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ORIGINAL RESEARCH **INTENSIVE CARE**

Prone vs supine position in intubated COVID-19 patients with ARDS: a systematic review and meta-analysis

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ABSTRACT

Background & Objective: The recent COVID-19 pandemic has tested the healthcare sector to the maximum, but it also has taught us some valuable lessons, especially in the context of intensive care, and particularly in the respiratory support. This review determined the effect of prone positioning in changes of partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio, partial pressure of carbon dioxide ($PaCO_2$), mortality rate, ICU length of stay and duration of mechanical ventilation in intubated COVID-19 patients with ARDS.

Methodology: A computer-aided comprehensive electronic bibliographic search from MEDLINE, EMBASE, and Science Direct were conducted. The search comprised the articles written in English and intubated adult (≥ 18 y old) patients with COVID-19. The primary outcome was comparing PaO_2/FiO_2 ratio between prone and supine position groups. Secondary outcomes were comparisons of $PaCO_2$, ICU discharge, and mortality rate. Review Manager version 5.4 (The Cochrane Collaboration) was used for statistical analyses of the included studies.

Results: A total of 7 articles were determined to be eligible, consisting of 1403 intubated COVID-19 patients with ARDS that showed prone position was associated with a higher PaO_2/FiO_2 ratio compared to the supine position (MD 60.17, 95% CI 46.86−73.47; $P < 0.00001$). Four studies reported the $PaCO_2$ measurements and showed no significant difference between prone and supine positions (MD 2.07, 95% CI -2.79−6.92; $P < 0.40$). Only two studies reported mortalities, one study had 262 deaths out of 648 patients (40.4%) and the other study lost 11 out of 20 patients (55%). One study reported median ICU stay and mechanical ventilation duration (16 days) were significantly longer in prone position group.

Conclusion: This meta-analysis showed that prone position improved PaO_2/FiO_2 ratio in intubated COVID-19 patients with ARDS. It also prolonged ICU stay and mechanical ventilation duration, but had no effect on mortality rate.

Abbreviations: APACHE-II- Acute Physiology and Chronic Health Evaluation-II; ARDS - acute respiratory distress syndrome; ICU – Intensive Care Unit; MD – Mean Difference; NOS - Newcastle-Ottawa scale; SOFA - Sequential Organ Failure Assessment

Key words: Prone Position; Supine Position; COVID-19; ARDS, Intubation; Meta-Analysis

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1. INTRODUCTION

The World Health Organization (WHO) declared a public health emergency on coronavirus disease 2019 (COVID-19), a global pandemic that impacted more than 200 countries and caused over 3.9 million deaths.[1] As of July 2021, there were 2.35 million COVID-19 cases in Indonesia with 61.868 reported deaths.[2] Approximately 67–85% of critically ill patients who were admitted to the intensive care unit (ICU) with COVID-19 developed hypoxemia, acute respiratory distress syndrome (ARDS) that required intubation and the mechanical ventilation.[3] It is well-known that respiratory failure with ARDS has poor outcomes; and COVID-19 patients with ARDS are no exception.[4] Some countries reported 61.5% fatality rate, especially those on mechanical ventilation.[5] In the United Kingdom, 4855 patients with COVID-19 needed advance respiratory support and 57% of them died.[6]

Over the last decades, ARDS interventions have been evaluated, in particular, prone position was an important non-pharmacologic strategy that showed lifesaving potential for invasively ventilated patients with moderate to severe ARDS.[7] Placing the patient in prone position optimizes the ventilation and decreases the intrapulmonary shunting which facilitates more effective oxygenation due to more uniform alveolar recruitment throughout the lung.[8] A meta-analysis of prone position in ARDS and acute lung injury showed that prone position during invasive mechanical ventilation improved oxygenation and reduced ICU mortality rate.[9] The Surviving Sepsis Campaign (SSC) COVID-19 subcommittee and WHO guidelines have recommend prone position for the management of COVID-19 associated ARDS.[10, 11] Recently, a hypothesis emerged stating that ARDS due to COVID-19 was different than non-COVID-19 ARDS whose features were severe hypoxemia with normal respiratory system compliance.[12] Gattinoni et al. suggested that there are two phenotypes of COVID-19 ARDS, which were "type L", characterized by low elastance, low ventilation-to-perfusion (V/Q) ratio, low lung weight, and low recruitability, and "type H", characterized by high elastance, high right-to-left shunt, high lung weight, and high lung recruitability (which was similar to non-COVID-19 ARDS).[12, 13]

