Vol 3 No. 2 October 2023
Solo Journal of Anesthesi, Pain and Critical Care
E-ISSN : 2797-0035
P-ISSN : 2776-1770

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
https://doi.org/10.20961/soja.V3i2.62253

Authors' affiliations :
[*]Faculty of Medicine, Universitas Jember, Jember, Indonesia
[✉]Correspondence:
yehuda.supranoto@gmail.com

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 PaO_2/FiO_2<150 mmHg [RR=0.867,95%CI(0.74,1.00),p=0.04] instead of patients with moderate ARDS (PaO_2/FiO_2 ≥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,

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome interfering the function of respiratory system that has a significant morbidity and mortality value[1]. 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 despite many new strategies 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-19 [3]. Three large studies using Randomized Controlled Trials (RCTs) study design were performed to assess whether higher PEEP could improve outcomes in patients with ARDS [4]. 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, one of an easy-to-implement 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

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 only[8].

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 response to increased PEEP 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 the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol registration number 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 posters, research protocols, 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 PaO_2/FiO_2. 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 higher/lower PEEP 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 PaO_2/FiO_2.

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

A 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 (cmH_2O),mortality event assessment, and alteration 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 as randomization 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 (Meta-analysis)

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 when the included 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 generated by Review 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 and analyzed in qualitative and quantitative way in the systematic review and meta-analysis methods.

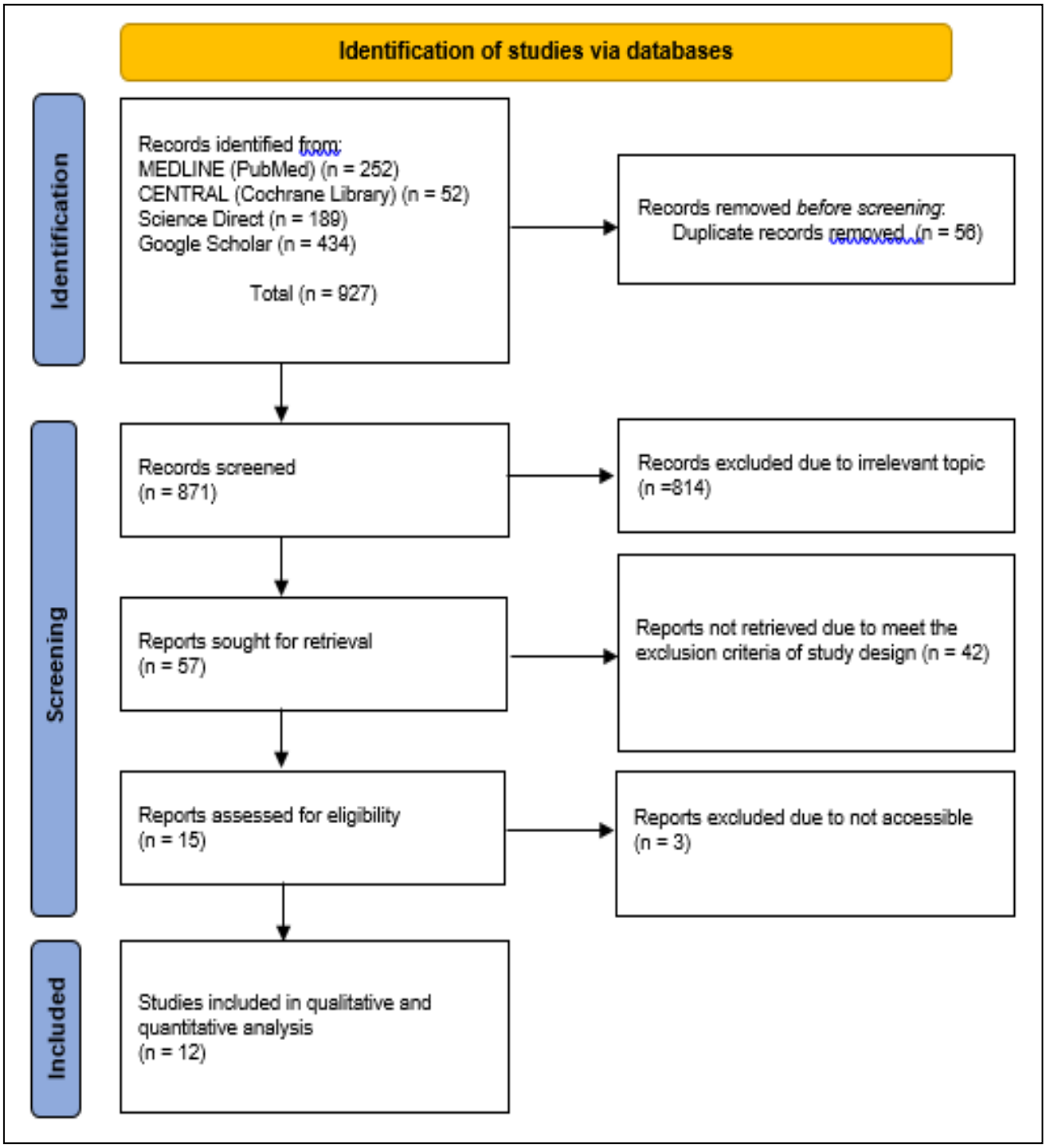

Figure 1. PRISMA Flow Diagram

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 PaO_2/FiO_2.

