EVIDENCE SUMMARY

RESEARCH QUESTION: Among COVID-19-associated acute respiratory distress syndrome patients, should lung protective ventilation, high PEEP, and driving pressure-limited strategies be used?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of a lung protective ventilation strategy (tidal volume 4-6mL/kg ideal body weight, plateau pressure less than 30cmH$_2$O, and an appropriate PEEP) among mechanically ventilated adult patients with COVID-19-associated ARDS.	Very Low	Strong
We suggest against the routine use of high PEEP strategy among mechanically ventilated adult patients with COVID-19-associated ARDS. We further suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection.	Very Low	Weak
We suggest to maintain the driving pressure less than 15cmH$_2$O among mechanically ventilated adult patients with COVID-19-associated ARDS.	Very Low	Weak

Consensus Issues

The difficulty of doing high quality studies or randomized controlled trials on critical patients is recognized hence, despite the certainty of evidence in this review, a strong recommendation was given for the use of lung protective ventilation in mechanically ventilated adult patients with COVID-19-associated ARDS. This strategy has been followed and utilized pre-COVID in patients with ARDS.

The immediate use of high PEEP was previously employed and advocated in mechanically ventilated patients to increase oxygenation in patients. However, in recent years, due to the identified harm of barotrauma and lung damage, the strategy has shifted to individualizing the use of PEEP based on the patient's clinical status, respiratory mechanics, and presentation. This is also suggested in the management of COVID-19-associated ARDS based on this review and consensus decision.

Based on the study by Ottolina [18], patients were grouped to higher PEEP strategy when median FiO$_2$ of 80% (IQR 70-100%) and a median PEEP of 14.7cmH$_2$O (IQR 13.7-16.7) was used. This follows the operational definition of higher and lower PEEP strategies according to The Acute Respiratory Distress Syndrome Clinical Network (ARDSNet) table.

KEY FINDINGS

- In this evidence review update, we synthesized current evidence on lung protective ventilation, use of higher versus lower positive end-expiratory pressure (PEEP), and driving-pressure limited strategy.
- For lung protective ventilation, one multicenter retrospective study (PRoVENT COVID) showed that the use of higher tidal volume was associated with similar to higher risk for mortality when compared with lower tidal volume. Certainty of evidence was very low due to non-randomized designs and small sample size.
- Data from two retrospective studies which examined the association of higher PEEP versus lower PEEP levels with mortality among adult patients with COVID-19-related acute respiratory distress syndrome (COVID-19 ARDS) on invasive mechanical ventilation. Pooled analysis of two studies showed that the use of higher PEEP when compared to lower PEEP showed no association with all-cause mortality. Subgroup analysis on adult patients with COVID-19 ARDS and acute kidney injury on mechanical ventilation demonstrated that higher PEEP levels was associated with all-cause mortality. Overall certainty of evidence was very low due to risk of bias and imprecision.
- A multicenter observational study demonstrated the association of higher dynamic driving pressure (>14cmH_2O vs 12cmH_2O) during the initial four days of IMV with mortality. Certainty of evidence was very low due to non-randomized designs and small sample sizes.

PREVIOUS RECOMMENDATIONS
As of 19 February 2021

We suggest the use of a lung protective ventilation strategy (tidal volume 4-8mL/kg predicted body weight and plateau pressure less than 30cmH_2O) in patients with COVID-19 infection and ARDS. *(Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of a higher PEEP strategy. We suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection. *(Low certainty of evidence)*

There is insufficient evidence to recommend a driving pressure limited strategy in patients with COVID-19 infection. We suggest to keep the driving pressure ≤14cmH_2O. *(Low certainty of evidence)*

Consensus Issues
During the early stages of the disease, COVID-19 ARDS may not be the same as the usual ARDS. In COVID-19-related ARDS, compliance can be high or normal even in patients with very low PaO_2/FiO_2 ratios. In these cases, the lungs are not recruitable and the use of high levels of PEEP will not lead to better oxygenation.

As the respiratory mechanics (compliance) in COVID-19 ARDS are not uniformly correlated with the severity of the hypoxemia, it is best to individualize PEEP based on compliance and driving pressure rather than titrating PEEP based on the severity of the PaO_2/FiO_2 ratio. Thus, a higher PEEP strategy (using the high PEEP/FiO_2 table) for moderate to severe ARDS is not recommended for all patients with COVID-19 infections, due to possible complications such as barotrauma.

We suggest titrating lung volumes (tidal volume 4-8mL/kg predicted body weight) and PEEP to maintain the plateau pressure less than 30 and to have the lowest driving pressure. A driving pressure of <14cmH_2O is recommended. The driving pressure is the difference between the plateau pressure and the PEEP, or tidal volume over the respiratory system compliance.