Several studies have suggested the need of outcome measurements after prone position maneuver for mechanically ventilated COVID-19 patients. Currently, there are very limited studies comparing prone position and supine position in intubated COVID-19 patients. The aim of this analysis was to determine the changes of partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio after prone position compared to supine position in intubated COVID-19 patients with ARDS. This review also examines the changes of partial pressure of carbon dioxide ($PaCO_2$), mortality rate, duration of mechanical ventilation and ICU length of stay.

2. METHODOLOGY

2.1. Search Strategy

This systematic review was conducted according to the PRISMA statement.[14] A computer-aided comprehensive electronic bibliographic search from MEDLINE, EMBASE, and ScienceDirect were conducted on the July 07, 2021, for articles published in the last 10 y (July 07, 2011−July 07, 2021). A grey literature search was not conducted. Boolean phrase, medical subject headings (MeSH), and truncations were used when searching each database. Multiple searches were conducted to ensure all relevant studies were identified. A manual search of the reference list from the articles retrieved for additional relevant studies was also undertaken. The keywords and terms used for the search were "COVID#19", "coronavirus disease 2019", "acute respiratory distress syndrome", "ARDS", "intubated", "prone position", "supine position", "prone*", "TI prone position", "AB prone position", "COVID#19 OR acute respiratory distress syndrome", "coronavirus disease 2019 OR acute respiratory distress syndrome", "COVID#19 OR ARDS", "coronavirus disease OR ARDS", "COVID#19 OR TI COVID#19", "COVID#19 OR intubated OR ARDS", "(COVID#19 OR intubated OR ARDS) AND prone position". The review was not registered.

Intubated COVID-19 patients were determined as the population, prone position as the intervention, supine position as the comparison and PaO_2/FiO_2 ratio, $PaCO_2$, mortality rate, ICU discharge, and duration of mechanical ventilation as the outcome. Potentially relevant articles from the three databases were included. The potential articles then were removed or excluded through a manually-systematic search of duplicate articles and a screening based on the title and abstract. The full-text of the remaining articles was examined based on the predefined review criteria and the remaining articles were included in the review. Two authors screened titles and abstracts independently based on the inclusion and exclusion criteria. Studies that met the criteria were coded with “yes” and were retrieved for full text screening. Studies coded with “no” were excluded from the review. Two authors independently screened the full text articles and finally included studies were approved by all authors.

2.2. Review Criteria

Included studies comprised of articles that was written in English, any other language was not included in the review. The subjects being human, adults (≥ 18 y old) diagnosed with COVID-19, intubated, comparing prone position and supine position, and measure the following outcomes: 1) PaO_2/FiO_2 ratio, 2) $PaCO_2$, 3) mortality rate, 4) duration of mechanical ventilation, and 5) ICU length of stay. Systematic reviews and meta-analyses were excluded from the review, as well as the case reports. Other exclusion criteria were case series, editorials, and non-intubated (using high flow nasal cannula or non-invasive ventilation) patients.

