

ORIGINAL RESEARCH

Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

Yehuda Tri Nugroho Supranoto^{⊠*}, I Made Putra Wira Negara*

Article Info : Submitted : 19-06- 2022 Accepted : 21-03-2023 Published : 31-10-2023 <u>https://doi.org/10.20961/s</u> oja.V3i2.62253

Authors' affiliations : *Faculty of Medicine, Universitas Jember, Jember, Indonesia ^{IM}Correspondence: yehuda.supranoto@gmail. <u>com</u>

ABSTRACT

Background: Different strategies of positive end-expiratory pressure (PEEP) in mechanical ventilation are crucial for patients with coronavirus disease 2019 (COVID-19)-associated acute respiratory distress syndrome (ARDS). PEEP acts as a "double-edged sword" for ARDS patients. PEEP could recover pulmonary atelectasis but can induce alveolar hyperinflation.

Objective: This review aimed to evaluate the effect of higher PEEP in patients with severe COVID-19-associated ARDS.

Method: This meta-analysis included randomized controlled trial (RCT) studies to assess the mortality rates, barotrauma events, and inflammatory mediators modulation due to higher PEEP strategies. The pooled effect of the mortality rates and barotrauma events were presented as risk ratios (RR) with 95% confidence of interval (CI) using random-effects model (REM) or fixed-effects model (FEM).

Results: We identified twelve RCTs comparing higher versus lower PEEP in ARDS patients. There was unsignificant result in overall mortality rates group [RR=0.94,95%CI(85,1.03),p=0.21] but not in mortality after positive response of oxygenation group [RR=0.88,95%CI(0.81,0.95),p=0.002] in higher PEEP group. In terms of patients without positive response of oxygenation, higher PEEP group had significantly higher mortality rates [RR=1.07,95%CI(1.00,1.15),p=0.06]. Higher PEEP significantly reduced the mortality rates in ARDS patients with PaO₂/FiO₂<150 mmHg [RR=0.867,95%CI(0.74,1.00),p=0.04] instead of patients with (PaO₂/FiO₂ moderate ARDS ≥150 mmHg) [RR=1.12. 95%CI(0.85,1.47), p=0.44]. There were no differences in overall barotrauma events [RR=1.03,95%CI(0.78,1.36),p=0.85] between higher and lower PEEP group. The use of higher and lower PEEP also contribute to the modulation of inflammatory mediators including TNF-α, IL-6, IL-1RA, and IL-8.

Conclusion: Higher PEEP could reduce the mortality of patients with ARDS who responded to the oxygenation. Higher PEEP does not increase the risk of overall barotrauma events. Higher PEEP can modulate the inflammatory mediators.

Keywords: ARDS, COVID-19; Meta-analysis; PEEP; Systematic review,

Copyright @ 2023 Authors. This is an open access article distributed under the terms of the Creative Commons Attribution- 4.0 International License (<u>https://creativecommons.org/licenses/by/4.0/</u>)

Medical Faculty of Universitas Sebelas Maret - PERDATIN Solo.



Yehuda Tri Nugroho Supranoto, I Made Putra Wira Negara Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome interfering the function of respiratory system that has a significant morbidity and mortality value¹. The use of mechanical ventilation in patients with impaired respiratory system due to ARDS may reduce mortality rates ². But, the mortality in mechanically ventilated patients with severe ARDS due to coronavirus disease 2019 (COVID-19) is still high in some developing countires strategies despite many new of protective lung ventilation. Those many approaches have been adopted to increase lung protection, one of which is ventilation improvement strategies, but despite these efforts, ARDS mortality remains high. Recent study from Ibarra-Estrada et al. in 2022, showed a huge benefit from the use of airway pressure release ventilation (APRV) with a relatively high Positive End-Expiratory Pressure (PEEP) in patients with severe ARDS due to COVID-19³. Three large studies using Randomized Controlled Trials (RCTs) study design were performed to assess whether higher PEEP could improve outcomes in patients with ARDS⁴. All those clinical trials conducted by administrating the

high PEEP found no improvement in patients with ARDS. However, other studies found that higher PEEP may provide an improvement condition or survival rate of patients with severe ARDS ^{4,5,6}.

High PEEP strategy can increase the ratio between partial pressure of oxygen with fraction of inspired oxygen (PaO2/FiO2) more significantly compared to low PEEP strategy. PEEP, of easy-to-implement one an intervention, is primarily used to prevent atelectasis and to correct hypoxemia caused by alveolar hypoventilation. A previous clinical research demonstrated that recruitment maneuvers with PEEP and subsequent maintenance of high levels of PEEP reversed alveolar collapse and improved oxygenation ^{4,7}. Another study showed better clinical outcomes with the routine use of low tidal volume but not with high ventilation PEEP in patients with ARDS. Recently, some clinical studies showed a high titrated PEEP strategies can reduce the mortality rates in patients with moderate to severe ARDS. A recent meta-analysis also showed that higher PEEP could improve survival in ARDS patients with PaO2/FiO2 less than 200mmHg. These findings suggest that a

SJA

higher PEEP should be used in patients who could potentially benefit from it 7,8 .

Despite all the findings about the benefit of high PEEP strategies, actually, it is also a double-edged sword when used in patients with mild to moderate and also sometimes in severe ARDS. PEEP can open collapsed alveoli and can also cause hyperinflation in the lungs. Therefore, higher PEEP may improve outcomes in collapsed lungs of patients with severe ARDS only⁸.

The application of PEEP prevents atelectrauma, as a result of cyclic crumble with some reopening of risky alveoli. Lamentably, PEEP can overdistend some non collapsed-alveoli, as PEEP will increase pressure inside the alveoli and therefore can make contributions to the development of ventilator associated lung injury^{1,8}.

Pulmonary barotrauma is a probably lifestyles-threatening trouble in sufferers on mechanical air flow. This is critical to prevent barotrauma for prolonged intervals as this can lead to sizeable morbidity and mortality in sufferers intubated within the extensive care unit. This condition mostly happened in patients with ARDS associated with severe COVID-19⁻³.

According to the findings from the research by Goligher, patients whose increased PEEP response to was followed by increased oxygenation, defined as a positive oxygenation response to PEEP, may have more benefit from higher PEEP levels. Thus, we speculated that PEEP could have different effects on clinical outcomes according to the nature of the clinical response to PEEP itself. We, therefore performed this systematic review and meta-analysis procedures to determine whether higher PEEP strategies further improves survival among specific subgroups of ARDS or ARDS related severe COVID-19 patients who exhibit increased oxygenation in the response to higher PEEP^{1,8}.

METHODS

This review was conducted adhering guideline from the Preferred **Reporting Items for Systematic Reviews** and Meta-Analyses (PRISMA). This review article's protocol has been registered in International the Register Prospective of **Systematic Reviews** (PROSPERO) with the registration number protocol CRD42022329519. The following criteria were considered for study eligibility were described in Table 1.



Tabel 1. Description of PICOS Targeted by the Systematic Review and Meta-Analysis.

Questions	Description										
Population	Mechanically ventilated, adult patients with ARDS or ARDS-										
	related COVID-19										
Intervention	Higher PEEP, above what is needed for oxygenation goals										
Comparation	Lower PEEP, titrated to oxygenation goals										
Outcome	1. Mortality (7 days, 28 days, 60 days, 180 days,										
	Hospital, ICU)										
	2. Barotrauma events										
	3. Inflammatory mediator alterations										
Study Design	Randomized Controlled Trial Studies										

Type of Studies

The type of studies that included in this review are original research or research report conducted with a population of patients with ARDS. Review articles including narrative reviews, systematic reviews with or without meta-analysis, non-comparative studies, in vitro studies, technical reports, editor's responses, scientific research protocols, posters, and conference abstracts were excluded. Articles that can not be accessed, irrelevant themes, and non-English are also excluded. We did not limit the year of publication for our included studies but only for the supporting articles, we selectively used articles from the last 5 years of publication.

Samples

The population in this study were patients with severe ARDS or low level

of PaO₂/FiO₂. Patients with other pulmonary diseases were excluded.

Outcomes

The outcomes provided by this review were (i) Mortality rates, (ii) barotrauma events and (iii) alteration of inflammatory mediators due to PEEP higher/lower strategies. Confirmed mortality was determined by overall mortality, mortality-based on time of follow up (7, 28, 60, 180 days), location (hospital and ICU) with or without positive oxygen response to PEEP, and ARDS severity classified by the level of PaO₂/FiO₂.

Index Test

Studies evaluating the mortality, barotrauma events, and alteration of inflammatory mediators after high PEEP intervention, were included. Studies without those outcome were excluded.



Reference Standard

The reference standard was randomized controlled trial studies performed by qualified professionals by evaluating the effect of high PEEP strategies on mortality rates and inflammatory mediators in patients with acute respiratory distress syndrome (ARDS).