INTRODUCTION

It is estimated that a third of hospitalized patients with COVID-19 develop COVID-19-related acute respiratory distress syndrome (COVID-19 ARDS) [1]. While the criteria for COVID-19 ARDS adopts the 2011 Berlin ARDS definition, recent studies suggest that compared to non-COVID-19 ARDS, unique features may be present in COVID-19 ARDS. These include preserved lung compliance, pulmonary thrombosis, and local vasodilation [2-4]. It is observed that invasive mechanical ventilation (IMV) settings often utilize relatively high PEEP [5,6]. Similar to non-COVID-19 ARDS, ranges of respiratory parameters vary, such as respiratory compliance (27-45mL/cmH_2O), plateau pressure (22-29cmH_2O), and driving pressure (10-16cmH_2O) [5]. Lung recruitability, based on the recruitment-to-inflation ratio, is likewise heterogeneous among patients with COVID-19 ARDS [2]. Currently, optimal IMV setting strategies may potentially improve respiratory status and survival among patients with COVID-19 ARDS [7]. This, likewise, poses challenges for clinicians who manage patients with COVID-19 ARDS. The risk of acquiring ventilator-induced lung injury in addition to alveolar damage due to COVID-19 is also recognized as a potential adverse event [8-9]. Among the existing approaches to IMV in COVID-19 ARDS include higher PEEP strategy, lung protective ventilation (which include the use of appropriate tidal volumes and plateau pressures), and driving-pressure limited strategies [7].

REVIEW METHODS

In this review update, we performed a systematic search of published, pre-prints, and unpublished studies on patients with COVID-19 ARDS and following interventions: (a) lung protective ventilation, (b) higher PEEP strategy, and (c) driving-pressure limited ventilation. The outcomes of interest were mortality, intensive care unit (ICU) length of stay, ICU discharge, and adverse events, particularly barotrauma and volutrauma. MEDLINE and Central databases were searched last 10 November 2022 using the following search terms: "COVID-19", "ARDS", "high PEEP", "lung protective ventilation", and "driving-pressure limited ventilation". The Clinical trials.gov database was searched last 09 February 2023 for ongoing clinical trials on IMV among patients with COVID-19 ARDS, while the World Health Organization (WHO) and National Institutes of Health (NIH) updated living guidelines on COVID-19 were accessed and reviewed. Updates through the McMaster Plus COVID-19 Evidence Alerts and Pubmed Alerts were also used to retrieve relevant articles up to 22 February 2022.The PRISMA flow diagram [10] is shown in Appendix 2. The Newcastle-Ottawa Scale was used to evaluate quality of cohort studies, while the AGREE II Instrument form was used to assess the WHO and NIH guidelines.

RESULTS

Our systematic search did not yield randomized controlled trials (RCTs) on the use of lung protective ventilation on adult patients with COVID-19 ARDS. Likewise, there were no RCTs on higher PEEP ventilation and driving pressure limited strategies among mechanically ventilated patients with COVID-19 ARDS nor were there studies on ventilation in children.

Characteristics of included studies

There was one study on lung protective ventilation, four retrospective studies on PEEP strategies for patients with COVID-19 ARDS, and one study on driving pressure limited strategies. All studies were done among adult patients, two were conducted in Italy, while one study each was done in Netherlands, China, USA, and Korea. The characteristics of included studies are summarized in Appendix 3. Results of two studies were pooled and included in the quantitative analysis as discussed below.

A. LUNG PROTECTIVE VENTILATION STRATEGY

The aims of lung protective ventilation are to limit tidal volume and plateau pressures to avoid lung damage due to overdistension as well as to set appropriate PEEP levels that minimize cyclic opening and closing of airways and lung units [11]. These include the following parameters: limit tidal volumes (4-8mL/kg predicted body weight [PBW]) and inspiratory pressures (plateau pressure, 30cmH_2O, defined as the pressure obtained after a 0.5-s inspiratory pause) [12]. In a multi-center retrospective study by Botta et al., (PRoVENT-COVID) which included 553 patients with COVID-19 ARDS, the following were the ventilation parameters: median tidal volume of 6.3 (IQR 5.7 to 7.1) mL/kg PBW, PEEP of 14 (IQR 11 to 15) cmH_2O and driving pressure of 14 (IQR 11.2 to 16.0). It was found that higher tidal volume was associated with the same or higher risk of 28-day mortality (OR 1.28, 95% CI 1.00-1.64); however, in multivariable models, it was not associated with ventilator-free days (MD -0.73 days, 95% CI -1.52 to 0.06) [13].

In 2021, Radjev et al. retrospectively analyzed outcomes of adult patients with COVID-19 who were placed on IMV using lung protective strategies with low tidal volumes at less than 8mL/kg of ideal body weight, plateau pressure of ≤30cmH_2O, and a lower driving pressure at 13-15cmH_2O. Barotrauma, in the form of subcutaneous emphysema, pneumothorax or pneumomediastinum, was observed in 17.35% (11/121 patients) [14].