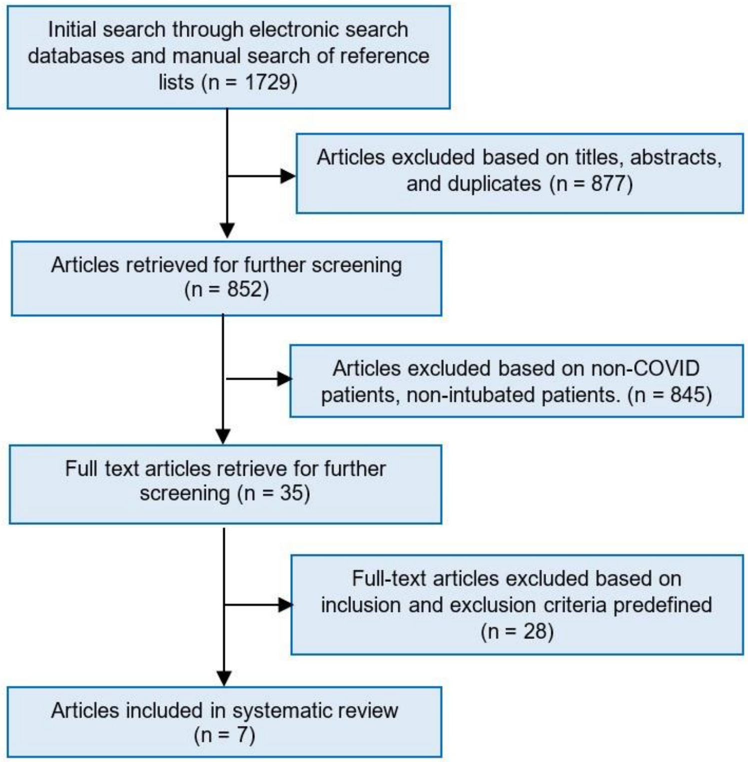

Figure 1: Selection of the included articles

2.3. Data Extraction

Two independent authors extracted data from the included articles. The data extracted were the type of interventions being compared (prone and supine position), outcome measures, including PaO_2/FiO_2 ratio (ratio of the first prone change), $PaCO_2$, mortality rate, ICU discharge, and duration of mechanical ventilation. Other data such as year of publication, study design, sample size, mean age, severity by Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) score, and duration of prone position were also extracted.

Review Manager version 5.4 (The Cochrane Collaboration) was used for statistical analyses. A two-sided $P < 0.05$ was denoted as statistically significant. For dichotomous outcomes, odds ratio (OR) was used, while for continuous outcomes, mean difference (MD), along with 95% confidence interval (CI) was used.

I^2 of less than 40% was considered insignificant, 40–60% was considered moderate heterogeneity, and more than 60% were categorized as substantial heterogeneity.[16]

2.4. Quality Assessment

The qualities of the studies included were independently assessed using Cochrane Risk of Bias Tool for randomized controlled trials (RCTs).[17] The tool examines 7 distinct domains, including randomization procedures, blindinmethods, and appropriate data reporting. Points are only rewarded when a criterion is fulfilled. All criteria were scored by the basis of ‘High risk of bias’ (-), ‘Low risk of bias’ (+), and ‘Unclear risk of bias’ (?). For non-RCTs, we used Newcastle Ottawa Scale (NOS).[18] NOS examines three categories, which are *Selection*, *Comparability*, and *Outcome* for cohort studies. While for case-control studies *Exposure* was examined instead of Outcome. The maximum score a study can obtain was 9. In the cohort segment, a maximum of 1 star for each question within the *Selection* and *Outcome* categories and a maximum of 2 stars can be given for *Comparability*. Meanwhile in the case-control segment, a maximum of 1 star for each question within the *Selection* and *Exposure* categories and a maximum of 2 stars for *Comparability* can be awarded. The cut-off to consider a study for low risk of bias was ≥7, the same as previous studies. GRADE (*Grading of Recommendations, Assessment, Development, and Evaluations*) approach was used to examine the certainty of evidence and was conducted by two authors independently.

Table 1: Quality Assessment of Included Cohort Studies: Newcastle-Ottawa Criteria

Study	Selection	Comparability	Outcome	Total Score		Overall risk of bias
Astua et al.	****	**	**	********	8	Low
Berrill et al.	****	**	**	*********	9	Low
Mittermaier et al.	****	**	**	********	8	Low
Weiss et al.	****	**	***	*********	9	Low
Gleissman et al.	****	**	**	********	8	Low
Clarke et al.	****	**	**	********	8	Low
Langer et al.	****	**	**	********	8	Low

3. RESULTS

3.1. Search Findings

The combined search using MEDLINE, EMBASE and Science Direct was conducted from July 07, 2019 –July 07, 2021. The search yielded 1,729 published studies. Based on the titles, abstract, and duplicates screened, 852 potential articles remained and full-text articles were retrieved out of them. The full-text articles were reviewed based on eligibility criteria, a total of 7 articles were determined to be eligible for inclusion in this eview (Figure 1). All of the studies were quality assessed using the Newcastle-Ottawa scale (NOS) and had low risk of bias (Table 1).