Data Sources and Search

А literature search was conducted using several electronic databases including PubMed, ScienceDirect, Cochrane Library, and Google Scholar. The search processes was carried out until May 2022. The keywords used in the electronic database were described using Boolean operators. All studies from this electronic database are stored in the online software Rayyan.ai.

Study Selection

After duplicates removal. retrieved articles were screened based on their topics and titles also abstracts by two independent reviewers (YTNS, and IMPWN). Potentially eligible full-text articles were assessed using the eligibility criterias described in previous explainations. Any emerging discrepancies were discussed by consensus among the review team. The

studies selection process was presented and recorded in the PRISMA flow diagram.

Data Extraction and Analysis

Data from included studies were extracted and stored in Microsoft Excel 2016. The following data were recorded: author and year of published, country, study design, sample size, ARDS severity, methods of PEEP selection, PEEP (cmH₂O),mortality event and alteration assessment, of inflammatory markers. All statistical test for the primary outcomes was conducted using Review Manager (RevMan) v5.3.

Risk of Bias Assessment

Two reviewers (YTNS and IMPWN) independently assessed the risk of bias in individual studies based on the Cochrane Risk of Bias 2 tool (RoB 2 Tool), which included several domains such randomization as sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment. incomplete outcome data, selective reporting, and other sources of bias. These studies graded as low risk, high risk, or unclear risk. Conflicts were resolved by discussion with those 2 reviewers (YTNS and IMPWN).



Quantitative Data Synthesis (Metaanalysis)

Risk ratio (RR) with the confidence interval (CI) of 95% were calculated in this study. To determine the pooled effect size, either random-effect model (REM) or fixed-effect model (FEM) of forest plot was used based on the heterogeneity level. REM was used included when the studies were considered heterogenous (high variability in studies' outcome results), indicated by an I^2 value higher than 50%. Otherwise, we used FEM forest plot.

Risk of Bias Across Studies (Publication Bias)

Subjective analysis of publication bias using funnel plots by Review generated Manager (RevMan) v5.3. The asymmetric shape of the funnel plot indicates the presence of publication bias. while the symmetrical shape of the funnel plot indicates the absence of publication bias.

Sensitivity Analysis

When the authors encountered an unclear decision due to conflicting results from some of the included studies, a sensitivity analysis was planned by repeating the meta-analysis, attempting to exclude studies to identify which studies were confounders.

RESULT

Study identification and selection

A PRISMA 2020 flow chart presenting the overall studies selection processes is demonstrated in Figure 1. PRISMA 2020 is the main checklist and guideline used for this systematic review and meta-analysis. Of 927 articles compiled during the initial search from four databases, 56 articles were duplications, 814 articles were excluded due to irrelevant topics or did not describe the use of PEEP for ARDS and ARDS associated severe COVID-19.

From all 57 articles included from the first screening, 42 articles were excluded since those were not retrieved due to meet the exclusion criterias of study design. Those articles are not randomized controlled trials type of studies. In addition, from 15 articles included in the second screening, three articles were excluded because they were described as unaccessible full-text articles. As a final decision, twelve studies were eligible enough to be used analyzed in qualitative and and quantitative way in the systematic review and meta-analysis methods.

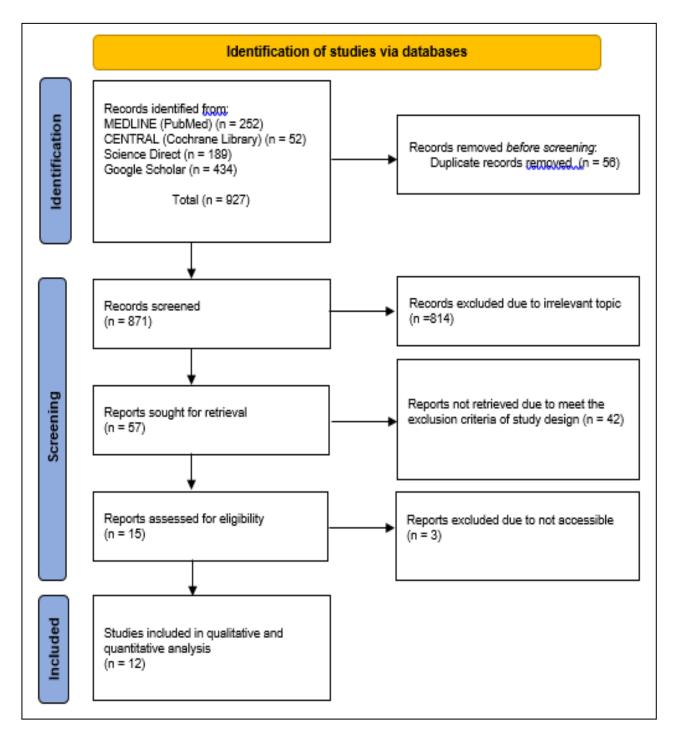


Figure 1. PRISMA Flow Diagram



Characteristic of Included Studies

The full details of explaination or extracted data from the twelve included studies were provided in the Table 1, Table 2, and Table 3. The subject of these studies patients with ARDS who received the intervention of higher PEEP or Lower PEEP strategies. We focused on mortality, barotrauma events, and inflammatory mediator alteration outcomes for indicating the potential of higher PEEP strategies for ARDS patients. All included studies used various severity ARDS based on the level of PaO₂/FiO₂.

Of the 12 studies included in the qualitative analysis, there were different types of strategies when using the high PEEP or Low PEEP. Various tidal volume and level of PEEP (cmH₂O) are presented on the Table 1. The mortality and barotrauma events outcome are detailed in the Table 2 which can describe whether higher PEEP can be favourable in patients with ARDS. In the Table 3 we can analysed that mechanical ventilation has the portion to alter the mediators inflammatory including proinflammatory cytokines such as Tumor necrosis factor (TNF), and Interleukin (IL). Higher PEEP also can modulate the activity of immune cells

especially the polimorphonuclear cells (PMN). It can also alter some pulmonary or bronchoalveolar protein markers such as surfactant protein D and intercellular adhesion molecule 1.

Risk of Bias in Individual Studies

We critically assessed the quality and risk of bias of each individual studies using Risk of Bias 2 Tool (RoB 2 Tool) recommended by Cochrane Handbook for Systematic Review of Intervention (Figure 2). Most of the studies had adequate information regarding the bias domains' judgement, leading to low and moderate risk of bias.. In overall risk of bias, majority of included studies show moderate risk of bias followed with low risk of bias. We compared the pooled effect size of Higher PEEP and Lower PEEP strategies in patients with ARDS in terms of mortality outcome and barotrauma event outcome. We used the number of outcomes event for each study that compared the higher and lower PEEP group. A moderate pooled effect size of mortality rates-based on time of follow up between higher PEEP group and lower PEEP group is showed in the Figure 3. The result indicated that there were no significant difference in overall mortality events between both group eventhoguh the trends is favourable to the higher PEEP group [RR = 0.94, 95% CI (85, 1.03), p = 0.21, $I^2 = 51\%$].



				14		ciudea Studies		
Amato, 1998Brazil29/24HP: 112 \pm 51 LP: 134 \pm 67VT maintained \leq 6ml/kg body weight Pressure control ventilation 40 cmH ₂ O PEEP at Pflex + 2 cmH ₂ O Pulmo recruitment maneuversVT set to 12 ml/Kg body weight Volume control ventilation Auto-PEEP set to O2 goalsWith positive oxygenation response to PEEP Mithout positive oxygenation response to PEEP at 916x + 2 cmH ₂ O Pulmo recruitment maneuversVT set to Pplat < UIP or <5- Brower, 2004 ¹¹ Without positive utilation28 days Hospital ICUBrower, 2004 ¹¹ UK276/273HP: 220 \pm 89 LP: 168 \pm 66 weight PEEP incremental start more than 12 cmH ₂ O, Recruitment maneuvers in the first 80 patients ARDSNetVT set to 9-11 ml/kgWith positive oxygenation oxygenation response to PEEP28 days Hospital ICUVillar, 2006 ¹² Spanish50/45HP: 139 \pm 43VT set to 5-8 ml/kg body VT set to 5-8 ml/kg bodyVT set to 9-11 ml/kgWith positive oxygenation oxygenation28 days Hospital ICU	Author, Year	Size		severity	Intervent	Oxygenation Response to	Mortality Outcome	
LP: 134 ± 67 body weight Pressure control ventilation < 40 cmH2Obody weight Volume control 			(II, HF/LF)		Higher PEEP	Lower PEEP		Assessments
LP: 142 ± 56 8 ml/kg body weight PEEP at Pflex + 2-3 cmH2OPaCO2 35-40 mmHg PEEP incremental 3- 15 cmH2Ooxygenation response to PEEPHospital ICUBrower, 2004 ¹¹ UK276/273HP: 220 ± 89 LP: 168 ± 66 VT set to 6 ml/kg body weight PEEP incremental start more than 12 cmH2O, Recruitment maneuvers in the first 80 patients ARDSNetLower PEEP/FiO2 but with set of Pplat < 30 cmH2OWithout positive oxygenation response to PEEP60 days Hospital ICUVillar, 2006 ¹² Spanish50/45HP: 139 ± 43 VT set to 5-8 ml/kg bodyVT set to 9-11 ml/kgWith positive oxygenation 28 days	Amato, 1998 ⁹	Brazil	29/24		body weight Pressure control ventilation < 40 cmH ₂ O PEEP at Pflex + 2 cmH ₂ O Pulmo recruitment	body weight Volume control ventilation Auto-PEEP set to O ₂		Hospital
LP: 168 ± 66 weight PEEP incremental start more than 12 cmH_2O, Recruitment maneuvers in the first 80 patients ARDSNetwith set of Pplat < 30 cmH_2Ooxygenation response to HOSPITAL PEEPHospital ICUVillar, 2006^{12}Spanish50/45HP: 139 ± 43 VT set to 5-8 ml/kg bodyVT set to 9-11 ml/kgWith positive oxygenation28 days	Ranieri, 1999 ¹⁰	Canada	18/19		8 ml/kg body weight	PaCO ₂ 35-40 mmHg PEEP incremental 3-	oxygenation response to	Hospital
	Brower, 2004 ¹¹	UK	276/273		weight PEEP incremental start more than 12 cmH ₂ O, Recruitment maneuvers in the first 80 patients	with set of Pplat < 30	oxygenation response to	Hospital
	Villar, 2006 ¹²	Spanish	50/45		ę .	e		•

