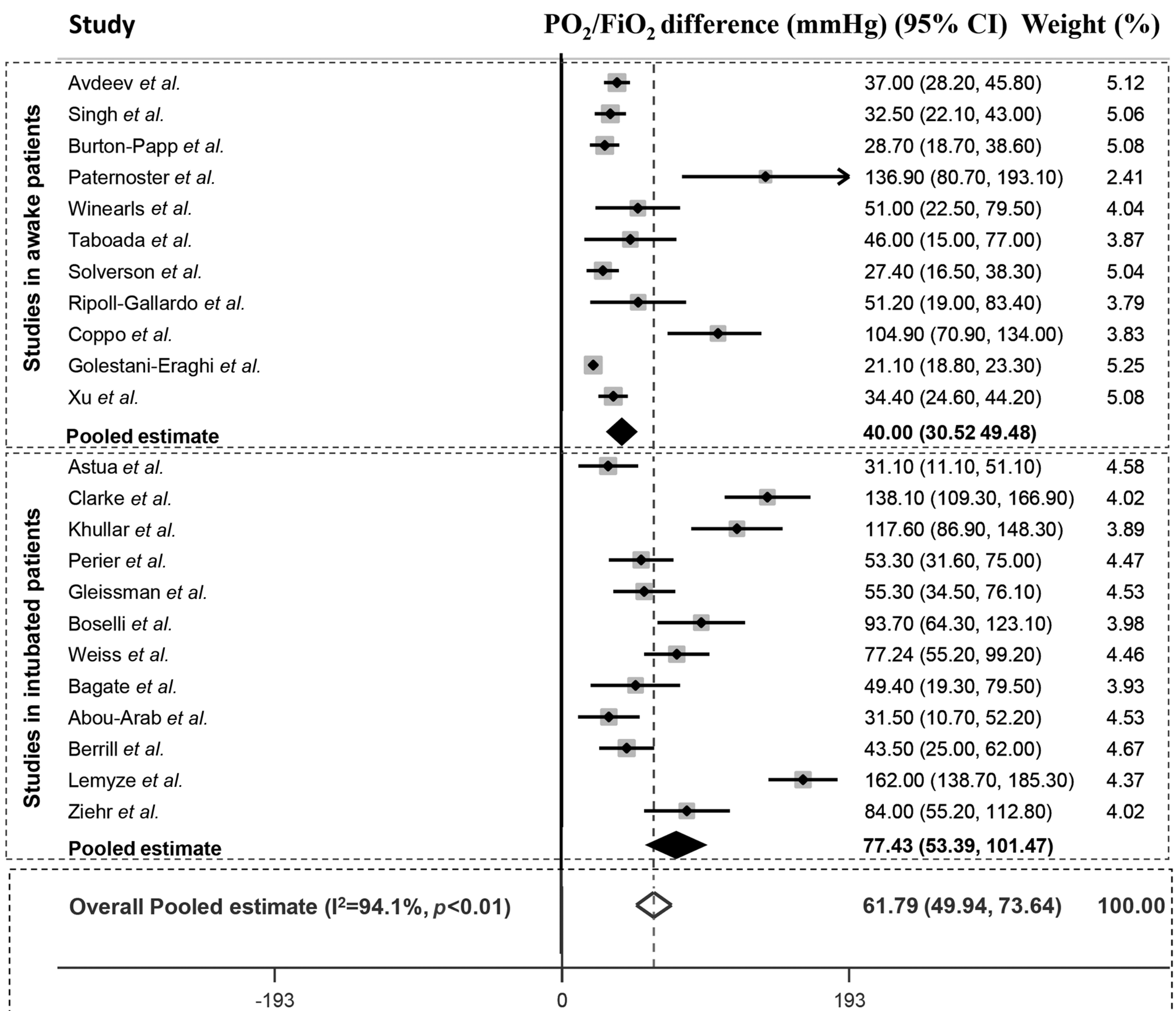

Figure 4. *Forest plot of post- minus pre-prone PO_2/FiO_2 differences.*

above findings across patients with critical COVID-19, but with different types and stages of disease evolution and under different ventilation strategies, confirms the concept of the wide implementation of prone positioning in the management of such patients, especially those in the awake status. In this analysis, about 20% of patients did not respond or showed <10% increase in PO_2/FiO_2, which means that not all patients might be responders. Ideally, the phenotype of pneumonia, best identified by a computed tomography scan, could indicate the lung recruitability and potential response (43). The available evidence regarding the effect of prone positioning lacks details about the association of response with pneumonia types, but suggests that prone positioning might be helpful in most patients receiving different types of ventilation. Most importantly, the beneficial effect on oxygenation might be evident after just a few hours. Thus, candidate patients can be selected after just a short-term trial of prone positioning.

Several mechanisms have been proposed for the beneficial effects of prone positioning. The improvement in the ventilation-perfusion disorder (V/Q mismatch), as well as in several oxygenation indicators, ensure a more homogeneous ventilation of alveoli sites and reduce transpulmonary pressures and intra-pulmonary shunt (44). On the other hand, the reported feasibility rates seem to be high (7-12, 21-37) and contraindications are only few including spinal instability, chest tubes, shock, hemodynamic instability, cardiac abnormalities and arrhythmias, burns and wounds, raised intracranial pressure, and pregnancy (2, 45).

The present analysis of raw data showed a trend for an association between the increase in PO_2/FiO_2 and baseline pre-prone PO_2/FiO_2 values, as well as an inverse association with BMI. Moreover, repeated sessions of prone positioning appeared to be associated with a sustained or even additional effect on oxygenation. The better response in patients with higher baseline PO_2/FiO_2 values could indicate the higher potential of these patients for alveolar recruitment in the early stages of the disease. On the other hand, higher BMI values were associated with a worse response. Whether this finding represents a worse response of the obese patients to