Indirect evidence from a meta-analysis by Bhattacharjee et al. among adult patients with non-COVID ARDS showed that based on four trials involving a total of 2,350 participants, the incidence of barotrauma among patients placed on lung recruitment maneuver was similar to that that of standard lung protective ventilation group (RR=1.27 (95% CI 0.68, 2.36), p=0.45) [15]. On the other hand, another meta-analysis by Aoyama and colleagues on lung protective ventilation in non-COVID patients with moderate to severe ARDS reported that the incidence of barotrauma was 7.2% (448 of 6,253 patients), however, there were no clinical trials on lung protective ventilation evaluating this outcome [16].

B. HIGHER VERSUS LOWER PEEP

Two studies among mechanically ventilated adult patients with COVID-19 ARDS were analyzed to determine the association of high PEEP levels with clinically relevant outcomes and adverse events [17,18]. Both articles were multi-center observational studies. In the study by Valk [17] The Acute Respiratory Distress Syndrome Clinical Network (ARDSNet) table (Figure 1) was utilized through FiO_2/PEEP combinations to define higher or lower PEEP strategy [17]. Covariate-balancing propensity score (CBPS) for matching was performed. Patient's age, sex, BMI, PaO_2/FiO_2, plasma creatinine concentration, hypertension, diabetes, use of angiotensin converting enzyme inhibitors, use of vasopressor or inotrope, fluid balance, blood pH, mean arterial pressure, heart rate, and respiratory compliance determined at baseline were considered in the matching process [17]. In the study by Ottolina, patients were grouped to higher PEEP strategy when median FiO_2 of 80% (IQR 70-100%) and a median PEEP of 14.7cmH_2O (IQR 13.7-16.7) was used [18]. Patients were grouped to low and medium PEEP strategies when a median FiO_2 of 70% (IQR 60%-70%) at PEEP of 9.6cmH_2O (IQR 60-80) and median FiO_2 of 80% (IQR 60-80%) at PEEP of 14.7cmH_2O (IQR 13.7-16.7), respectively [18]. Using the ARDSNet table, low and medium PEEP strategies in the study of Ottolina were still within the lower PEEP/FiO_2 combination. Ottolina and colleagues performed an adjusted odds analysis using age, sex, SOFA score, serum creatinine, CRP, and cardiovascular disease [18].

Based on the two observational studies, the use of higher PEEP strategy when compared to lower PEEP strategy showed inconclusive results in terms of mortality (OR 1.58 95% CI 0.80-3.12; I^2=67%). In a specificity analysis among patients with COVID-19 ARDS regardless of renal status, the use of higher PEEP strategy was likewise inconclusive (OR 1.18 95% CI 0.80-1.74) (Figure 2).

Lower PEEP/F_{IO_2} Combination*

F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP, cm H_2O	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

Higher PEEP/F_{IO_2} Combination†

F_{IO_2}	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0
PEEP, cm H_2O	12	14	14	16	16	18	20	20	20	20	22	22	22–24

Figure 1. Operational definitions for HIGHER versus LOWER PEEP strategies according to ARDSNet Table as used in Valk 2021 and Ottolina 2022 [11]. Definition of abbreviations: F_{IO2}. Fraction of inspired oxygen; **PEEP**, Positive end-expiration pressure *From: Sahetya SK, Goligher EC, Brower RG. Fifty Years of Research in ARDS. Setting Positive End-Expiratory Pressure in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2017 Jun 1;195(11):1429-1438. doi: 10.1164/rccm.201610-2035CI. Erratum in: Am J Respir Crit Care Med. 2018 Mar 1;197(5):684-685. PMID: 28146639; PMCID: PMC5470753.*

Need for renal replacement therapy

Two observational studies [17,18] reported on the need for renal replacement therapy as outcome among mechanically intubated patients with COVD-19 ARDS. The use of a higher PEEP strategy when compared to lower PEEP strategy show inconclusive effect on the need for renal replacement therapy (OR 8.90; 95% CI 0.27-29.62; I^2=97%).

Safety outcomes

Among patients with COVID-19 ARDS and acute kidney injury or failure, the use of higher PEEP strategy was associated with increased mortality (OR 2.39 95% CI 1.19-4.80) [17,18]. While more incidence of pneumothorax was observed in the higher PEEP strategy (4 out of 228 or 17.54%) when compared with lower PEEP strategy (1 out of 225 or 0.4%), the difference was likewise not statistically significant (OR 4.00; 95% CI 0.44-36.07). Furthermore, a retrospective study by Guven and colleague involved patients with COVID-19 ARDS admitted during the early part of the pandemic, divided into two groups: barotrauma group (n=10) and non-barotrauma group (n=65). The barotrauma group had significantly higher maximum PEEP levels compared to the non-barotrauma group (15.3 +/- 1.1 cmH2O versus 13.6 +/-1.7, p=0.0150). [19]

The summary of findings on mortality, duration of ventilator free days and mechanical ventilation, and adverse events is shown in Table 1.