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3.2. Characteristics of the included articles

The seven studies included in this review were cohort studies (Table 2).[19-25] All of the studies were quality assessed using NOS and had low risk of bias (Table 2). The sample size varied in between a study having only 9 subjects and another having 648, which was a multi-centered study. We could not find any randomized controlled trials in this area.

All the recruited COVID-19 patients were from ICUs where the participants were mechanically ventilated. The mean age of all of the included studies ranged between 53 and 63 y. Three included studies calculated APACHE II score during the first 24 h of ICU admission, two of the studies calculated both APACHE II and SOFA scores. Furthermore, two other studies only used SOFA and two studies did not use either of the two scales. The APACHE II varied from an average of 10 to 26.2 and SOFA score ranged from 6.8 to 8.2. The duration of prone position sessions was similar across seven studies, averaging around 16 h of prone position. The studies recorded PaO_2/FiO_2 ratio on supine position, ranging from a mean of 17.5 as the lowest and 123 as the highest. All the studies included adult (18−75 y of age) COVID-19 patients, confirmed by laboratory results, with ARDS as defined by Berlin criteria, and were mechanically ventilated. Three studies mentioned PaO_2/FiO_2 ratio and had a similar cut-off, which was ≤ 150 mmHg and FiO_2 ≤ 0.6.

	Prone			Supine				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Astua 2020	152.8	11.2	31	108	5.4	31	22.9%	44.80 [40.42, 49.18]
Berrill 2020	151.9	58.9	34	87.8	38.1	20	12.4%	64.10 [38.20, 90.00]
Clarke 2020	286	113.3	20	123	40	20	5.0%	163.00 [110.34, 215.66]
Gleissman 2020	144.7	56	44	104	27.6	44	16.2%	40.70 [22.25, 59.15]
Langer 2020	158	80	648	98	36.3	409	22.0%	60.00 [52.91, 67.09]
Mittermaier 2020	191.6	36.1	9	136.9	23.5	9	11.5%	54.70 [26.56, 82.84]
Weiss 2020	211.5	91.5	42	134.3	54	42	9.9%	77.20 [45.07, 109.33]
Total (95% CI)			**828**			**575**	**100.0%**	**60.17 [46.86, 73.47]**

Heterogeneity: Tau² = 195.95; Chi² = 35.72, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 8.86 (P < 0.00001)

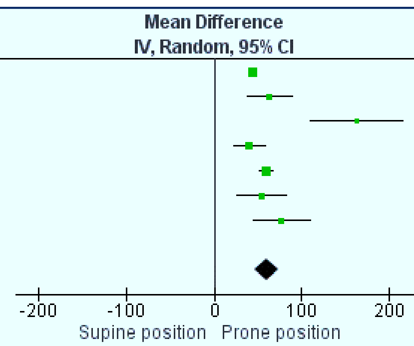

Figure 2: Forest plot of prone PaO2/FiO2 ratio

Table 2: Characteristics of the included studies

Author Year	Design	Partici-pants (n)	Age (y)	Apache II	SOFA	Interv-ention	PaO2/FiO2		PaCO2		Mortality Rate	ICU LOS		MV Duration*	
							SP	PP	SP	PP		SP	PP	SP	PP
Berrill et al. 2020	Cohort	34	58.5 ± 11.1	14 ± 4.7	NR	PP	87.8 ± 38.1	151.9 ± 58.9	NR	NR	NR	NR	NR	NR	NR
Mittermaier et al. 2020	Cohort	9	62 ± 14.2	26.2 ± 6.5	7.4 ± 4.9	PP	136.9 ± 23.5	191.6 ± 36.1	NR	NR	NR	50.4 ± 34.9	NR	NR	NR
Langer et al. 2021	Cohort	648	63 ± 10.4	10 ± 3.7	4 ± 1.5	PP	98 ± 36.3	158-80	52 ± 10.4	53 ± 11.9	262	17.7 ± 4.9	13 ± 4.1	12 (7-21)	16 (10-30)
Weiss et al. 2020	Cohort	42	59.9 ± 13.4	NR	6.8 ± 2.5	PP	17.5 ± 42.2	211.5 ± 91.5	51.8 ± 12.8	51 ± 9.8	11	NR	NR	NR	NR
Gleissman et al. 2020	Cohort	44	61 ± 13.0	NR	NR	PP	104 ± 27.6	144.7-56	46.3 ± 8.4	48 ± 9.2	NR	NR	NR	NR	NR
Clarke et al. 2020	Cohort	20	52.8 ± 11.6	NR	8.2 ± 3.4	PP	123 ± 40.0	286 ± 113.3	56 ± 11.4	53.4 ± 9.8	NR	NR	NR	NR	NR
Astua et al. 2020	Cohort	31	58.3 ± 1.7	NR	NR	PP	108.0 ± 5.4	152.8 ± 11.2	59.7 ± 2.4	68.9 ± 3.5	NR	NR	NR	NR	NR