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 (cmH_2O) 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 inflammatory mediators 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%].

Table 2. Characteristics of Included Studies

Author, Year	Country	Sample Size (n, HP/LP)	ARDS severity (PaO2/FiO2) (mmHg)	Intervention		With or Without Positive Oxygenation Response to PEEP (Δ Mean PaO_2/FiO_2)	Mortality Outcome Assessments
				Higher PEEP	Lower PEEP		
Amato, 1998[9]	Brazil	29/24	HP: 112 ± 51 LP: 134 ± 67	VT maintained < 6ml/kg body weight Pressure control ventilation < 40 cmH_2O PEEP at Pflex + 2 cmH_2O Pulmo recruitment maneuvers	VT set to 12 ml/Kg body weight Volume control ventilation Auto-PEEP set to O_2 goals	With positive oxygenation response to PEEP	28 days Hospital ICU
Ranieri, 1999[10]	Canada	18/19	HP: 149 ± 66 LP: 142 ± 56	VT set to Pplat < UIP or < 5-8 ml/kg body weight PEEP at Pflex + 2-3 cmH_2O	VT maintained until $PaCO_2$ 35-40 mmHg PEEP incremental 3-15 cmH_2O	Without positive oxygenation response to PEEP	28 days Hospital ICU
Brower, 2004[11]	UK	276/273	HP: 220 ± 89 LP: 168 ± 66	VT set to 6 ml/kg body weight PEEP incremental start more than 12 cmH_2O, Recruitment maneuvers in the first 80 patients ARDSNet	Lower PEEP/FiO_2 but with set of Pplat < 30 cmH_2O	Without positive oxygenation response to PEEP	60 days Hospital ICU
Villar, 2006[12]	Spanish	50/45	HP: 139 ± 43 LP: 124 ± 54	VT set to 5-8 ml/kg body weight	VT set to 9-11 ml/kg body weight	With positive oxygenation response to PEEP	28 days Hospital

				Pressure control ventilation PEEP at Pflex + 2 cmH_2O	PEEP ≥ 5 cmH_2O to O_2 goals		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_2O Pulmo recruitment maneuvers	Lower PEEP/FiO_2 Pplat < 30 cmH_2O	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_2O	PEEP maintained 5-9 cmH_2O 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_2O Inspiratory TPP < 25 cmH_2O 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_2O	Lower PEEP/FiO_2	With positive oxygenation response to PEEP	7 days Hospital ICU

				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_2O 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_2O 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_2O	Lower PEEP/FiO_2 but with set of Pplat < 30 cmH_2O	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*

Table 3. Mortality and Barotrauma Outcomes After PEEP Intervention

Author, Year	Mortality Rates-based on Time of Follow Up								Mortality Rates-based on Location				Barotrauma Events	
	7 days		28 days		60 days		180 days		In Hospital		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 4. Pro-Inflammatory Cytokines, Immune Cells, and Pulmonary Protein Markers Alteration After PEEP Intervention

Author, year	Pro inflammatory cytokines alteration after PEEP intervention		Immune cells alteration after PEEP Intervention		Pulmonary protein marker alteration after PEEP Intervention	
	HP	LP	HP	LP	HP	LP
Ranieri et al., 1999	Soluble TNF-αsR55↓ Soluble TNF-αsR75↓ IL-1RA↓, IL-1β ↓, TNF-α ↓ , IL-8 ↓, IL-6↓	Soluble TNF-αsR55↑ Soluble TNF-αsR75↑ IL-1RA↑, IL-1β ↑, TNF-α ↑ , IL-8 ↑, IL-6↑	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 ↑, TNF-α ↑				

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

Quantitative Data Synthesis (Meta-Analysis)

