Efficacy and safety of different mechanical ventilation strategies for patients with acute respiratory distress syndrome: Systematic review and network meta-analysis

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Research

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Abstract

Background: Acute respiratory distress syndrome (ARDS) leads to life-threatening acute hypoxemic respiratory failure in clinic and usually requires mechanical ventilation. Low tidal volume ventilation is now universally accepted as management treatment for this condition. However, recruitment maneuvers (RM) and positive end-expiratory pressure (PEEP) remain controversial. Therefore, we performed a network meta-analysis to identify the RM and PEEP levels of patients with ARDS.

Methods: We searched PubMed, OVID, Embase, and the Cochrane Central Register of Controlled Trials (Central) databases. The primary outcome was death in the 28th day, and the secondary outcomes included death in hospital, ventilator-free days, and barotrauma. Data for study characteristics, methods, and outcomes were extracted. The relative effect sizes were estimated by risk ratios (RRs) for binary variables and standard mean difference (SMD) for continuous variables. Relative ranking of the interventions was conducted using surface under the cumulative ranking. Multiple intervention comparisons based on the Bayesian and frequentist frameworks were performed to integrate the efficacy of all included strategies.

Results: Thirty randomized controlled trials comprising 4410 patients were included in the network meta-analysis. None of the ventilation strategies was significantly superior over others for all outcomes. According to the relative rank probabilities, low PEEP showed the lowest probability of harming death in the 28th day, whereas RM+low PEEP showed the highest probability of benefitting death in hospital and ventilator-free days. Low PEEP showed the highest probability of benefitting barotrauma. The overall quality of the evidence per grade was moderate to low.

Conclusions: No ventilation strategy is significantly superior over others. RM+low PEEP has the highest probability of benefitting survival. The evidence has low overall quality and should be further studied.

Background

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury characterized by damaged pulmonary capillary endothelial and alveolar epithelial and increased vascular permeability, leading to life-threatening acute hypoxemic respiratory failure in clinic[1]. ARDS was first reported 50 years ago [2], and a number of positive clinical trials for its treatment, such as mechanical ventilation with a low tidal volume [3], neuromuscular blockers in early ARDS[4], and prone positioning[5], have been conducted over the past decades. However, evidence indicating that any pharmacological agent can effectively improve ARDS outcomes is insufficient[6]. Approximately 40.1% of patients with ARDS need invasive ventilation, and the overall hospital mortality remains 40%[7]. Thus far, mechanical ventilation is the cornerstone of therapy for ARDS.

Mechanical ventilation for ARDS focuses on limiting further lung injury through a combination of lung-protective ventilation [8]. Ventilation with low tidal volumes[3] is a milestone ventilation strategy for patients with ARDS. On the basis of this research, clinical practice guidelines endorsed by multiple professional societies recommend lowering of the tidal volume and airway pressure as the basic strategies for ventilation[9, 10]. In addition to tidal volume, other parameters of mechanical ventilation, such as positive end-expiratory pressure (PEEP) and lung recruitment maneuvers, can affect the outcomes of patients with ARDS. In previous studies, higher PEEP for patients with ARDS who responded to increased PEEP through improved oxygenation, reduced hospital mortality, ICU mortality, and 28 d mortality[11]; lung recruitment maneuvers (RM) with higher PEEP may reduce mortality[12], whereas other studies have a different conclusion[13]. Traditional pairwise meta-analysis can only be used to compare specific parameters between ventilation strategies but not for the entire set of parameters relevant to different ventilation strategies, thereby causing conflict. In this case, a network meta-analysis is advantageous for comparing the effectiveness of multiple interventions. To date, network meta-analysis has not been conducted on multiple mechanical ventilation strategies. Therefore, this work aimed to identify the most effective mechanical ventilation strategy through network meta-analysis. We compared the different PEEP setting strategies with or without lung recruitment maneuvers in terms of low tidal volume ventilation. The effectiveness and safety of various ventilation strategies were also evaluated to identify the optimal ventilation strategy for ARDS.

Methods

We performed our systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses extension statement for network meta-analysis[14].

Eligibility criteria

Randomized controlled trials (RCTs) were used to compare different mechanical ventilation strategies for adult patients with ARDS. Inclusion criteria were adults with ARDS who received treatment with low tidal volume mechanical ventilation strategies. Pediatric ARDS or adults who did not receive low tidal volume of mechanical ventilation strategy were excluded.

The types of mechanical strategies included lower PEEP, higher PEEP, RM+ higher PEEP, RM+ lower PEEP, and RM+PEEP titration. Lower PEEP is the minimum PEEP reaching the clinical goals, including the ARDSNet PEEP/FiO_2 protocol[15] or minimum PEEP to maintain $PaO_2 > 60$ mmHg and $FiO_2 < 0.6$. Higher PEEP is the maximum PEEP without increasing the maximal inspiratory plateau pressure above 28–30 cm H_2O or initial PEEP levels higher than a comparator strategy used to determine PEEP. PEEP titration included PEEP titration according to the best respiratory-system static compliance, maximum SaO_2, or esophageal pressure.