prone positioning due to increased intra-abdominal pressure transmitted across the diaphragm, a worse feasibility rate of prone positioning sessions, or a chance finding is not clear and requires further research. Current literature seems to be inconclusive, showing that depending on the mechanics used, proning maneuvers have the potential to induce intra-abdominal hypertension, which can adversely influence the respiratory outcomes (46). It should be mentioned that meta-regression analysis did not confirm the inverse relationship between the increase in PO_2/FiO_2 with prone positioning and BMI; yet meta-regression examines the associations between outcome and characteristics, which are aggregate and summarized at the level of the study that in turn can introduce ecological bias.

Despite the evidence in favor of the prone positioning on oxygenation, there were no sufficient data regarding the benefit in terms of outcome. In fact, the available evidence is scarce, although a trend for a slight decrease in the risk for intubation or death was evident. Future randomized studies are warranted to investigate this topic.

The findings of this meta-analysis should be interpreted by considering several limitations. Most important is the heterogeneity among these studies and the lack of details regarding the prone positioning schedule (duration and frequency of prone positioning sessions). Moreover, the main source of evidence is derived from restricted-sized studies, either of retrospective or prospective design. Yet, the meta-analysis of both raw and aggregate data allowed larger sample sizes to be analyzed. However, a small study effect was evident, implying publication bias.

The added value of the present meta-analysis lies on the (i) analysis of both raw (the largest so far database with peer-reviewed data) and aggregate data, and (ii) use of strict methodological criteria (only crossover studies) and sensitivity analyses performed separately in awake and intubated patients. Two relevant meta-analyses were recently published presenting consistent findings (47, 48). However, these analyses included studies only in awake patients, as well as both peer-reviewed and non-peer-reviewed studies or studies employing either crossover or parallel arm design (47, 48). The latter constitutes a criterion with high clinical relevance since in crossover studies each patient serves as a control of her/his own.