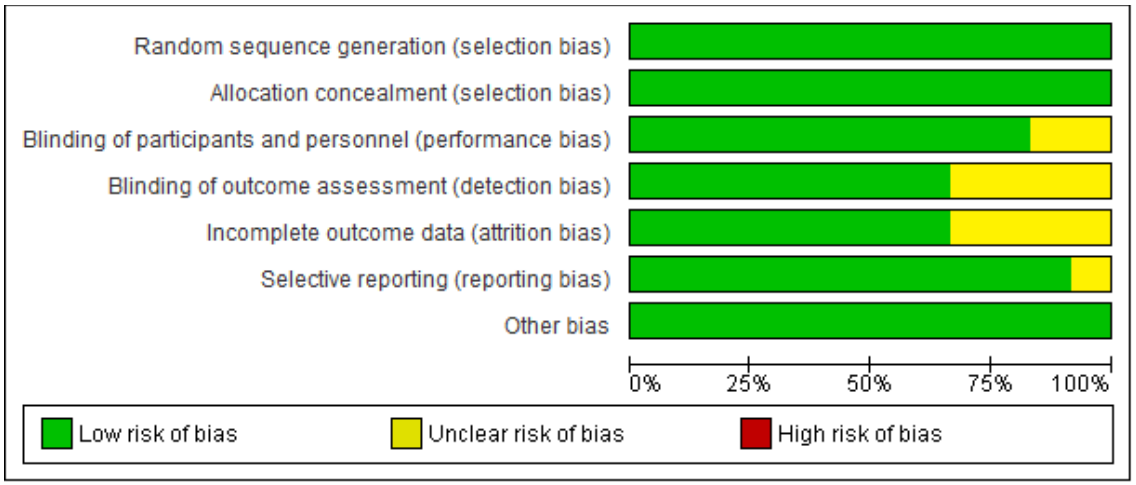

Figure 2. Risk of Bias Assessment based on Risk of Bias 2 (RoB 2) Tools (Recommended by Cochrane Handbook for Systematic Review of Intervention)

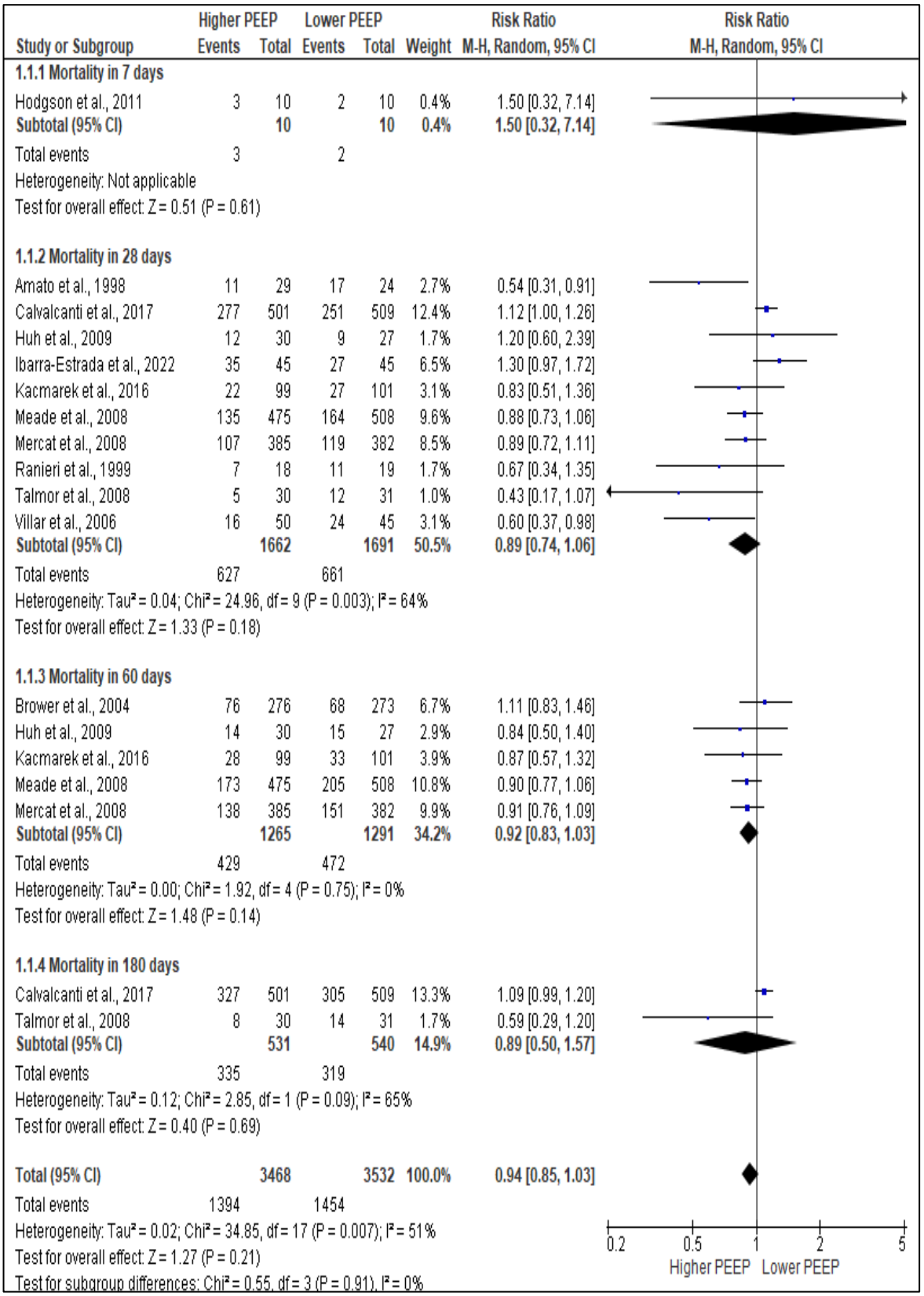

Figure 3. Forest Plot and Funnel Plot for Mortality Rates-Based on Time of Follow Up Between Higher PEEP Group and Lower PEEP Group

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%].