The primary outcome was 28-day mortality, and the secondary outcome included in-hospital mortality, length of ventilator-free days, and barotrauma.

Data sources and searches

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed), OVID (http://ovidsp.ovid.com/), Embase (http://www.embase.com), and the Cochrane Central Register of Controlled Trials (Central) (http://www.cochranelibrary.com) databases to find relevant articles up to 30 December 2019 in all languages without limitations concerning publication dates and languages. We used the combinations of the terms “acute respiratory distress syndrome” (or “acute lung injury” or “acute respiratory failure”) and “mechanical ventilation” (or “positive end-expiratory pressure” or “recruitment maneuver” or “open lung” or “lung recruitment” or “alveolar recruitment maneuver”).

Study selection and data collection

Two reviewers (WH and PW) independently assessed the eligibility of all identified citations in accordance with the abovementioned criteria. Data was extracted and the study quality were assessed independently by two reviewers (WH and PW). Disagreements between reviewers were settled by a third reviewer (FJ) when needed. During data collection, if the median, the first, and third quartiles were recorded in clinical trial studies, then the equation ($X \approx (0.7+0.39/n)\ (q1+q3)/2+(0.3-0.39/n)\ m$)[16]was used to transform information to the sample mean and the equation ($SD \approx (q3-q1)/1.35$) to transform information to standard deviation[17] to avoid data loss.

Risk of bias in individual studies

The risk of bias in individual studies was classified to three levels (low risk of bias, unclear risk of bias, and high risk of bias) on the basis of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Risk of bias analysis was performed USING Review Manager® Version 5.3 for Windows (RevMan, The Cochrane Collaboration, Oxford, UK).

Statistical analysis

Traditional pairwise meta-analysis was used for direct comparisons with the meta module of STATA (Version 15.0; StataCorp, College Station, TX). Network meta-analyses in a Bayesian framework were performed using a Markov Chain Monte Carlo simulation technique in Aggregate Data Drug Information System (ADDIS) software (version 1.16.8). Network meta-analyses in a frequentist framework were performed with STATA.

Risk ratios (RRs) were used to estimate the relative effect sizes for binary variables, while standard mean difference (SMD) was used for continuous variables. The 95% confidence interval (CI) was used for the direct meta-analysis and CrI for the network meta-analysis.

Heterogeneity between studies was assessed with I2 statistics and p-value. Statistical significance was set at a p-value of 0.05. Heterogeneity was considered low, moderate, or high for the estimated I2 values under 25%, between 25% and 50%, and over 50%, respectively. If $p < 0.05$ or $I2 > 50\%$, the random-effects model was used for pairwise meta-analyses; otherwise fixed-effects model was used.

The comparison of the fit of consistency and inconsistency models was evaluated to determine the global inconsistency. The node splitting approach was also used to calculate the inconsistency of the model, and $P < 0.05$ was considered as significant heterogeneity, and the random effects model was used to calculate pooled effect size; otherwise, the consistency model was used to calculate the pooled effect size. The residual deviance statistics and deviance information criteria were used to evaluate the model fit for the consistent and inconsistent models.

The ranking probabilities for each mechanical ventilation strategy under different endpoints were assessed to provide basis for selecting alternatives. For each ventilation strategy, surface under the cumulative ranking (SUCRA) was used to estimate the ranking probabilities of assuming any possible rank. SUCRA was plotted using the cumulative ranking curves and the surface under them was calculated; according to the SUCRA, the priority of the strategy can be estimated. SUCRA was calculated using a previously reported equation [16]. The ranking probabilities were calculated using the Bayesian framework and the frequentist framework, and cumulative ranking probabilities curve were drawn using GraphPad Prism 5.

Results

Characteristics of enrolled studies

A total 878 articles were obtained according to the search strategy. After screening, 31 articles were excluded due to duplicates. A total of 124 articles remained after screening based on their title and abstract. Among the 124 articles, 2 were case reports, 3 were letters, 48 were review articles, 17 were not randomized control trials, 16 had no relevant data, and 4 did not adopt low tidal volume ventilation strategy in the control groups. Finally 13 randomized-controlled trials involving 4410 patients were enrolled for the network meta-analysis. Patients with ARDS received one of the five mechanical ventilation strategies (recruitment maneuver combined with PEEP titration, recruitment maneuver combined with higher PEEP, recruitment maneuver combined with lower PEEP, higher PEEP, and lower PEEP). Literature screening and results are shown in Figure 1A. The main characteristics of all studies are reported in Table 1.

Risk of bias within studies

The risk of bias within studies was assessed using the Cochrane Collaboration Reviewer Manager 5.3 tool, and the results are shown in Figure 1B. An article (Lim 2003) did not describe random methods. For safety reasons, blinding treating clinicians to group assignment was not feasible. Although few studies reported blinding of participants, patients who needed mechanical ventilation received sedation, which did not affect the results. Three articles had high risk of other bias, and one of them (Brower 2004) modified the high-PEEP strategy by eliminating the steps with a PEEP of less than 12 cm of water and requiring a minimum PEEP of 14 cm of water for the first 48 h. An article reported by Meade et al. had a programming error occurring late in the study, thereby disrupting the specified randomization blocks. The bias in another research (Constantin 2019) was caused by different treatments between the focal ARDS and the non-focal ARDS.