Table 1. Summary of findings on mortality, duration of ventilator free days and mechanical ventilation, and adverse events

CRITICAL OUTCOMES	No. of Studies & participants	Effect Estimate	95% Confidence Interval	Interpretation	Certainty for Evidence
All-cause mortality (all patients)	2 Prospective multi-center cohort studies (n=670)	OR 1.58	0.80 to 3.12	INCONCLUSIVE	Very Low
All-cause Mortality among all patients with COVID-19 ARDS (mixed patient population with and without acute kidney injury)	1 Prospective multi-center matched cohort study (n=468)	OR 1.18	0.80 to 1.74	INCONCLUSIVE	Very Low
All-cause Mortality among all patients with COVID-19 ARDS with acute kidney injury or failure	1 Prospective multicenter matched cohort (n=202) study (n=202)	OR 2.39	1.19 to 4.80	HARM (Favors Lower PEEP Strategy)	Very Low

Serious Adverse Event: Pneumothorax	1 Prospective multi-center matched cohort study (n=468)	OR 4.00	0.44 to 36.07	INCONCLUSIVE	Very Low
Need for renal replacement therapy	2 Prospective multi-center cohort studies (n=670)	OR 8.90	0.27 to 291.62	INCONCLUSIVE	Very Low
Ventilator-free Days in 28 days	1 Prospective multi-center matched cohort study (n=468)	MD -2.84 Days	-2.84 to -0.74	BENEFIT (Favors HIGH PEEP Strategy)	Low
Duration of mechanical ventilation	1 Prospective multi-center matched cohort study (n=468)	MD 2 days	-2.66 to 6.66 days	INCONCLUSIVE	Very Low

A retrospective observational study on twenty adult patients with COVID-19 ARDS [20], determined lung recruitability based on the following parameters: static respiratory system compliance (C_{STAT}), PaO_2, and $PaCO_2$ in a one group before and after measurement of lung recruitability. The effect of higher PEEP strategy at 15cmH_2O after a five-minute of baseline period at PEEP of 5cmH_2O on static respiratory system compliance (MD 0.90L/cmH_2O; 95% CI -1.40 to 3.20), PaO_2 (MD -1.70cmH_2O; 95% -7.39 to 3.99), and $PaCO_2$ (MD 0.40cmH_2O; 95% CI -3.61 to 4.41) were all inconclusive. The summary of findings on respiratory system compliance is shown in Table 2.

Table 2. Summary of findings on respiratory system compliance

IMPORTANT OUTCOMES	No. of Studies & participants	Effect Estimate	95% Confidence Interval	Interpretation	Certainty for Evidence
Static respiratory compliance	1 Retrospective cohort (n=20)	MD 0.90L/cm	-1.40 to 3.20	INCONCLUSIVE	VERY LOW
Partial Pressure of Oxygen (PO_2)	1 Retrospective cohort (n=20)	MD 6.8cmH_2O	7.39 to 3.99	INCONCLUSIVE	VERY LOW
Partial Pressure of Carbon dioxide (PCO_2)	1 Retrospective cohort (n=20)	MD 0.40cmH_2O	-3.61 to 4.41	INCONCLUSIVE	VERY LOW

Hemodynamic response to HIGHER PEEP in COVID-19 ARDS

One prospective observational study [21] with nine mechanically ventilated patients with COVID-19 ARDS investigated on the effect of HIGHER PEEP strategy on hemodynamic, oxygenation, and ventilatory outcomes. Results showed that the use of HIGHER PEEP strategy when compared with a LOWER PEEP strategy did not improve arterial oxygen content (MD 1.51mmHg; 95% CI -1.27 to 4.30), cardiac output (MD -1.43L/min; 95% CI -3.69 to 0.85), oxygen delivery (MD 147.58L/min; 95% -26.10 to 108=9.23), and PF Ratio (MD 41.57; 95% -26.10, 109.23) (Figures 4 and 5).

a. Driving pressure limited strategies

Among mechanically ventilated patients, driving pressure is the difference between plateau pressure and positive end-expiratory pressure (Pplat-PEEP) [22-23]. Multiple factors increase driving pressure, such as increase in tidal volume, decrease in respiratory system compliance, higher plateau pressure and lower PEEP [23].

Direct Evidence

A multicenter study done in Korea showed that among 129 adult patients with COVID-19 ARDS (median age=69, range 62-78, 60% males), higher dynamic driving pressure during the initial four days of IMV was associated with mortality (14cmH_2O vs 12cmH_2O, p=0.003) [21]. Based on the said study by Lee, et al, multi-variate analysis showed that higher dynamic pressures during the initial four days of ventilation was associated with increased mortality (adjusted OR 1.16, 95% CI 1.0-1.33, p=0.046) [24].