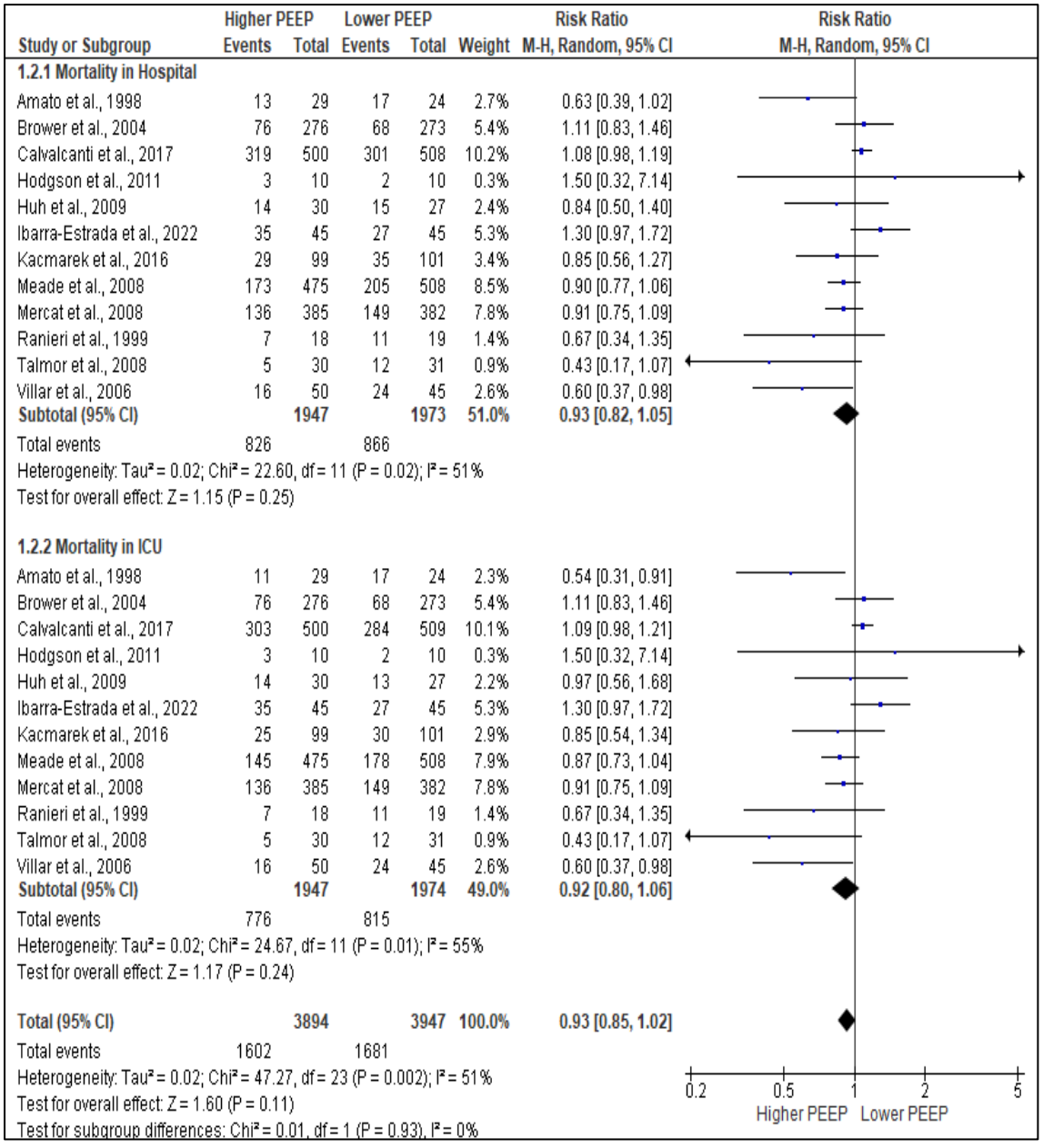

Figure 4. Forest Plot for Mortality Rates-Based on Location Between Higher PEEP Group and Lower PEEP Group

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%*).