Table 2. Characteristics of Included Studies

Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS



				Pressure control ventilation PEEP at Pflex $+ 2 \text{ cmH}_2\text{O}$	$\begin{array}{l} \text{PEEP} \geq 5 \text{ cmH}_2\text{O to} \\ \text{O}_2 \text{ goals} \end{array}$		ICU
Meade, 2008 ¹³	3 Countries	475/508	HP: 145 ± 48 LP: 144 ± 50	VT set to 6 ml/kg body weight High PEEP/FiO ² with Pplat < 40 cmH ₂ O Pulmo recruitment maneuvers	Lower PEEP/FiO ₂ Pplat < 30 cmH ₂ O	With positive oxygenation response to PEEP	28 days 60 days Hospital ICU
Mercat, 2008 ¹⁴	France	385/302	HP: 144 ± 58 LP: 143 ± 57	PEEP titrated incremental to Pplat 30 cmH ₂ O	PEEP maintained 5-9 cmH ₂ O to meet O ₂ goals	With positive oxygenation response to PEEP	28 days 60 days Hospital ICU
Talmor, 2008 ¹⁵	USA	30/31	HP: 147 ± 56 LP: 145 ± 57	PEEP used to keep end- expiratory TPP within 0- 10cmH ₂ O Inspiratory TPP < 25 cmH ₂ O Esophageal balloon implemented	Lower PEEP/FiO ₂	With positive oxygenation response to PEEP	28 days 180 days Hospital ICU
Huh, 2009 ¹⁶	Korea	30/27	HP: 115 ± 8.5 LP: 111 ± 6.3	High PEEP/FiO ₂ with Saturation decrease > 2% and drop of static complicance	Lower PEEP/FiO ₂	With positive oxygenation response to PEEP	28 days 60 days Hospital ICU
Hodgson, 2011 ¹⁷	Australia	10/10	HP: 155 ± 8 LP: 149 ± 12	Stepwise recruitment with PEEP incremental to 30 cmH ₂ O	Lower PEEP/FiO ₂	With positive oxygenation response to PEEP	7 days Hospital ICU

Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS



				After that decremental PEEP to desaturation of O ₂			
Kacmarek, 2016 ¹⁸	USA	99/101	HP: 133.4 ± 37.8 LP: 128.3 ± 30.5	Stepwise recruitment with PEEP incremental to 35-45 cmH ₂ O After that decremental PEEP to best dynamic compliance	Lower PEEP/FiO ₂	With positive oxygenation response to PEEP	28 days 60 days Hospital ICU
Calvalcanti, 2017 ⁷	9 Countries	501/509	HP: 119.5 ± 43.5 LP: 117.2 ± 41.9	Maximum alveolar recruitment by lung compliance + 2 cmH ₂ O Pulmo recruitment maneuvers	Lower PEEP/FiO ₂	Without positive oxygenation response to PEEP	28 days 180 days Hospital ICU
Ibarra-Estrada, 2022 ³	USA	45/45	HP: 140 ± 42 LP: 149 ± 50	VT maintained between 4 to 6 ml/kg body weight P-high = Pplat < 30 cmH ₂ O	Lower PEEP/FiO ₂ but with set of Pplat < 30 cmH ₂ O	With positive oxygenation response to PEEP	28 days Hospital ICU

HP, Higher PEEP group; LP, Lower PEEP group; VT, Tidal Volume; Plat, Plateu of Pressure; Pflex, Pressure inflection point

Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS



Author, Year			Mortality F	lates-based	d on Time	of Follow	Up		Morta	lity Rates-	based on]	Location	Barotra	uma Events
	7	days	28	days	60	days	180) days	In H	ospital	In	ICU		
	HP	LP	HP	LP	HP	LP	HP	LP	HP	LP	HP	LP	HP	LP
Amato, 1998 ⁹			11/29	17/24					13/29	17/24	11/29	17/24		
Ranieri, 1999 ¹⁰			7/8	11/19					7/18	11/19	7/18	11/19	2/29	10/24
Brower, 2004 ¹¹					69/276	75/273			76/276	68/273	76/276	68/273		
Villar, 2006 ¹²			16/50	24/45					16/50	24/45	16/50	24/45	60/276	27/273
Meade, 2008 ¹³			135/475	164/508	173/475	205/508			173/475	205/508	145/475	178/508	2/50	4/45
Mercat, 2008 ¹⁴			107/385	119/382	138/385	151/382			136/385	149/382	136/385	149/382	53/475	46/508
Talmor, 2008 ¹⁵			5/30	12/31			8/30	14/31	5/30	12/31	5/30	12/31	26/385	22/382
Huh, 2009 ¹⁶			12/30	9/27	14/30	15/27			14/30	15/27	14/30	13/27		
Hodgson, 2011 ¹⁷	3/10	2/10							3/10	2/10	3/10	2/10	3/30	3/27
Kacmarek, 2016 ¹⁸			22/99	27/101	28/99	33/101			29/99	35/101	25/99	30/101	0/10	0/10
Calvalcanti, 2017 ⁷			277/501	251/509			327/501	305/509	319/500	301/508	303/500	284/509		
Ibarra-Estrada, 2022 ³			35/45	27/45					35/45	27/45	35/45	27/45	28/501	8/509

Table 3. Mortality and Barotrauma Outcomes After PEEP Intervention



Table 4. Pro-Inflammatory Cytokines, Immune Cells, and Pulmonary Protein Markers Alteration After PEEP Intervention

Author, year		tory cytokines EEP intervention	alteration	ne cells after PEEP rention	Pulmonary protein marker alteration after PEEP Intervention		
	HP	LP	HP	LP	HP	LP	
Ranieri et al., 1999		Soluble TNF- $\alpha sR55\uparrow$ Soluble TNF- $\alpha sR75\uparrow$ IL-1RA \uparrow , IL-1 $\beta\uparrow$, TNF- $\alpha\uparrow$, IL-8 \uparrow , IL-6 \uparrow	PMN↓	PMN ↑			
Brower et al., 2004	IL-6 ↓	IL-6 ↓			Surfactan protein D ↑, intercellular adhesion molecule 1↑	Surfactan protein D ↑, intercellular adhesion molecule 1↑	
Hodgson et al., 2011	IL-8 ↓, TNF-α ↓	IL-8 \uparrow , TNF- α \uparrow					

TNF, Tumor Necrosis Factor; IL-1Ra; Interleukin 1 Receptor Antagonist; PMN, Polimorphonuclear Cells

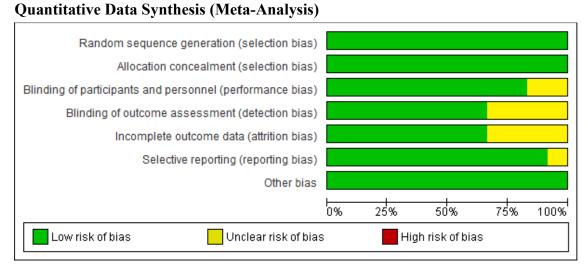


Figure 2. Risk of Bias Assessment based on Risk of Bias 2 (RoB 2) Tools (Recommended by Cochrane Handbook for Systematic Review of Intervention)



Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

Higher PEEP Lower PEEP Risk Ratio Risk Ratio Study or Subgroup Events Total Weight M.H., Random, 95% CI M.H., Random, 95% CI Hodgson et al, 2011 3 10 2 10 0.4% 1.50 [0.32, 7.14] Subtotal (95% CI) 10 10 0.4% 1.50 [0.32, 7.14] Image: Comparison of the compariso		Higher PEEP				Risk Ratio	Risk Ratio
1.1.1 Mortality in 7 days Hodgson et al., 2011 3 10 2 10 0.4%, 1.50 [0.32, 7.14] Subtotal (95% CI) 10 10 0.4%, 1.50 [0.32, 7.14] Total events 3 2 Heterogenelly, Not applicable Testfor overall effect Z = 0.51 (P = 0.61) 1.1.2 Mortality in 28 days Arrato et al., 1998 11 29 17 24 2.7%, 0.54 [0.31, 0.91] Calvalcanti et al., 2007 277 501 251 509 12.4%, 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7%, 1.20 [0.60, 2.39] Ibara-Estraa et al., 2012 35 45 27 45 6.5%, 1.30 [0.97, 1.72] Kacmarek et al., 2018 135 475 164 508 9.6%, 0.88 [0.73, 1.06] Meade et al., 2008 107 385 119 382 8.5%, 0.89 [0.74, 1.06] 110 Total events 627 661 104 105, 0.23, 0.98		-			Veinht		
Hodgson et al., 2011 3 10 2 10 0.4% 1.50 [0.32, 7.14] Subtotal (95% CI) 10 10 0.4% 1.50 [0.32, 7.14] Total events 3 2 Heterogeneity. Not applicable Test for overall effect $Z = 0.51$ (P = 0.61) 1.12 Mortality in 28 days Arrato et al., 1998 11 29 17 24 2.7% 0.54 [0.31, 0.91] Cavacianti et al., 2017 27 501 251 509 12.4% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] Ibara-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 31% 0.83 [0.51, 1.36] Mecade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Mecade et al., 2008 107 385 119 382 8.5% 0.98 [0.72, 1.11] Ranieri et al., 2008 16 50 24 45 3.1% 0.67 [0.34, 1.35] Talmor et al., 2008 16 50 24 45 3.1% 0.68 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity. Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect $Z = 1.33$ (P = 0.18) 1.13 Mortality in 60 days Brower et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.12] Mecade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.10] Mecade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mecade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mecade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mecade et al., 2008 133 38 151 382 9.9% 0.84 [0.50, 1.40] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity. Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); P = 0% Test for overall effect $Z = 1.48$ (P = 0.14) 1.14 Mortality in 180 days		Lionto To	Total Events	Total	reight	in the number of the second seco	in the trained of the second sec
Subtotal (95% Cl) 10 10 0.4% 1.50 [0.32, 7.14] Total events 3 2 Heterogeneity. Not applicable Test for overall effect. Z = 0.51 (P = 0.61) 1.12 Mortality in 28 days Armato et al., 1998 11 29 17 24 2.7% 0.54 [0.31, 0.91] Calvalcanti et al., 2017 277 501 251 509 1.24% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] Ibarra-Estrada et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Meade et al., 2008 135 475 164 508 0.88 [0.73, 1.06] 14 Merca tet al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Taimor et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2008 16 50 24 45 3.1% 0.60 [0.37, 0.38] Subtotal (95% Cl) 1662 1691 50.5% 0.89 [0.74, 1.06] 104		3	10 2	10	0.4%	1 50 10 32 7 1 41	
Heterogeneity: Not applicable Test for overall effect $Z = 0.51$ (P = 0.61) 1.1.2 Mortality in 28 days Amato et al., 1998 11 29 17 24 2.7% 0.54 [0.31, 0.91] Cabalcanit et al., 2017 277 501 251 509 12.4% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] Ibarra-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 31% 0.83 [0.51, 1.36] Merca et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Merca et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Talmor et al., 2008 10 7 385 119 382 8.5% 0.89 [0.72, 1.11] Talmor et al., 2008 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% Ct) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity: Tau ² = 0.04; Ch ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2008 173 475 205 508 10.8% 0.87 [0.57, 1.32] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% Ct) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau ² = 0.00; Ch ² = 1.92, df = 4 (P = 0.75); P = 0% Test for overall effect $Z = 1.48$ (P = 0.14) 1.1.4 Mortality in 180 days	(95% CI)		10				
Test for overall effect $Z = 0.51$ (P = 0.61) 1.1.2 Mortality in 28 days Amato et al., 1998 11 29 17 24 2.7% 0.54 (0.31, 0.91) Calvalcanti et al., 2017 277 501 251 509 12.4% 1.12 [1.00, 1.26] Hun et al., 2029 12 30 9 27 1.7% 1.20 [0.60, 2.39] Ibarra-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Merca et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Merca et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Merca et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Talimor et al., 2008 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity. Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 128 99 33 101 3.9% 0.87 [0.57, 1.32] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Merca et al., 2008 128 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity. Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); P = 0% Test for overall effect $Z = 1.48$ (P = 0.14) 1.14 Mortality in 180 days			2				
1.1.2 Mortality in 28 days Amato et al., 1988 11 29 17 24 2.7% 0.54 [0.31, 0.91] Calvaicanti et al., 2017 277 501 251 509 12.4% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] bara-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 31% 0.83 [0.51, 1.36] Meade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Merca tet al., 2008 107 385 119 382 8.5% 0.89 [0.74, 1.05] Taimore tal., 2008 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] 11 Taimore tal., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] 14 Huh et al., 2004 76							
Amato et al., 1998 11 29 17 24 2.7% 0.54 [0.31, 0.91] Calvalcanti et al., 2017 277 501 251 509 12.4% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] barra-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Merade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Mercat et al., 2008 137 385 119 382 8.5% 0.89 [0.72, 1.11] Ranieri et al., 1999 7 18 11 19 1.7% 0.67 [0.34, 1.35] Talmor et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2006 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% Cl) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% Cl) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect Z = 1.48 (P = 0.14) 1.14 Mortality in 180 days	verall effect: Z = 0.51	i (P = 0.61)					
Calvalcanti et al., 2017 277 501 251 509 12.4% 1.12 [1.00, 1.26] Huh et al., 2009 12 30 9 27 1.7% 1.20 [0.60, 2.39] barra-Estrada et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Meade et al., 2008 135 475 164 508 9.6% 0.89 [0.72, 1.11] Ranieri et al., 2008 135 475 164 508 9.6% 0.89 [0.72, 1.11] Ranieri et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Ranieri et al., 2008 5 30 12 31 1.0% 0.43 [0.71, 1.07] Villar et al., 2006 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] 111 Total events 627 661 661 64% 111 [0.83, 1.46] 114 Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] 144 Kacmarek et al., 2008	tality in 28 days						
Huh et al., 2009 12 30 9 27 1.7% $1.20[0.60, 2.39]$ Ibarra-Estrada et al., 2022 35 45 27 45 6.5% $1.30[0.97, 1.72]$ Kacmarek et al., 2016 22 99 27 101 3.1% $0.83[0.51, 1.36]$ Meade et al., 2008 135 475 164 508 9.6% $0.88[0.73, 1.06]$ Mercat et al., 2008 107 385 119 382 8.5% $0.89[0.72, 1.11]$ Ranieri et al., 2008 5 30 12 31 1.0% $0.43[0.17, 1.07]$ Villar et al., 2008 5 30 12 31 1.0% $0.43[0.17, 0.98]$ Subtotal (95% Cl) 1662 1691 50.5\% $0.89[0.74, 1.06]$ Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9(P = 0.003); P = 64% Test for overall effect Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] 455 Huh et al., 2008 173	al., 1998	11	29 17	24	2.7%	0.54 [0.31, 0.91]	