Indirect Evidence

Presently, there are no clinical trials on driving pressure limited strategies for COVID-19 ARDS. Indirect evidence from a systematic review involving four studies (n=3,252) on non-COVID-19 ARDS showed that higher driving pressure was associated with higher mortality (pooled RR=1.44, 95% CI 1.11-1.88, I^2=85%). Among the included studies, the median cut-off of driving pressure was 15cmH_2O (range 14-16cmH_2O) [25].

Certainty of evidence

For studies on lung protective ventilation and driving-pressure limited strategy, aside from the lack of studies to directly address the PICO questions on COVID-19 ARDS, the retrieved studies were non-randomized studies and had relatively small sample. Thus, the overall certainty of evidence is deemed to be very low. Of the two studies on all-cause mortality among patients with COVID-19 ARDS placed on high PEEP versus low PEEP, the overall certainty of evidence is low due to risk of bias attributed to non-randomized study designs.

RECOMMENDATIONS FROM OTHER GROUPS

Updated recommendations from the clinical practice guidelines of the World Health Organization (WHO) and US National Institutes of Health (NIH) are shown in Table 3.

Table 3. Recommendations from other groups

Group	Recommendation	Strength of Recommendation / Certainty of Evidence
World Health Organization (WHO) Living Guidelines on Clinical management of COVID-19 (January 13, 2023) [26]	"We recommend implementation of mechanical ventilation using lower tidal volumes (4-8mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure <30cmH_2O)"	Strong recommendation
	"In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure."	Conditional recommendation
National Institutes of Health (NIH) COVID-19 living guidelines (December 1, 2022) [27]	"For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, the Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy"	BIIa (Moderate quality of evidence)
Australian Guideline Consensus Recommendation [28]	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP >10cmH_2O) over a lower PEEP strategy."	Consensus recommendation

ONGOING STUDIES AND RESEARCH GAPS

New studies on different IMV strategies for COVID-19 ARDS [29-34] are presently ongoing. Longitudinal studies on IMV strategies and outcomes on pediatric patients with COVID-19 ARDS are lacking. Most of the existing studies on respiratory parameters such as lung compliance, are focused on the initial days after IMV commencement; long-term studies on these may also be recommended.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST, PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Mechanical ventilation for patients with ARDS requires significant intensive care resources, manpower, and substantial health care costs. Patients with ARDS also often have long hospitalization stays [29]. A study on per-patient cost of inpatient care for adult patients with COVID-19 in the US estimates the cost to be USD 59,742 for a patient on IMV, and adjusted cost differential for ARDS was estimated to be USD 43,912 [30]. Based on a paper on non-COVID ARDS by Bice et al., depending on the likelihood of survival, incremental cost-effectiveness ratio (ICER) range from USD 29,000 to 110,000 per QALY [29]. There are no local studies on cost effectiveness of mechanical ventilation strategies for COVID-19 ARDS. In our setting, availability of mechanical ventilators, ICU bed availability, and staffing should be considered.