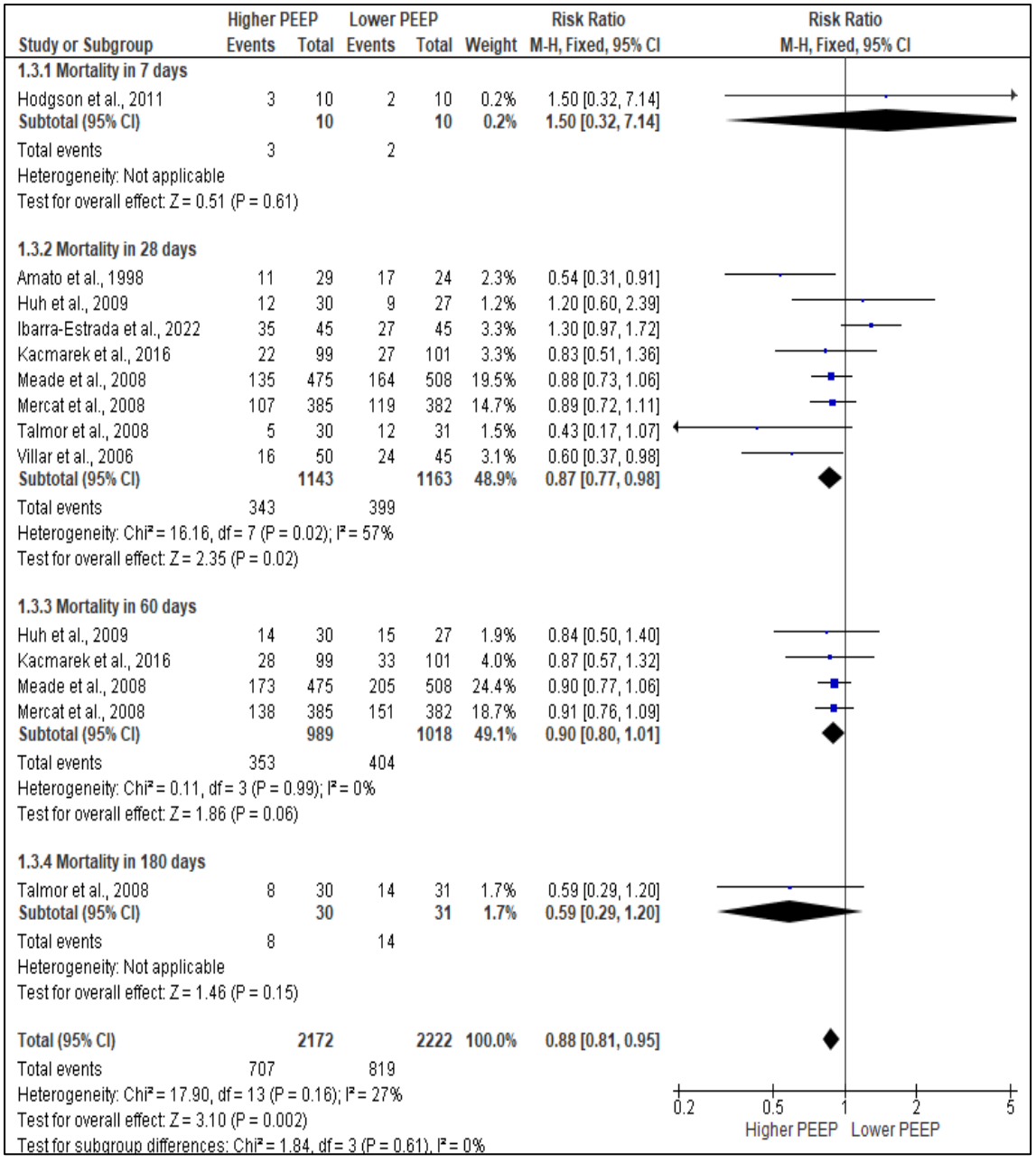

Figure 5. Forest Plot for Mortality Rates-Based on Time of Follow Up with Positive Response to PEEP

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, I^2= *50%*), with positive response of 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 (ΔPaO2/FiO2 > 0) after higher PEEP intervention