Ibarra-Estrada et al., 2022 35 45 27 45 6.5% 1.30 [0.97, 1.72] Kacmarek et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Meade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Mercat et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Ranieri et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2006 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] \bullet Total events 627 661 \bullet \bullet \bullet \bullet Heterogeneity. Tau ² = 0.04; Ch ² = 24.96, df = 9 (P = 0.003); P = 64% \bullet \bullet \bullet \bullet \bullet \bullet Huh et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] \bullet \bullet	nti et al., 2017	277 5	501 251	509	12.4%	1.12 [1.00, 1.26]	
Kacmarek et al., 2016 22 99 27 101 3.1% 0.83 [0.51, 1.36] Meade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Mercat et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Ranieri et al., 1999 7 18 11 19 1.7% 0.67 [0.34, 1.35] Talmor et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2006 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity. Tau [*] = 0.04; Chi [*] = 24.96, df = 9 (P = 0.003); P = 64% Testfor overall effect Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] \bullet Huh et al., 2009 14 30 15 27 2.9% 0.94 [0.50, 1.40] \bullet Kacmarek et al., 2016 28 </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Meade et al., 2008 135 475 164 508 9.6% 0.88 [0.73, 1.06] Mercat et al., 2008 107 385 119 382 8.5% 0.89 [0.72, 1.11] Ranieri et al., 1999 7 18 11 19 1.7% 0.67 [0.34, 1.35] Talmor et al., 2008 5 30 12 31 1.0% 0.43 [0.17, 1.07] Villar et al., 2006 16 50 24 45 3.1% 0.60 [0.37, 0.98] Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] • Total events 627 661 • • • • Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% • • • • Test for overall effect Z = 1.33 (P = 0.18) • • • • • Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] • Kacmarek et al., 2016 28 99 33 101 3.9% 0.97 [0.57, 1.32] • Meade et al., 2008 173 475				45			⊢ •−−
Mercat et al., 2008 107 385 119 382 8.5% 0.89 $[0.72, 1.11]$ Ranieri et al., 1999 7 18 11 19 1.7% 0.67 $[0.34, 1.35]$ Talmor et al., 2008 5 30 12 31 1.0% 0.43 $[0.72, 1.11]$ Villar et al., 2006 16 50 24 45 3.1% 0.60 $[0.37, 0.98]$ Subtotal (95% CI) 1662 1691 50.5% 0.89 $[0.74, 1.06]$ Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); I ² = 64% Test for overall effect: Z = 1.33 (P = 0.18) 111 $[0.83, 1.46]$ 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] 1.4 Kacmarek et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] 1.6 Mercat et al., 2008 138 385 151 38							
Ranieri et al., 1999 7 18 11 19 1.7% 0.67 $[0.34, 1.35]$ Talmor et al., 2008 5 30 12 31 1.0% 0.43 $[0.17, 1.07]$ Villar et al., 2006 16 50 24 45 3.1% 0.60 $[0.37, 0.98]$ Subtotal (95% CI) 1662 1691 50.5% 0.89 $[0.74, 1.06]$ Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect: Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.90 [0.77, 1.06] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.76, 1.09] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] 93 Subt							+
Taimor et al., 2008 5 30 12 31 1.0% 0.43 $[0.17, 1.07]$ Villar et al., 2006 16 50 24 45 3.1% 0.60 $[0.37, 0.98]$ Subtotal (95% Cl) 1662 1691 50.5% 0.89 $[0.74, 1.06]$ Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64% Test for overall effect: Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.90 [0.77, 1.06] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.76, 1.09] Subtotal (95% Cl) 1265 1291 34.2% 0.92 [0.83, 1.03] \bullet Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); P = 0% Test for overall effect: Z = 1.48 (P = 0.14) \bullet							+
Villar et al., 2006165024453.1%0.60 [0.37, 0.98]Subtotal (95% Cl)1662169150.5%0.89 [0.74, 1.06]Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); P = 64%Test for overall effect $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 20047627668273 6.7% 1.11 [0.83, 1.46]Huh et al., 2009143015272.9%0.84 [0.50, 1.40]Kacmarek et al., 20162899331013.9%0.87 [0.57, 1.32]Meade et al., 200817347520550810.8%0.90 [0.77, 1.06]Subtotal (95% Cl)1265129134.2%0.92 [0.83, 1.03]Total events429472Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); P = 0%Test for overall effect $Z = 1.48$ (P = 0.14) 1.1.4 Mortality in 180 days							
Subtotal (95% CI) 1662 1691 50.5% 0.89 [0.74, 1.06] Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); I ² = 64% Test for overall effect: Z = 1.33 (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] • Total events 429 472 472 472 472 472 472 472 472 472 472 474 474 474 474 474 4	•			31	1.0%		•
Total events 627 661 Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); I ² = 64% Test for overall effect: $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] \bullet Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: $Z = 1.48$ (P = 0.14) \bullet 1.1.4 Mortality in 180 days \bullet \bullet \bullet \bullet \bullet \bullet							
Heterogeneity: Tau ² = 0.04; Chi ² = 24.96, df = 9 (P = 0.003); I ² = 64% Test for overall effect: $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: $Z = 1.48$ (P = 0.14) 1.1.4 Mortality in 180 days	(95% CI)		1662	1691	50.5%	0.89 [0.74, 1.06]	•
Test for overall effect: $Z = 1.33$ (P = 0.18) 1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] • Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% • • Test for overall effect: $Z = 1.48$ (P = 0.14) • • • 1.1.4 Mortality in 180 days • • • •							
1.1.3 Mortality in 60 days Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] • Total events 429 472 Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0% • • Test for overall effect: Z = 1.48 (P = 0.14) • • •			df = 9 (P = 0.0	03); i² = 64	4%		
Brower et al., 2004 76 276 68 273 6.7% 1.11 [0.83, 1.46] Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days	verall effect: Z = 1.33	3 (P = 0.18)					
Huh et al., 2009 14 30 15 27 2.9% 0.84 [0.50, 1.40] Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] • Total events 429 472 + + + + Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: Z = 1.48 (P = 0.14) + 1.1.4 Mortality in 180 days - - - -	tality in 60 days						
Kacmarek et al., 2016 28 99 33 101 3.9% 0.87 [0.57, 1.32] Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] ● Total events 429 472 + + + + Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0% Test for overall effect: Z = 1.48 (P = 0.14) + + 1.1.4 Mortality in 180 days - - - + +	t al., 2004	76 2	276 68	273		1.11 [0.83, 1.46]	
Meade et al., 2008 173 475 205 508 10.8% 0.90 [0.77, 1.06] Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] ● Total events 429 472 Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days							
Mercat et al., 2008 138 385 151 382 9.9% 0.91 [0.76, 1.09] Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days							
Subtotal (95% CI) 1265 1291 34.2% 0.92 [0.83, 1.03] Total events 429 472 Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days							
Total events 429 472 Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 4 (P = 0.75); I² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days							
Heterogeneity: Tau ² = 0.00; Chi ² = 1.92, df = 4 (P = 0.75); I ² = 0% Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days				1291	34.2%	0.92 [0.83, 1.03]	•
Test for overall effect: Z = 1.48 (P = 0.14) 1.1.4 Mortality in 180 days							
			11 = 4 (P = 0.75), ~= 0%			
Samanaana otan, 2011 - 321 - 301 - 303 - 303 - 13,370 - 1,03 [0,33, 1,20]		377 5	501 205	500	12.204	1 00 00 00 1 201	
Talmoretal., 2008 8 30 14 31 1.7% 0.59 [0.29, 1.20]							
Subtotal (95% CI) 531 540 14.9% 0.89 [0.50, 1.57]							
Total events 335 319					1 110 10	eres forest up 1	
Heterogeneity: Tau ² = 0.12; Chi ² = 2.85, df = 1 (P = 0.09); l ² = 65%): ≧= 65%			
Test for overall effect: $Z = 0.40$ (P = 0.69)			n = 1 (1 = 0.00	/,1 = 00 /0			
Total (95% CI) 3468 3532 100.0% 0.94 [0.85, 1.03]	% CI)	34	3468	3532 1	00.0%	0.94 [0.85, 1.03]	•
Total events 1394 1454							Ť
				007): I P = 6	51%		
Test for everall effect 7 = 1.27 /P = 0.21			ω = τη γ = 0.				
Test for subgroup differences: Chi ² = 0.55, df = 3 (P = 0.91), I ² = 0%			5 df = 3 (P = 0	91) J ² = 0	%		Higher PEEP Lower PEEP