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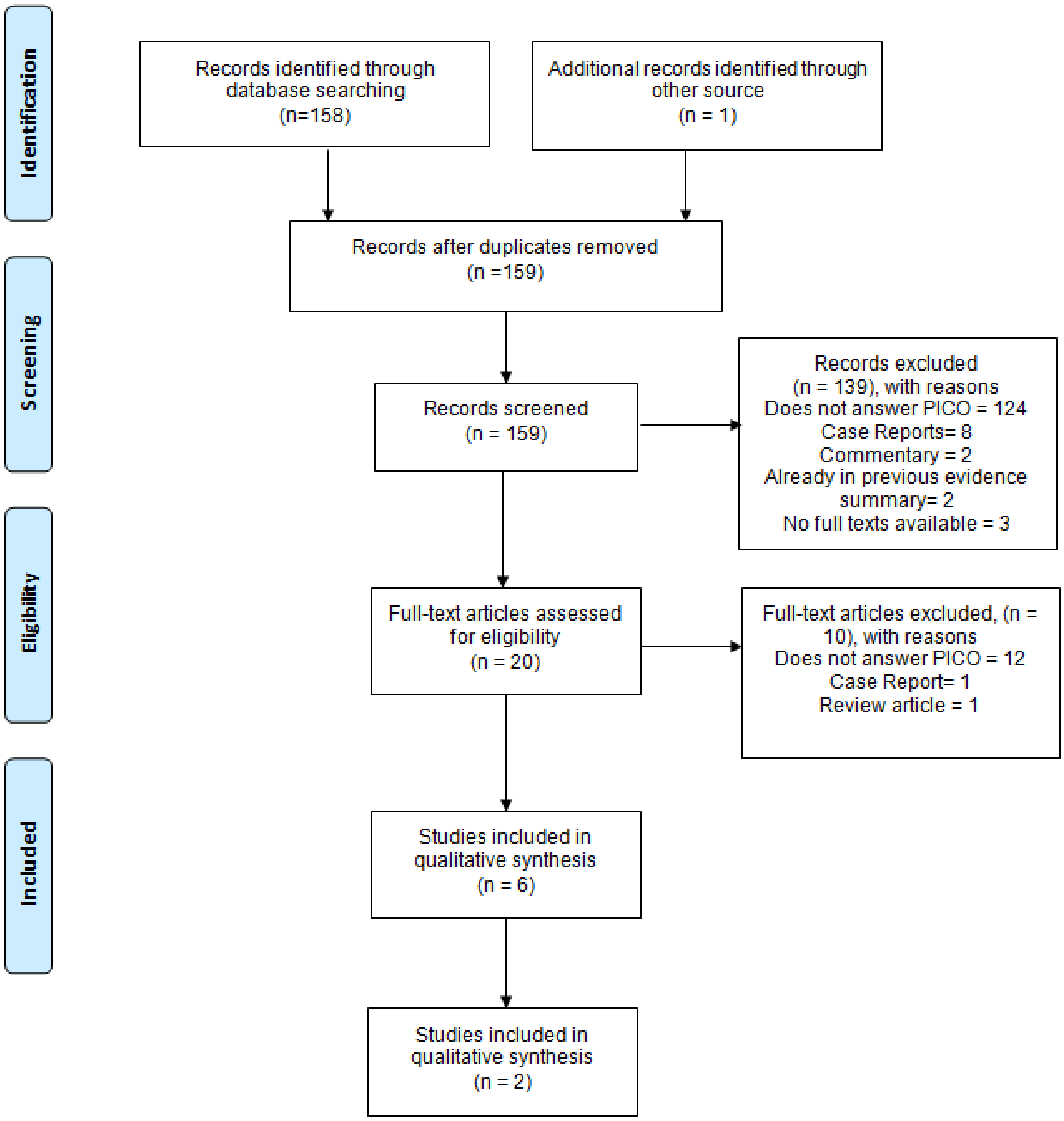
Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)			It is estimated that a third of hospitalized patients with COVID-19 develop COVID-19-related acute respiratory distress syndrome (COVID-19 ARDS) [1].
Benefits	Large (1)	Moderate	Small (1)	Trivial (4)	**Lung Protective ventilation** The barotrauma group had significantly higher maximum PEEP levels compared to the non-barotrauma group (15.3 +/- 1.1 cmH2O versus 13.6 +/-1.7, p=0.0150). [15] **higher tidal volume was associated with the same or higher risk of 28-day mortality (OR 1.28, 95% CI 1.00-1.64);** **Higher PEEP** **use of higher PEEP strategy when compared to lower PEEP strategy showed inconclusive results in terms of mortality** (OR 1.58 95%CI 0.80 to 3.12; I2=67%). **Driving Pressure Limited strategies** **higher dynamic driving pressure during the initial four days of IMV was associated with mortality (14 cmH2O vs 12 cmH2O, p=0.003) [21].** Indirect evidence from a systematic review involving four studies (n=3,252) on non-COVID-19 ARDS showed that higher driving pressure was associated with higher mortality (pooled RR = 1.44, 95% CI 1.11-1.88, I2=85%).
Harm	Large (2)	Moderate (2)	Small (1)	Trivial (1)	The use of higher PEEP strategy was associated with increased mortality (OR 2.39 95% CI 1.19 to 4.80) [11,12].
Certainty of Evidence	High	Moderate (1)	Low (1)	Very low (4)	
Balance of effects	Favors treatment	Probably favors treatment (2)	Does not favor treatment (2)	Favors no treatment (2)	Pooled results of the two studies (n=670) showed that the **use of higher PEEP compared to lower PEEP showed inconclusive results in terms of**