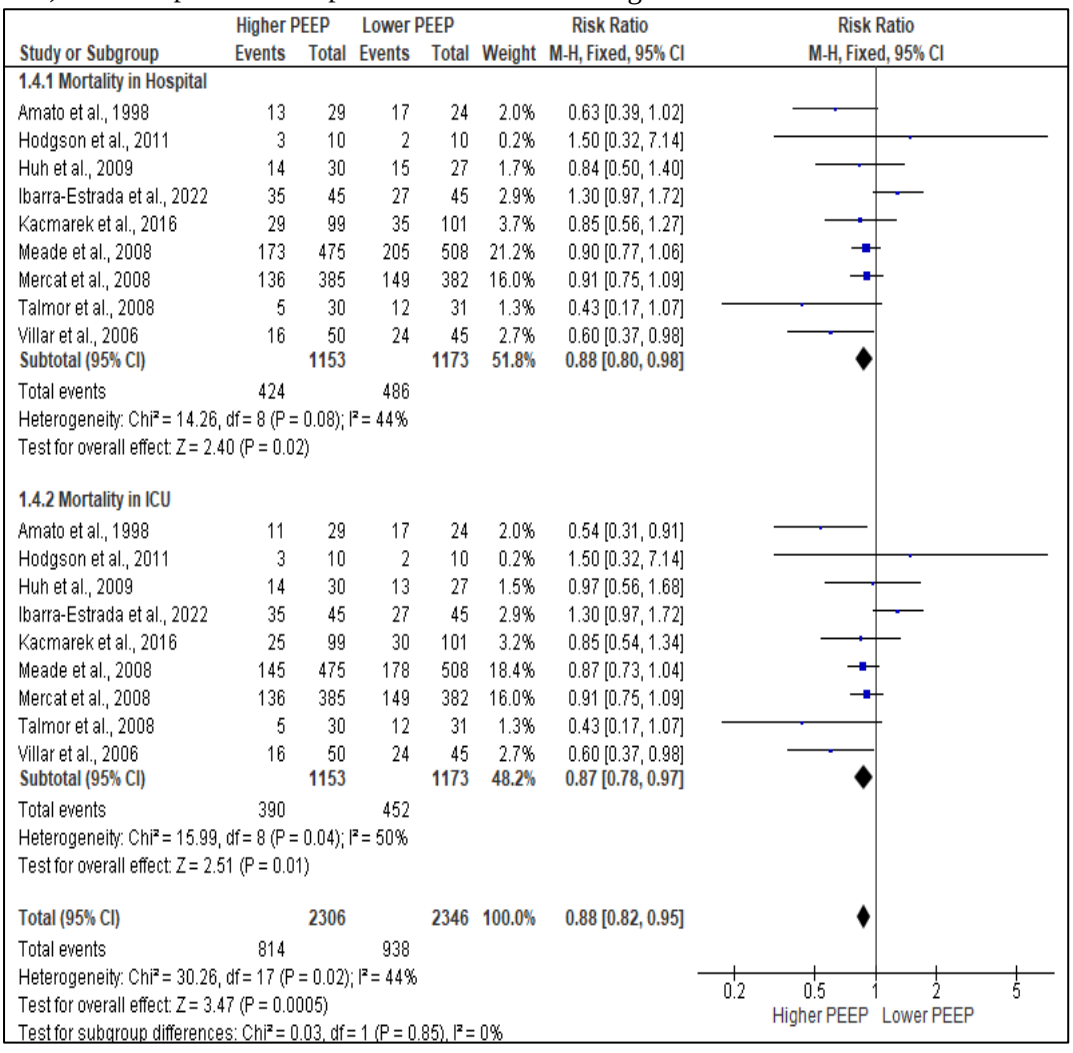

Figure 6. Forest Plot for Mortality Rates-Based on Location, with Positive Response to PEEP

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%]

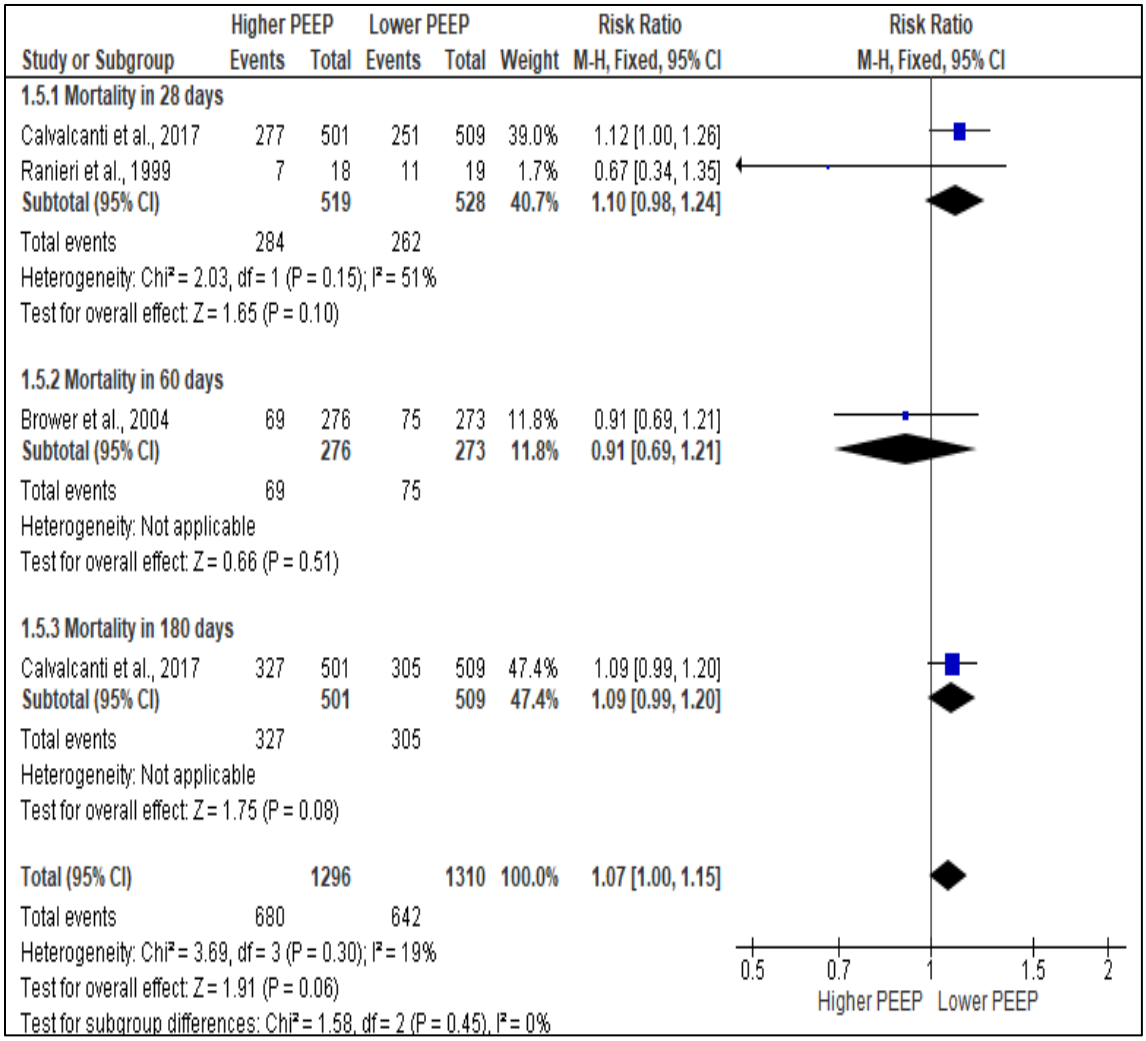

Figure 7. Forest Plot for Mortality Rates-Based on Time of Follow Up without Positive Response to PEEP