Figure 3. Forest Plot and Funnel Plot for Mortality Rates-Based on Time of Follow Up Between Higher PEEP Group and Lower PEEP Group



A pooled effect size of mortality rates-based on location whether in the hospital or specifically in the intensive care unit (ICU) between higher PEEP group and lower PEEP group is showed in the Figure 4. The result indicated the same as previous that there were no significant difference in overall mortality events based on the location of patients' death between both group eventhough the trends is favourable to the higher PEEP group [RR = 0.93, 95% CI (0.85, 1.02), p = 0.11, $I^2 = 51\%$].

	Higher F	EEP	Lower F	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 Mortality in Hospital							
Amato et al., 1998	13	29	17	24	2.7%	0.63 [0.39, 1.02]	
Brower et al., 2004	76	276	68	273	5.4%	1.11 [0.83, 1.46]	
Calvalcanti et al., 2017	319	500	301	508	10.2%	1.08 [0.98, 1.19]	++-
Hodgson et al., 2011	3	10	2	10	0.3%	1.50 [0.32, 7.14]	
Huh et al., 2009	14	30	15	27	2.4%	0.84 [0.50, 1.40]	
Ibarra-Estrada et al., 2022	35	45	27	45	5.3%	1.30 [0.97, 1.72]	
Kacmarek et al., 2016	29	99	35	101	3.4%	0.85 [0.56, 1.27]	
Meade et al., 2008	173	475	205	508	8.5%	0.90 [0.77, 1.06]	-++
Mercat et al., 2008	136	385	149	382	7.8%	0.91 [0.75, 1.09]	-++
Ranieri et al., 1999	7	18	11	19	1.4%	0.67 [0.34, 1.35]	
Talmor et al., 2008	5	30	12	31	0.9%	0.43 [0.17, 1.07]	•
Villar et al., 2006	16	50	24	45	2.6%	0.60 [0.37, 0.98]	
Subtotal (95% CI)		1947		1973	51.0%	0.93 [0.82, 1.05]	◆
Total events	826		866				
Heterogeneity: Tau ² = 0.02; •	Chi ² = 22.6	0, df = 1	11 (P = 0.0	02); I ² =	51%		
Test for overall effect: Z = 1.1							
1.2.2 Mortality in ICU Amato et al., 1998	11	29	17	24	2.3%	0.54 [0.31, 0.91]	
Brower et al., 2004	76	276	68	273	5.4%	1.11 [0.83, 1.46]	_ _
Calvalcanti et al., 2017	303	500	284	509	10.1%	1.09 [0.98, 1.21]	
Hodgson et al., 2011	3	10	2	10	0.3%	1.50 [0.32, 7.14]	
Huh et al., 2009	14	30	13	27	2.2%	0.97 [0.56, 1.68]	
Ibarra-Estrada et al., 2022	35	45	27	45	5.3%	1.30 [0.97, 1.72]	
Kacmarek et al., 2016	25	99	30	101	2.9%	0.85 [0.54, 1.34]	
Meade et al., 2008	145	475	178	508	7.9%	0.87 [0.73, 1.04]	
Mercat et al., 2008	136	385	149	382	7.8%	0.91 [0.75, 1.09]	-++
Ranieri et al., 1999	7	18	11	19	1.4%	0.67 [0.34, 1.35]	
Talmor et al., 2008	5	30	12	31	0.9%	0.43 [0.17, 1.07]	←
Villar et al., 2006	16	50	24	45	2.6%	0.60 [0.37, 0.98]	
Subtotal (95% CI)		1947		1974	49.0%	0.92 [0.80, 1.06]	◆
Total events	776		815				
Heterogeneity: Tau ² = 0.02; •	Chi ² = 24.8	7, df = 1	11 (P = 0.)	01); I² =	55%		
Test for overall effect: Z = 1.1	17 (P = 0.2	4)					
Total (95% CI)		3894		3947	100.0%	0.93 [0.85, 1.02]	•
Total events	1602		1681				
Heterogeneity: Tau ² = 0.02;			23 (P = 0.)	002); I ř :	= 51%		0.2 0.5 1 2 5
Test for overall effect: Z = 1.8	60 (P = 0.1	1)					Higher PEEP Lower PEEP
Test for subgroup difference	es: Chi ² = 0	.01, df=	= 1 (P = 0,	.93), l ² =	0%		ingrotteet conviteet

Figure 4. Forest Plot for Mortality Rates-Based on Location Between Higher PEEP

Group and Lower PEEP Group



Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

We conduct the sensitivity analysis and recreated the forest plot classified by the response of oxygenation after PEEP intervention. In the figure 5, there were totally significant for the outcome of mortality-based on time to follow up with positive response of oxygenation to PEEP in the favour of higher PEEP group compared to the lower PEEP group [RR = 0.88, 95% CI (0.81, 0.95), p = 0.002, I^2 = 27%).

	Higher F		Lower			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.3.1 Mortality in 7 days							
Hodgson et al., 2011 Subtotal (95% CI)	3	10 10	2	10 10	0.2% 0.2%	1.50 [0.32, 7.14] 1.50 [0.32, 7.14]	
Total events	3		2				
Heterogeneity: Not applicab	le						
Test for overall effect: Z = 0.6	51 (P = 0.6	1)					
1.3.2 Mortality in 28 days							
Amato et al., 1998	11	29	17	24	2.3%	0.54 [0.31, 0.91]	
Huh et al., 2009	12	30	9	27	1.2%	1.20 [0.60, 2.39]	
Ibarra-Estrada et al., 2022	35	45	27	45	3.3%	1.30 [0.97, 1.72]	
Kacmarek et al., 2016	22	99	27	101	3.3%	0.83 [0.51, 1.36]	
Meade et al., 2008	135	475	164	508	19.5%	0.88 [0.73, 1.06]	+
Mercatietial., 2008	107	385	119	382	14.7%	0.89 [0.72, 1.11]	
Talmor et al., 2008	5	30	12	31	1.5%	0.43 [0.17, 1.07]	•
Villar et al., 2006	16	50	24	45	3.1%	0.60 [0.37, 0.98]	
Subtotal (95% CI)		1143		1163	48.9%	0.87 [0.77, 0.98]	•
Total events	343		399				
Heterogeneity: Chi ² = 16.16, Test for overall effect: Z = 2.3			I²= 57%				
1.3.3 Mortality in 60 days							
Huh et al., 2009	14	30	15	27	1.9%	0.84 [0.50, 1.40]	
Kacmarek et al., 2016	28	99	33	101	4.0%	0.87 [0.57, 1.32]	
Meade et al., 2008	173	475	205	508	24.4%	0.90 [0.77, 1.06]	
Mercat et al., 2008	138	385	151	382	18.7%	0.91 [0.76, 1.09]	
Subtotal (95% CI)		989		1018	49.1%	0.90 [0.80, 1.01]	◆
Total events	353		404				
Heterogeneity: Chi ² = 0.11, d	df = 3 (P = 1	0.99); i ²	= 0%				
Test for overall effect: Z = 1.8							
1.3.4 Mortality in 180 days							
Talmor et al., 2008	8	30	14	31	1.7%	0.59 [0.29, 1.20]	
Subtotal (95% CI)		30		31	1.7%	0.59 [0.29, 1.20]	
Total events	8		14				
Heterogeneity: Not applicab	le						
Test for overall effect: Z = 1.4	46 (P = 0.1	5)					
Total (95% CI)		2172		2222	100.0%	0.88 [0.81, 0.95]	•
Total events	707		819				
Heterogeneity: Chi ² = 17.90,		,	; I² = 27%				
Test for overall effect: Z = 3.1							Higher PEEP Lower PEEP
<u>Test for subgroup difference</u>	es: Chi ^z = 1	.84, df:	= 3 (P = 0,	.61), I ^z =	0%		angeotteet convited

Figure 5. Forest Plot for Mortality Rates-Based on Time of Follow Up with Positive Response to PEEP

We also conducted or recreated the forest plot for mortality rates based on the location with positive response of oxygenation to PEEP. Surprisingly, In the figure 6, there were significant result for the outcome of mortality-based on location, both in the hospital [RR = 0.88, 95% CI (0.80, 0.98), p = 0.02, I^2 = 44%). or especially in the ICU [RR = 0.87, 95% CI (0.78, 0.97), p = 0.01,

oxygenation to PEEP in the fovour of higher PEEP group compared to the lower PEEP group [RR = 0.88, 95% CI (0.82, 0.95), p = 0.0005, $I^2 = 44\%$). By this result, we can say that the study from Goligher et al is applicable in this review because there were significantly lower mortality rates in the higher PEEP group if there were a positive response of oxygenation ($\Delta PaO2/FiO2 > 0$)

0%), with posi	Higher I	respo	Lower	of		after higher F	Risk Ratio
Study or Subgroup	Events				Woinht	M-H, Fixed, 95% Cl	M-H, Fixed, 95% C
1.4.1 Mortality in Hospital	LYCIILS	Total	LVCIILS	Total	Weight	m-n, neu, 55% ci	m-n, nxeu, 55% c
Amato et al., 1998	13	29	17	24	2.0%	0.63 [0.39, 1.02]	
Hodgson et al., 2011	3	29 10	2	24 10	0.2%	1.50 [0.32, 7.14]	
Huhetal., 2009	5 14	30	15	27	0.2%	0.84 [0.50, 1.40]	
Ibarra-Estrada et al., 2022	35	30 45	27	45	2.9%	1.30 [0.97, 1.72]	
Kacmarek et al., 2016	29	40 99	35	40	2.9% 3.7%	0.85 [0.56, 1.27]	
Meade et al., 2008	173	99 475	205	508	21.2%	• • •	
	173	385	200 149	382		0.90 [0.77, 1.06]	
Mercatietial., 2008					16.0%	0.91 [0.75, 1.09]	
Talmor et al., 2008	5 16	30 50	12 24	31 45	1.3%	0.43 [0.17, 1.07]	
Villar et al., 2006 Subtotal (95% CI)	16	1153	24	45 1173	2.7% 51.8%	0.60 [0.37, 0.98] 0.88 [0.80, 0.98]	
	424	1155	400	1113	01.0%	0.00 [0.00, 0.90]	•
Total events	424	- 0.000	486				
Heterogeneity: Chi² = 14.26, Test for overall effect: Z = 2.4			≕ 44%0				
	io (i - 0.0	2)					
1.4.2 Mortality in ICU							
Amato et al., 1998	11	29	17	24	2.0%	0.54 [0.31, 0.91]	<u> </u>
Hodgson et al., 2011	3	10	2	10	0.2%	1.50 [0.32, 7.14]	
Huh et al., 2009	14	30	13	27	1.5%	0.97 [0.56, 1.68]	
Ibarra-Estrada et al., 2022	35	45	27	45	2.9%	1.30 [0.97, 1.72]	<u>├</u>
Kacmarek et al., 2016	25	99	30	101	3.2%	0.85 [0.54, 1.34]	
Meade et al., 2008	145	475	178	508	18.4%	0.87 [0.73, 1.04]	
Mercat et al., 2008	136	385	149	382		0.91 [0.75, 1.09]	
Talmor et al., 2008	5	30	12	31	1.3%	0.43 [0.17, 1.07]	
Villar et al., 2006	16	50	24	45	2.7%	0.60 [0.37, 0.98]	
Subtotal (95% CI)		1153		1173	48.2%	0.87 [0.78, 0.97]	•
Total events	390		452				
Heterogeneity: Chi ² = 15.99,	df = 8 (P =	= 0.04); (²= 50%				
Test for overall effect: Z = 2.5		~ ~					
	,						
Total (95% CI)		2306		2346	100.0%	0.88 [0.82, 0.95]	•
Total events	814		938				
Heterogeneity: Chi ² = 30.26,	df = 17 (P	9 = 0.02)	² = 44%				
Test for overall effect: Z = 3.4	47 (P = 0.0	005)					U.2 U.5 1 2 Higher PEEP Lower P
Test for subgroup difference	es: Chi ^z = I	0.03. df =	= 1 (P = 0	.85). ² =	0%		righter Ler Lowerr