Table II. *Characteristics of the studies reporting adjusted risk for intubation and/or mortality in patients who were subjected to prone positioning versus those who were not.*

Study	Setting, Country	N	ICU (%)	Males (%)	Age, years (mean±SD)	Oxygen delivery mode	Patients proned (%)	Adjusted OR for intubation (95%CI)	Adjusted HR for intubation (95%CI)	Adjusted OR for mortality (95%CI)	Adjusted HR for mortality (95%CI)
Shelhamer *et al.* (38)	ICU, USA	261	100	62	64±13	Endotracheal intubation	24				0.57 (0.42-0.76)
Carrillo Hernandez-Rubio *et al.* (39)	IRCU, Spain	70	0	77	61±4	HFNC, NIV	46	0.05 (0.01-0.54)			
Thomson *et al.* (40)	ICU, UK	156	100	72	62±12	Supplemental oxygen, NIMV, endotracheal intubation	49			0.76 (0.16, 3.56)	
Padrao *et al.* (41)	ED, Brazil	166	0	68	58±14	Supplemental oxygen	34		0.90 (0.55-1.49)		
Ferrando *et al.* (42)	ICU, Spain	199	100	74	63±12	HFNC	28		0.88 (0.54-1.44)		1.05 (0.40-2.72)

CI: Confidence intervals; ED: emergency department; HFNC: high flow nasal cannula; HR: hazard ratio; ICU, intensive care unit; IRCU: intermediate respiratory care unit; NIMV: non-invasive mechanical ventilation; NR: not reported; OR: odds ratio;

Accumulating evidence suggests a beneficial effect of prone positioning on oxygenation in patients with critical COVID-19, either in the awake or the intubated status, and under heterogeneous conditions in terms of ventilation support and prone positioning protocols. Many important details are missing and future well-designed studies should address the following issues: (i) optimal prone positioning protocol (duration and frequency of cycles) and optimal type of delivery (type of beds, type of central lines used, types of oxygen delivery); (ii) type of patients who are more likely to benefit from this (body phenotype, comorbidities, lung phenotype); (iii) whether prone positioning improves the outcome of intubation (in the awake patients), as well as death.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Conceptualization, A.K. and G.P.; Methodology, A.K., K.G.K., V.R., I.P.T., K.S., G.P. and PROPCOR Consortium-7 Investigators (O.A-A., B.A., A.J.A., K.A., F.B-A., D.B., C.B., E.B., A.D., L.G., P.J., E.K. S.K., S.L., W.L., A.J.M., E.K.M., A.R-G., P.S., T.W., Q.X.); Software, A.K., K.G.K., V.R. and I.P.T.; Formal Analysis, A.K. and K.G.K.; Investigation, A.K., K.G.K., V.R., I.P.T. and T.N.; Resources, A.K., K.G.K., V.R., I.P.T., T.N., K.S., G.P., and PROPCOR Consortium-7 Investigators (O.A-A., B.A., A.J.A., K.A., F.B-A., D.B., C.B., E.B., A.D., L.G., P.J., E.K. S.K., S.L., W.L., A.J.M., E.K.M., A.R-G., P.S., T.W., Q.X.); Data Curation, K.G.K., V.R., I.P.T. and PROPCOR Consortium-7 Investigators (O.A-A., B.A., A.J.A., K.A., F.B-A., D.B., C.B., E.B., A.D., L.G., P.J., E.K. S.K., S.L., W.L., A.J.M., E.K.M., A.R-G., P.S., T.W., Q.X.); Writing – Original Draft Preparation, A.K., K.G.K. and T.N.; Writing – Review & Editing, K.S., G.P. and PROPCOR Consortium-7 Investigators (O.A-A., B.A., A.J.A., K.A., F.B-A., D.B., C.B., E.B., A.D., L.G., P.J., E.K. S.K., S.L., W.L., A.J.M., E.K.M., A.R-G., P.S., T.W., Q.X.); Visualization, A.K. and K.G.K.; Supervision, A.K., K.S. and G.P.; Project Administration, A.K., K.G.K., K.S. and G.P.

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