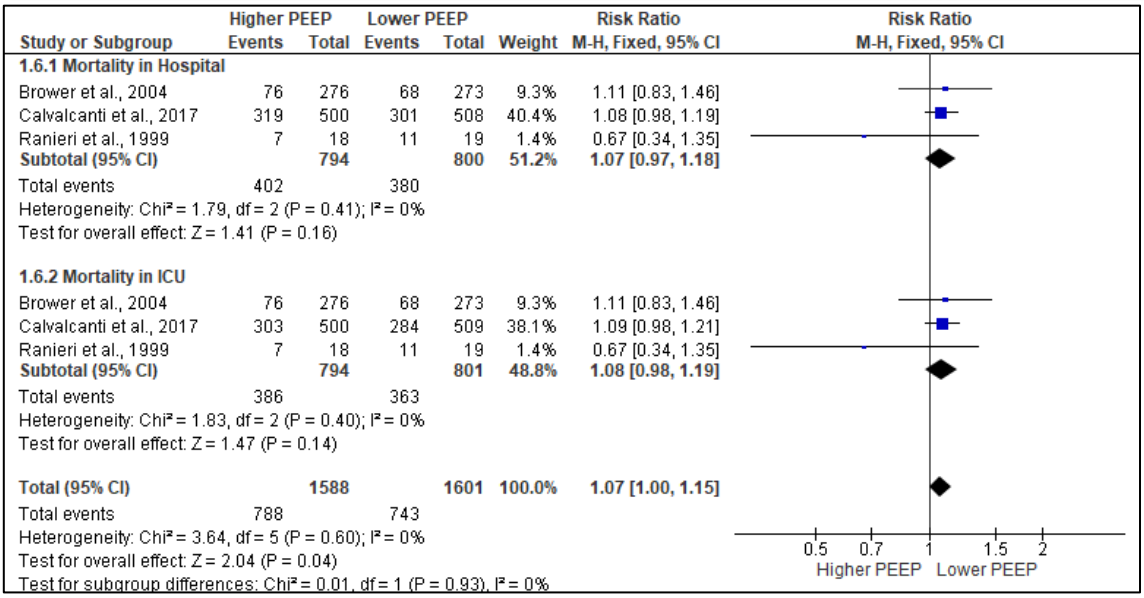

Figure 8. Forest Plot and Funnel Plot for Mortality Rates-Based on location, without Positive Response to PEEP

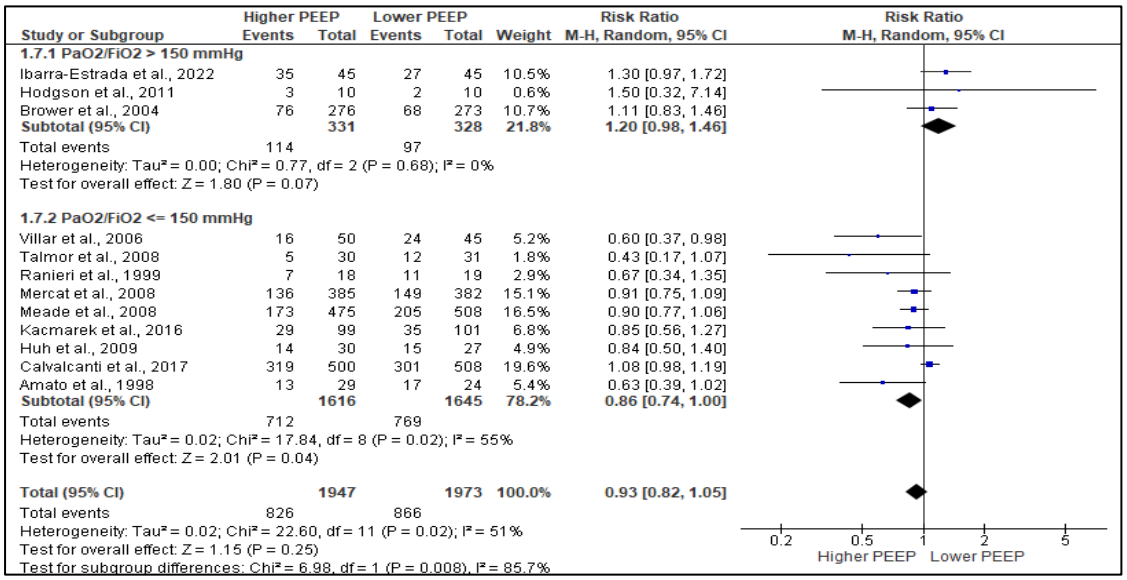

Figure 9. Forest Plot and Funnel Plot for Mortality Rates in Hospital-Based on ARDS Severity

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 ≤ 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 ≤ 150) [RR=0.86, 95% CI (0.74, 1.00), p = 0.04, I^2 =55%].