*Data are expressed as mean and standard deviation or ± *) median and interquartile range.*

Apache II: Acute Physiology and Chronic Health Evaluation; LOS: Length of Stay; NR: Not Reported; PP: Prone Position; SP: Supine Position; SOFA: Sequential Organ Failure Assessment

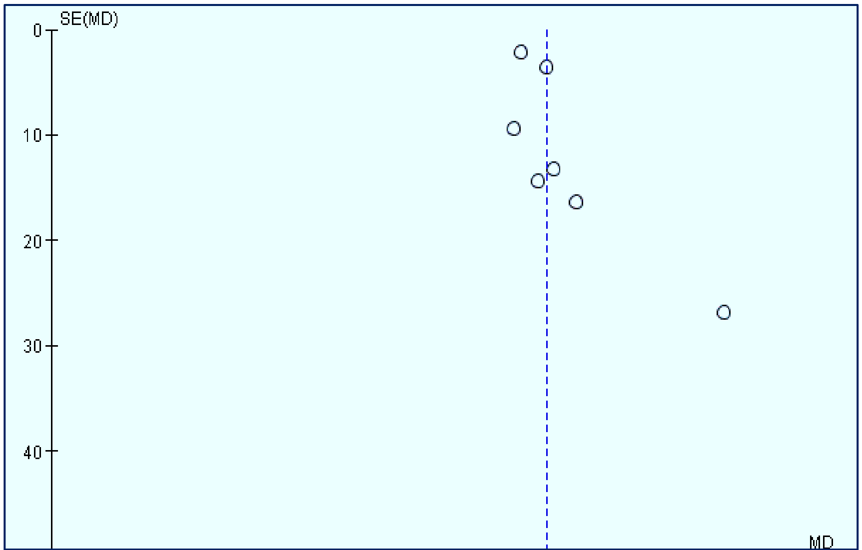

Figure 3: Funnel Plot of PaO_2/FiO_2 ratio

Out of seven studies, only two studies mentioned mortalities whereas five other studies did not report. Langer et al. had 262 deaths out of 648 patients (40.4%) and Weiss et al. lost 11 out of 20 patients (55%). In addition, this study reported mechanical ventilation duration with median of 16 days (interquartile range 10-30) were significantly longer in prone position group compared to supine position group. [23,25]

Two studies by Langer et al. and Mittermaier et al. displayed ICU length of stay.[23, 24] However, Mittermaier et al. did not compare between prone position and supine position. The study analyzed 23 samples and divided into 3 subgroups, one of which was prone position analysis. There was overlapping of samples between the subgroups. The average length of stay (in days) was 50.4 with standard deviation of 34.9. One study compared the two groups and reported that patients in prone position had a significantly longer stay in the ICU with median of 16 days (IQR 11−28).

3.3. Outcome measures

The combined data of seven studies, consisting of 1403 COVID-19 patients who had severe ARDS and were intubated, showed that prone position group was associated with higher PaO_2/FiO_2 ratio compared to supine position group (MD 60.17, 95% CI 46.86 to 73.47; $P < 0.00001$; Figure 2). The statistical heterogeneity was observed to be extensive ($I^2 = 87\%$) and the funnel plot resulted in asymmetrical shape, suggestive of publication bias (Figure 3).