								<u>mortality based on low to very low quality evidence.</u> In terms of harms, one metanalysis examined the incidence of barotrauma while on lung protective ventilation. Indirect evidence (as this was done in non-COVID patients with moderate to severe ARDS) showed that the incidence of barotrauma was 7.2%, however, there were no clinical trials on lung protective ventilation evaluating this outcome.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)	Probably NO important uncertainty or variability (1)	No important uncertainty or variability				
Resources Required	Uncertain (4)	Varies (1)	Large cost (1)	Moderate cost	Negligible cost	Moderate savings	Large savings	Mechanical ventilation for patients with ARDS **<u>requires significant intensive care resources, manpower and substantial health care costs.</u>** <u>Patients with ARDS also often have **long hospitalization stays[1].**</u> A study on per-patient cost of inpatient care for adult patients with COVID-19 in the US estimates the cost to be USD 59,742 for a patient on IMV, and adjusted cost differential for ARDS was estimated to be USD 43,912.[2]
Certainty of evidence of required resources	No included studies (6)	Very low	Low	Moderate	High			
Cost effectiveness	No included studies (6)	Probably / Favors the comparison	Probably favors the intervention	Favors the intervention	Does not favor either (1)			**In our setting, availability of mechanical ventilators, ICU bed availability and staffing should be considered.**
Equity	Uncertain (3)	Varies (1)	Reduced	Probably reduced (3)	Probably no impact	Probably increased	Increased	
Acceptability	Varies (2)	No (1)	Probably no (2)	Yes	Probably yes (1)			For the use: 2 (weak) **Against the use: 4 (weak)**
Feasibility	Varies (3)	No	Probably no (1)	Yes	Probably yes (2)			No additional considerations or comments

Appendix 2: PRISMA Flow Diagram



Appendix 3: Characteristics of Included Studies

a. Lung Protective Ventilation

Author Study Design	Population / Setting	Intervention/s	Control	Outcomes
Rajdev 2021 Retrospective cohort study	121 adult patients with COVID-19 ARDS on IMV from March to November 2020 USA (single-center)	IMV using lung protective ventilation strategies	None	Primary: incidence of barotrauma Secondary: length of stay, mortality

b. High PEEP

Author Study Design	Population / Setting	Intervention/s	Control	Outcomes
Valk 2021 Retrospective cohort study	933 adult patients with COVID-19 ARDS on IMV from March 1 to June 1, 2020 Netherlands (multi-center)	High PEEP vs low PEEP	None	Primary: Ventilator-free days (VFD) and survival at 28 days post intubation Secondary: acute kidney injury, use of renal replacement therapy, ICU mortality rates, ICU length of stay, hospital length of stay, need for adjunctive treatment for refractory hypoxemia, number of days with continuous sedation, complications
Ottolina 2022 Retrospective cohort study	101 adult patients with COVID-19 ARDS on IMV from February 21 to April 28, 2020 Italy (single-center)	Low PEEP (9.6 cmH_2O), Medium PEEP (12.0 cmH_2O), high PEEP (14.7 cmH_2O)	None	Primary: ICU mortality, incidence of AKI

c. Driving Pressure Limited Strategies

Author Study Design	Population / Setting	Intervention/s	Control	Outcomes
Lee 2022 Retrospective cohort study	129 adult patient with COVID-19 ARDS on IMV from February 1, 2020 to February 28, 2021 Korea (multi-center)	IMV with dynamic driving pressure	None	Primary: ICU mortality Secondary: VFD, hospital length of stay, tracheostomy, renal replacement therapy during ICU stay, superinfection, hospital, 28-day and 6-day mortality

Appendix 4: GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high PEEP	low PEEP	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	observational studies	serious[a]	serious[b]	not serious	not serious	none	99/263 (37.6%)	82/263 (31.2%)	**OR 1.3325** (0.9287 to 1.9117)	**65 more per 1,000** (from 16 fewer to 152 more)	⨁◯◯◯ Very low	CRITICAL
Pneumothorax												
1	observational studies	serious[a]	not serious	not serious	not serious	none	4/228 (1.8%)	1/225 (0.4%)	**OR 4.00** (0.44 to 36.07)	**13 more per 1,000** (from 2 fewer to 134 more)	⨁◯◯◯ Very low	CRITICAL
All-cause mortality among patients with COVID-19 ARDS (mixed patient population)												
1	observational studies	serious[a]	not serious	not serious	not serious	none	77/231 (33.3%)	69/232 (29.7%)	**OR 1.18** (0.80 to 1.74)	**36 more per 1,000** (from 44 fewer to 127 more)	⨁◯◯◯ Very low	CRITICAL
Need for Renal Replacement Therapy												
2	observational studies	serious[a]	serious[b]	not serious	not serious	none	72/266 (27.1%)	43/265 (16.2%)	**OR 8.90** (0.27 to 291.62)	**471 more per 1,000** (from 113 fewer to 820 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. non-randomized study design

b. heterogeneity in patient factors, time point in assessment in respiratory parameters