Figure 6. Forest Plot for Mortality Rates-Based on Location, with Positive Response to PEEP



Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

In terms of patients without positive response of oxygenation to PEEP, whether mortality-based on time of follow up (Figure 7) or based on location of patients' death (Figure 8), the results showed a lower mortality rates in the lower PEEP group group [RR = 1.07, 95% CI (1.00, 1.15), p = 0.06, $I^2 = 19\%$ and RR= 1.07, 95% CI (1.00, 1.15), p = 0.04, I^2 = 0%]

	Higher P	EEP	Lower F	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.5.1 Mortality in 28 days	6						
Calvalcanti et al., 2017	277	501	251	509	39.0%	1.12 [1.00, 1.26]	
Ranieri et al., 1999 Subtotal (95% CI)	7	18 519	11	19 528	1.7% 40.7%	0.67 [0.34, 1.35] 1.10 [0.98, 1.24]	← ← ←
Total events	284		262				
Heterogeneity: Chi ² = 2.03	3, df = 1 (F	^o = 0.15)); I ^z = 51%	, ,			
Test for overall effect: Z =	1.65 (P =	0.10)					
1.5.2 Mortality in 60 days	6						
Brower et al., 2004 Subtotal (95% CI)	69	276 276	75	273 273	11.8% 11.8%	0.91 [0.69, 1.21] 0.91 [0.69, 1.21]	
Total events	69		75				
Heterogeneity: Not applic	able						
Test for overall effect: Z =	0.66 (P =	0.51)					
1.5.3 Mortality in 180 day	IS						
Calvalcanti et al., 2017	327	501	305	509	47.4%	1.09 [0.99, 1.20]	- - -
Subtotal (95% CI)		501		509	47.4%	1.09 [0.99, 1.20]	◆
Total events	327		305				
Heterogeneity: Not applic	able						
Test for overall effect: Z =	1.75 (P =	0.08)					
Total (95% CI)		1296		1310	100.0%	1.07 [1.00, 1.15]	◆
Total events	680		642				
Heterogeneity: Chi ² = 3.6	• •); i² = 19%	, ,			0.5 0.7 1 1.5 2
Test for overall effect: Z =	,	,					Higher PEEP Lower PEEP
Test for subgroup differer	nces: Chi²	= 1.58,	df = 2 (P :	= 0.45),	2 = 0%		





Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

	Higher P	EEP	Lower F	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.6.1 Mortality in Hospita	al						
Brower et al., 2004	76	276	68	273	9.3%	1.11 [0.83, 1.46]	
Calvalcanti et al., 2017	319	500	301	508	40.4%	1.08 [0.98, 1.19]	+=-
Ranieri et al., 1999 Subtotal (95% CI)	7	18 794	11	19 800	1.4% 51.2%	0.67 [0.34, 1.35] 1.07 [0.97, 1.18]	
Total events	402		380				
Heterogeneity: Chi ² = 1.7	79, df = 2 (F	² = 0.41)); l² = 0%				
Test for overall effect: Z =	= 1.41 (P =	0.16)					
1.6.2 Mortality in ICU							
Brower et al., 2004	76	276	68	273	9.3%	1.11 [0.83, 1.46]	
Calvalcanti et al., 2017	303	500	284	509	38.1%	1.09 [0.98, 1.21]	+=-
Ranieri et al., 1999 Subtotal (95% CI)	7	18 794	11	19 801	1.4% 48.8%	0.67 [0.34, 1.35] 1.08 [0.98, 1.19]	•
Total events	386		363				-
Heterogeneity: Chi ² = 1.8	33. df = 2 (F	$P = 0.40^{\circ}$); I ² = 0%				
Test for overall effect: Z =	= 1.47 (P =	0.14)					
Total (95% CI)		1588		1601	100.0%	1.07 [1.00, 1.15]	•
Total events	788		743				
Heterogeneity: Chi ² = 3.8	64, df = 5 (F	P = 0.60); I² = 0%				0.5 0.7 1 1.5 2
Test for overall effect: Z =	= 2.04 (P =	0.04)					Higher PEEP Lower PEEP
Test for subgroup differe	ences: Chi ^z	= 0.01.	df = 1 (P :	= 0.93),	² = 0%		Agneri El El Concri El

Figure 8. Forest Plot and Funnel Plot for Mortality Rates-Based on location, without Positive Response to PEEP

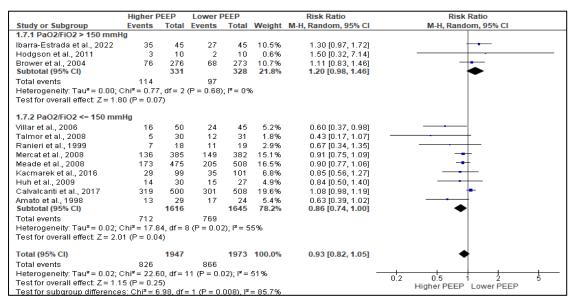


Figure 9. Forest Plot and Funnel Plot for Mortality Rates in Hospital-Based on ARDS Severity

Since higher PEEP intervention on ARDS patients is a double-edged sword, we also conducted a forest plot that described the outcome mortality rates but with a subgroup analysis of different ARDS severity level (PaO2/FiO2 > 150 mmHg and \leq 150 mmHg). The result showed a significant difference between higher PEEP group and lower PEEP group (Figure 9). The mortality rate tends to be lower in the higher PEEP group when the level of ARDS is more severe (PaO2/FiO2 \leq 150) [RR=0.86, 95% CI (0.74, 1.00), p = 0.04, $I^2 = 55\%$].



Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

The results showed the same in the outcome of barotrauma events (Figure 10). It showed a not significant result in the overall barotrauma event between higher and lower PEEP group [RR = 1.03, 95% CI (0.78, 1.36), p = 0.85, $I^2 = 41\%$]. In terms of subgroup analysis for patients with positive response of oxygenation to PEEP, the result is the same unsignificant [RR = 1.03, 95% CI (0.78, 1.38), p = 0.85, I^2 = 41%]. But, in terms of subgroup analysis for patients withoit positive response of oxygenation the result is significant which the mortality rates is higher in the higher PEEP group [RR = 2.51, 95% CI (1.73, 3.63), p < 0.00001, I^2 = 13%].

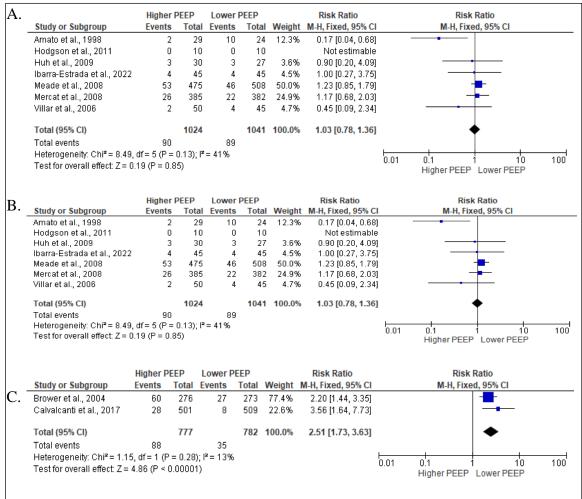


Figure 10. (A) Forest Plot for Overall Barotrauma Events. (B) Forest Plot for Barotrauma Events in Patients with Positive Response of Oxygenation to PEEP. (C) Forest Plot for barotrauma Events in patients without Positive Oxygenation to PEEP

DISCUSSION

Our meta-analysis showed that high PEEP did not improve overall mortality outcome in patients with ARDS. However, sensitivity analysis showed that high PEEP can reduce the mortality for those who response well with oxygenation. In addition, in patients with ARDS who do not show a positive response of oxygenation, high PEEP can increase the incidence of clinically objectified barotrauma and mortality. This result showed a similarity from the previous study that recruitment maneuvers in combination with higher PEEP can reduce the mortality rates in patients with ARDS.