Four studies reported the $PaCO_2$ measurement during prone position and supine position with 1331 patients combined. It showed no significant difference between prone position and supine position (MD 2.07, 95% CI -2.79 to 6.92; $P < 0.40$; Figure 4). Heterogeneity was observed as substantial ($I^2 = 95\%$). Quality of evidence using GRADE approach was found to be very low for both analysis (Table 3).

4. DISCUSSION

This study demonstrated that COVID-19 patients with ARDS were associated with a higher PaO_2/FiO_2 ratio in the prone position group compared to supine position group. The findings of this meta-analysis agree with prior studies, suggesting that prone positioning may improve oxygenation of injured lungs. The included articles were all cohorts, as there are no randomized controlled trials (RCTs) available, and were quality assessed using NOS which seven of the studies had a low risk of bias. However, the heterogeneity was substantial, and the funnel plot suggested publication bias. The

Table 3: Certainty assessment using GRADE approach

Studies	Design	No. of patients		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect (95% CI)	Certainty
		PP	SP							
PaO_2/FiO_2	Cohort	828	575	Not serious	Substantial [a]	Not serious	Not serious	Very serious [b]	MD 60.17 [46.86−73.47]	Very low
$PaCO_2$	Cohort	785	546	Not serious	Substantial [a]	Not serious	Not serious	Very serious [b]	MD 2.07 [-2.79−6.92]	Very low

Results of 5 studies; CI: Confidence interval; MD: Mean difference; [a] Substantial heterogeneity
[b] Funnel plot suggested of publication bias

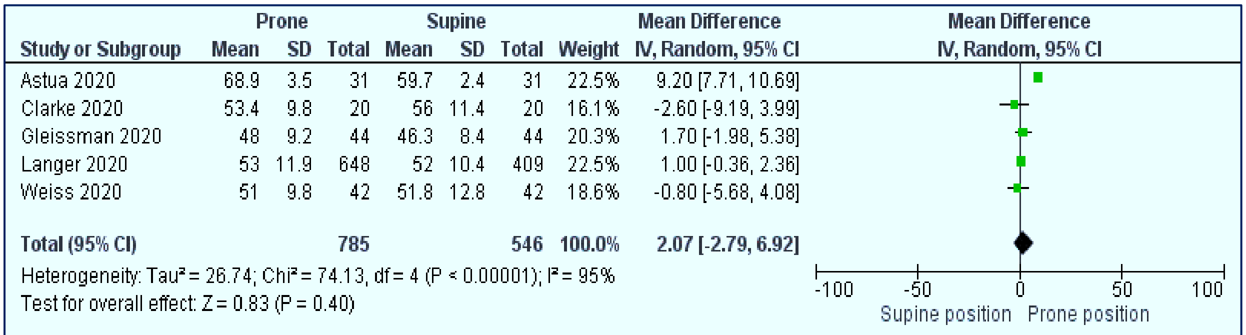

Figure 4: Forest Plot of $PaCO_2$

PaO_2/FiO_2 ratio is an integral component to diagnose ARDS. It is one of the key parameters in the Berlin criteria.[26] The severity of the disease can be based on the ratio starting from 200−300 mmHg as mild, 100−200 as PaO_2/FiO_2 levels, thus, making it become a valuable diagnostic, prognostic and clinical management tool.[27]

Several studies have proven that prone position helped improve the ventilation-perfusion ratio due to expansion of the collapsed dorsal lung, reduction of the pleural distribution of the lung stress and strain.[25,28] The

PROSEVA study concluded that the 28-day mortality for severe ARDS patients assigned to prone position group was 16% and the unadjusted 90-day mortality was 23.6% compared to those in supine position, where the figures were 32.8% and 41% respectively.[29] However, post hoc analysis suggested that, although there was a substantial improvement of gas exchange and reduction of mortality, there was no association between them.[30] Nonetheless, newer studies have contradicted this result. Park et al. found that oxygenation improvement of COVID-19 ARDS after prone position was associated with clinical outcomes.[31] Another study by Camporota and team also found that there was a significant oxygenation response of patients with COVID-19 ARDS and was associated with improved survival.[32] Since the pandemic began large numbers of hospitalized COVID-19 patients fulfilled the criteria of ARDS, which required invasive mechanical ventilation and a high level of patient care.[2,6,19] Numerous studies recommended prone positioning to help improve oxygenation and decrease work of breathing.