Appendix 5: Forest Plots

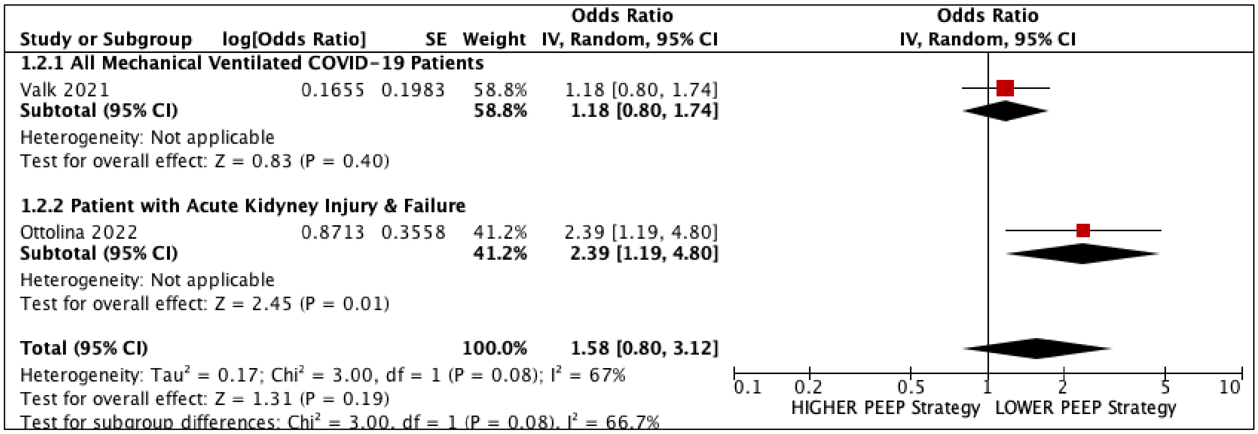


Figure 1. Forest plot for all-cause mortality. In Valk 2021, patient's age, sex, BMI, PaO_2/FiO_2, plasma creatinine concentration, hypertension, diabetes, use of angiotensin converting enzyme inhibitors, use of vasopressor or inotrope, fluid balance, blood pH, mean arterial pressure, heart rate, and respiratory compliance determined at baseline were considered in the matching process. In Ottolina (2022), age, sex, SAFA score, serum creatinine, CRP, and cardiovascular disease were used in adjusted odds analysis.

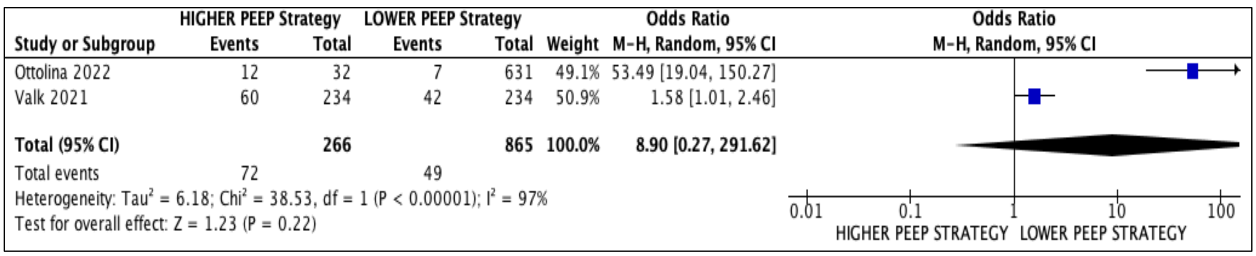


Figure 2. Forest plot for need for renal replacement therapy

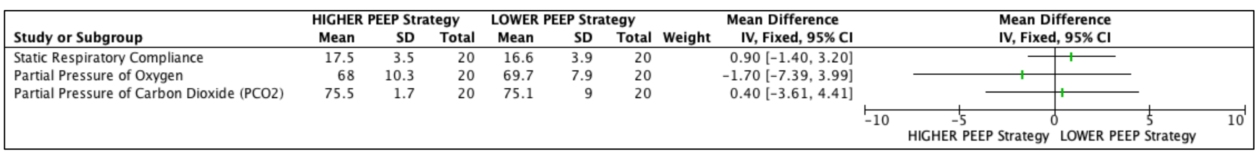


Figure 3. Difference in means for lung compliance at baseline (PEEP 5cmH_2O) and after five minutes at HIGHER PEEP (15 cm H2O) among mechanical ventilated patients with COVID-19 ARDS.

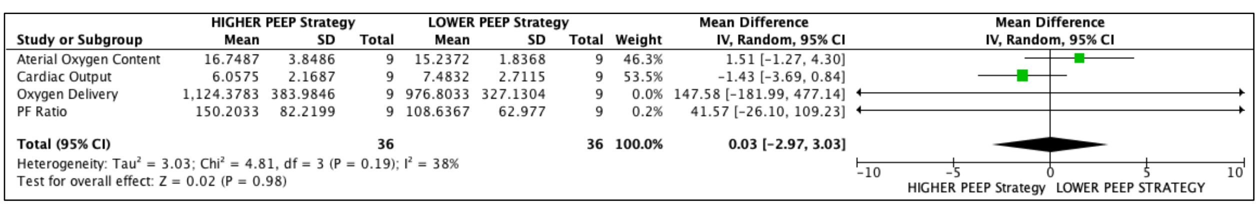


Figure 4. Forest plot for hemodynamic response to HIGHER PEEP strategy.