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%].

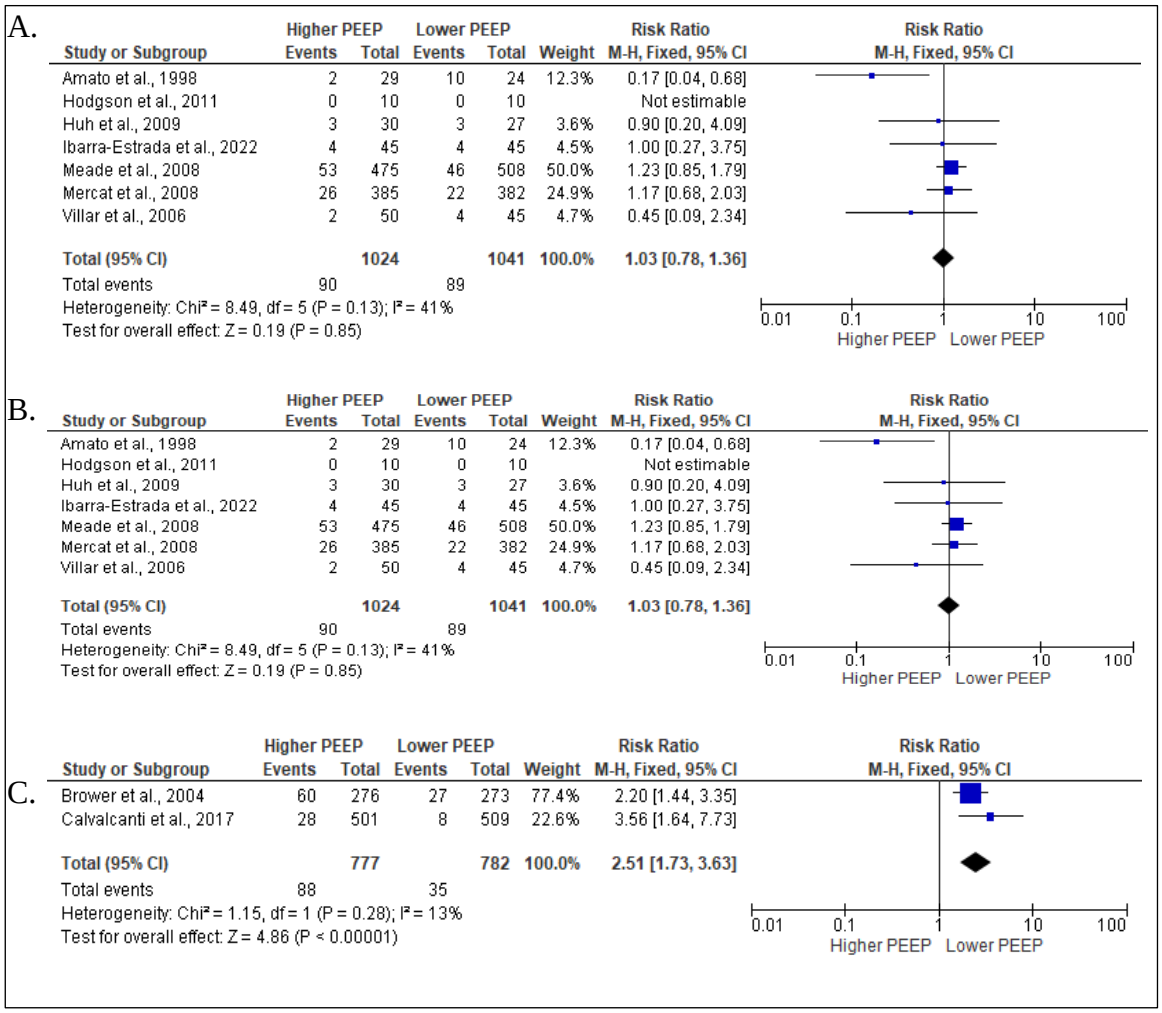

Figure 10. (A) Forest Plot for Overall Barotrauma Events. (B) Forest Plot for Barotrauma Events in Patients with Positive Response of Oxygenation to PEEP. (C) Forest Plot for barotrauma Events in patients without Positive Oxygenation to PEEP

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, stress index and transpulmonary pressure. Oxygenation-guided 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, severe COVID-19 can induce 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 meta-analysis 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

1. 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).
2. 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.
4. 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.

5. 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. 2017;318(14):1335–45.
8. Walkey AJ, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, Meade MO, et al. Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome: A systematic review and meta-analysis. 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, Maclntyre N (Duke U, Matthay 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-

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 using low tidal volumes, 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.
14. 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.
15. 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 [Internet]. 2011;15(3):R133. Available from: http://ccforum.com/content/15/3/R133
18. 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.