The evidence from the previous studies showed that the high PEEP does not significantly decrease the mortality rates in patients with ARDS. These results must be considered to be carefully interpreted since there was a large variation in the PEEP level between the different results of different studies. The study from Huh et al., used a high PEEP of 10 cmH2O while Amato et al., used a high PEEP of 16.3 cmH2O even there were similarity among low PEEP level which is varied between 6.5 to 13 cmH2O. Since there were different level of PEEP in the different studies, therefore it may have led to the different results. Subgroup results showed that the PEEP level in the lower PEEP group impacted also in the hospital and ICU mortality.

Patients' characteristics also impacted the final results of this studies since the baseline characteristic of each patients in every studies is different. Baseline of mean value of PaO2/fiO2 or ARDS severity is ranged from 110 to 165 mmHg. Oxygenation response to PEEP was also totally significantly related to the severity of ARDS. The potential lung recruitment and response to PEEP was stronger in more severe ARDS (PaO2/FiO2 \leq 150 mmHg) compared to the less severe ARDS (PaO2/FiO2 > 150 mmHg). A previous meta-analysis also showed that a high PEEP reduced mortality in patients with ARDS but not acute lung injury(4). The severity of ARDS can be used as the guide to titrate PEEP. There are many methods for PEEP titration such as oxygenation, index stress and transpulmonary pressure. Oxygenationguided PEEP provided PEEP levels related to oxygenation response to PEEP in the pulmonary that is progressively increased to moderate or severe ARDS.

We did not find a significant result in the barotrauma events outcome between both groups. Barotrauma events tend to be rarely happening in the lower PEEP group in the patients without positive oxygenation response to PEEP. This condition occured because of there were not any hyperinflation in the alveoli.

In several clinical trials, higher PEEP techniques have been shown to enhance survival in ARDS sufferers on the price of a multiplied danger of pneumothorax. To make certain good enough oxygenation, PEEP might be raised at the chance of extended Pplat and barotrauma. Sufferers regularly require an excessive level of PEEP to maintain oxygenation, putting them at chance for barotrauma.

In this review, we included more patients with moderate to severe ARDS which is actually indicates that more lung area can have the positive response to increased PEEP. But, however, in patients with ARDS and without positive oxygenation response to PEEP, high PEEP can increase the chance of barotrauma events.

Inflammatory mediators also are the markers of ARDS severity in the level of molecular perspective. The infiltration of immune cells in the lungs can reduce the pulmonary compliance. Interestingly, the use of mechanical ventilator and PEEP strategies can modulate this inflammatory molecular patterns. Ranieri et al., 1999 stated that the use of higher PEEP strategies can reduce the infiltration of PMN cells in patients with severe ARDS. It is also in line with the research conducted by Brower et al in 2004 and Hodgson et al in 2011 that found some decrement of IL-6 and TNF- α ^{10,11,17}. As we know, COVID-19 induce severe can hyperinflammation called cytokine storm. Until now, one of the current strategies to treat COVID-19 is preventing the development of inflammatory mediators with some antiinflammatory drugs. By this research we provided some evidence that mechanical ventilator also contributes to the modulation of cytokine production in ARDS or ARDS associated COVID-19. We also encourage the clinicians to put some awareness of this research data that higher or lower PEEP strategies are crucial thing in the treatment of ARDS especially in patients with severe COVID-19 due to maintain their inflammatory reactions.



There is a limitation of this study. The positive response of oxygenation to PEEP is based on the mean values of PaO2/FiO2 reported in each study not as the individual patient data. That finding means most of the patients in the study with positive response of oxygenation to PEEP were in their respective groups. Another limitation is that the methods for the titration of PEEP were different between included articles, which may have impacted to the robustness of this study.

CONCLUSION

This systematic review and metaanalysis showed valuable evidence that higher PEEP strategies can reduce the mortality events in patients with ARDS especially to the patients who have positive response of oxygenation to the high PEEP. Since High PEEP may increase the chance to the barotrauma event, the use of high PEEP strategy needs to be careful and considered to see the response of oxygenation. In the perspective of COVID-19 management, the use of the best PEEP strategies can help the clinician to reduce the inflammatory mediators and have the potential to increase the survival rates of those patients.

CONFLICT OF INTEREST

There were no conflict of interest between the authors.

REFERENCE

- Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nat Rev Dis Prim. 2018;5(1).
- Li Bassi G, Suen JY, Dalton HJ, White N, Shrapnel S, Fanning JP, et al. An appraisal of respiratory system compliance in mechanically ventilated covid-19 patients. Crit Care. 2021;25(1):1– 22.
- 3. Ibarra-Estrada MA, García-Salas Y, Mireles-Cabodevila E, López-Pulgarín JA, Chávez-Peña Q, García-Salcido R, et al. Use of Airway Pressure Release Ventilation in Patients with Acute Respiratory Failure Due to COVID-19: Results of a Single-Center Randomized Controlled Trial. Crit Care Med. 2022;50(4):586-94.
- Guo L, Xie J, Huang Y, Pan C, Yang Y, Qiu H, et al. Higher PEEP improves outcomes in ARDS patients with clinically



objective positive oxygenation response to PEEP: A systematic review and meta-analysis. BMC Anesthesiol. 2018;18(1):1–11.

- Banavasi H, Nguyen P, Osman H, Soubani AO. Management of ARDS – What Works and What Does Not. Am J Med Sci. 2021;362(1):13–23.
- 6. Rajdev K, Spanel AJ, McMillan S, Lahan S, Boer B, Birge J, et al. Pulmonary Barotrauma in COVID-19 Patients With ARDS on Invasive and Non-Invasive Positive Pressure Ventilation. J Intensive Care Med. 2021;36(9):1013–7.
- 7. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, De Moraes Paisani D, Damiani LP, Guimarães HP, et al. Effect of lung recruitment and titrated Positive End-Expiratory Pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome - A randomized clinical trial. JAMA -J Am Med Assoc.
- Walkey AJ, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, Meade MO, et al. Higher PEEP versus lower PEEP

2017;318(14):1335-45.

strategies for patients with acute respiratory distress syndrome: A systematic review and metaanalysis. Ann Am Thorac Soc. 2017;14:S297–303.

- 9. Amato MBP, Valente Barbas CS, Medeiros DM, Magaldi RB, De Pinto Schettino G, Lorenzi-Filho G, et al. Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. Pneumologie. 1998;52(5):285.
- 10. Ranieri VM, Suter PM, Tullio R
 De, Dayer JM, Brienza A, Bruno
 F, et al. Effect of Mechanical
 Ventilation on Inflammatory
 Mediators in Patients with Acute
 Respiratory Distress Syndrome: A
 Randomized Controlled Trial.
 1999;
- 11. Brower RG (Johns HU, Lanken PN (University of P, MacIntyre N U. Matthay (Duke MA (University of C, Hospital), Morris A (LDS, et al. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. N Engl J Med. 2004;351(4):687–96.
- 12. Villar J, Kacmarek RM, Pérez-



Meta-Analysis of Higher PEEP Strategies' Effects on Mortality Rates and Inflammatory Mediators in Patients with ARDS: A Perspective Review on Patients with Severe COVID-19-Associated ARDS

Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. Crit Care Med. 2006;34(5):1311-8.

- 13. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy low tidal volumes. using recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA - J Am Med Assoc. 2008;299(6):637-45.
- Mercat A, Richard J-CM, Vielle B, Jaber S, Osman D, Diehl J-L, et al. Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome. Surv Anesthesiol. 2008;52(6):272–3.
- Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical Ventilation Guided by Esophageal Pressure in

Acute Lung Injury. N Engl J Med. 2008;359(20):2095–104.

- 16. Huh JW, Jung H, Choi HS, Hong SB, Lim CM, Koh Y. Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. Crit Care. 2009;13(1):1–9.
- 17. Hodgson CL, Tuxen D V., Davies AR, Bailey MJ, Higgins AM, Holland AE, et al. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. Crit Care 2011;15(3):R133. [Internet]. Available from: http://ccforum.com/content/15/3/ R133
- Kacmarek RM, Villar J, Sulemanji D, Montiel R, Ferrando C, Blanco J, et al. Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. Crit Care Med. 2016;44(1):32–42.