Additionally, this review also examined $PaCO_2$ levels between the two groups and found that there was no significant association between the prone position with $PaCO_2$ level which was contradicts the prior studies.[29,33-36] Altered ventilation-perfusion ratio is a fundamental cause of abnormal gas exchange, which a low ratio induces hypoxemia and a high ratio induces hypercapnia.[33] Under normal physiology, $PaCO_2$ is the primary control for air exchange, specifically for the minute ventilation or amount of air exchanged in the lungs per minute.[28,34] It is responsible for affecting the pH; if there is an increase in $PaCO_2$ then the pH will decrease and increase minute ventilation. Whereas, a decrease in $PaCO_2$ will increase pH and decrease minute ventilation.[29, 35] A study conducted in 2003 by Gattinoni et al. showed a reduction of $PaCO_2$ level in ARDS patients in response to prone position.[13] It stated that prone positioning reduced areas of distended lungs and the physiological dead-space, therefore it reduced shunts and resulted in reduction in PaCO2.[36] We included four cohort studies with low risk of bias to measure the outcome in $PaCO_2$ level, and found the heterogeneity was extensive. The possible mechanism that prone position did not significantly affect the level of $PaCO_2$ was prone position using pressure-controlled ventilation would have a reduction of the chest wall compliance that reduced the tidal volume and minute ventilation.[37] Furthermore, prone position using volume-controlled ventilation would have the increased pleural pressure that reduced the venous return and affected the regional perfusion and increased the dead space.[37] Langer and colleague called it the CO_2-non responders.[24]

Two articles mentioned mortality, Weiss et al. showed 55% and Langer et al. showed 40.4% of patients died in their study.[23,25] Furthermore, Langer et al. compared mortality between prone position versus supine position group and reported that 112/409 (28%) patients died in the supine position group.[24,25] However, the significance was not calculated by the author.

Langer et al. compared ICU length of stay between the groups. For ICU length of stay, prone position patients had a significantly longer median of 16 days (IQR 11−28) compared to median 12 days (IQR 7−21) for the supine position group. This result supported other studies suggesting that prone positioning had longer time to death and in parallel to the beneficial changes of physiological parameters such as PaO_2/FiO_2 ratio.[38-41] The mechanical ventilation duration was also significantly longer in prone position group compared to supine position group.[23] The result might represent that prone positioning was applied as a salvage procedure on ARDS patients with more severe conditions. Another included study mentioned ICU length of stay with an average of 50.4 days.[24] However, Mittermaier et al. did not compare between prone position and supine position.[24] The study analyzed 23 samples and divided into 3 subgroups, one of which was about prone position analysis. There were overlapping of samples between the subgroups, therefore, no direct comparison of prone position and supine position can be made. Thus, analysis of results from Langer and Mittermaier could not be performed.

5. LIMITATIONS

All trials included in this review were observational studies in nature, while RCT studies were not yet available. Other limitations were the high degree in heterogeneity, risk of publication bias, no standardized prone position protocol, and the certainty of the measured outcome was very low.

6. CONCLUSION

Based on the results obtained from this meta-analysis, it can be concluded that intubated COVID-19 patients with ARDS had better PaO_2/FiO_2 ratio when in prone position. We found that there was no difference for $PaCO_2$ in prone position. Other outcomes such as mortality rate, ICU length of stay, and mechanical ventilation days could not be determined. Due to the limited number of studies with small sample size, high heterogeneity of measured outcomes, and very low certainty of evidence, further randomized clinical studies are needed.

7. Availability of data

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

8. Acknowledgments

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9. Competing interests

The authors declare that they have no competing interests. No external or industry funding was involved in this study. applicable.

10. Authors' contribution

DA, AS. SKM: Conceptualization; Data curation; Methodology; Project administration; Formal analysis; Writing - original draft; Supervision; Validation; Visualization; Writing - review & editing; Investigation.

HA, APN: Data curation; Investigation; Methodology; Software; Visualization; Writing - original draft; Writing - review & editing.

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