Heterogeneity and inconsistency assessment

In the pairwise meta-analyses, moderate to high heterogeneity was detected; for death in 28 days, the I^2 of RM+PEEP titration versus RM+lower PEEP is 64.5%. For ventilator-free days the I^2 of RM+PEEP titration versus lower PEEP is 56.8%, and that for higher PEEP versus lower PEEP is 71.3%. For barotrauma, the I^2 of RM+PEEP titration versus lower PEEP is 66.9%. The comparisons of other strategies show low heterogeneity. The results of the pairwise meta-analyses are shown in Table 2.

In the Bayesian framework, the fit of the consistency model for all outcomes was similar or better to that of inconsistency model (Table 3), suggesting low global inconsistency. The node-splitting analysis for primary and secondary outcomes in Bayesian framework showed no significant inconsistency between the direct effects and indirect effects (Table 4).

In the frequentist framework, the global inconsistency test showed low inconsistency for all outcomes ($p>0.05$) as shown in Figure 2. The node-splitting analysis in the frequentist framework showed that in terms of death in hospital, RM+higher PEEP versus higher PEEP and higher PEEP vs. lower PEEP had local inconsistency ($p<0.05$); otherwise, no significant inconsistency was detected between the direct effects and the indirect effects (Table 5).

Table 1. Characteristics of intensive care unit patients with acute respiratory distress syndrome included in randomized controlled trials

Study [references]	Center	Sample size (average age)	Ventilation strategies	Female(%)	PaO_2/FiO_2 (cmH2O)	APACHEII score	Plateau pressure (cmH2O)	pulmonary ARDS（%）
Lim 2003[18]	1	20(60)	RM+ higher PEEP	10%				75%
		19(61)	RM+ lower PEEP	10.5%				78.9%
		8(60)	Higher PEEP	12.5%				87.5%
Brower 2004[15]	23	276(49)	Higher PEEP	43%	151±67		27±6	58%
		273(54)	Lower PEEP	47%	165±77		24±7	53%
Meade 2008[19]	30	475(54.5)	RM+ higher PEEP	40.6%	144.8±47.9	24.8±7.8	30.4±5.5	69%
		508(56.9)	Lower PEEP	39.6%	144.6±49.2	25.9±7.7	29.3±6.0	75.9%
Mercat 2008[20]	37	385(60)	Higher PEEP	32%	144±58		23.7±4.9	70%
		382(60)	Lower PEEP	33%	143±57		22.9±5.3	75%
Tamlor 2008[21]	1	30(54.5)	RM+PEEP titration	37%	147±56	26.3±6.4	29±7	23.3%
		31(51.2)	RM+Lower PEEP	45%	145±57	26.8±6.5	29±5	16.1%
Huh 2009[22]	1	30(55)	RM+PEEP titration	37%	115.0±8.5	22.0±1.1		66.7%
		27(62)	Lower PEEP	40%	110.8±6.3	20.0±1.4		66.7%
Xi 2010[23]	14	55(62.2)	RM+ lower PEEP	30.9%	104.8±60.2*	21.5±6.7	24.2±5.3	45.4%
		55(65.5)	Lower PEEP	27.3%	115.9±38.3*	23.1±8.6	23.4±5.3	38.2%
Hodgson 2011[24]	1	10(60)	RM+PEEP titration	30%	155±8	20.1±3	28.9±1.2	50%
		10(58)	Lower PEEP	40%	149±12	20.1±2	27.1±1.2	60%
Kacmarek 2016[25]	20	99(52.2)	RM+PEEP titration	42.4%	121±37	18±10	27±5	68%
		101(53.4)	Lower PEEP	33.7%	114±33	17±6	27±5	66%
ART 2017[26]	120	501(51.3)	RM+PEEP titration	37.5%	119.5±43.5		25.8±4.7	62.5%
		509(50.6)	Lower PEEP	37.5%	117.2±41.9		26.2±5.2	61.5%
Beitler 2019[27]	14	102(58)	RM+PEEP titration	37.3%	99.2±41.5*	27±8	28.0±5.9*	80.4%
		98(57.5)	RM+lower PEEP	55.1%	94.2±40.0*	28±7	27.4±3.7*	89.8%
Kung 2019[28]	4	60(66.8)	RM+PEEP titration	45/15	133.4±47.0	20.4±5.8	25.3±3.9	86.7%
		60(63.7)	Lower PEEP	44/16	129.7±42.0	21.5±6	25.7±4.6	76.7%
Constantin2019[29]	20	82(63)	RM+PEEP titration	21%	121±4		26±1	73%
		204(61)	Lower PEEP	28%	115±4		24±1	73%

*means the data was transformed from median (interquartile range) to mean（SD）

Table 2. Results of head-to-head comparisons according to pairwise meta-analyses on different outcomes

Ventilation strategy		N	I^2	Heterogeneity	RR/SMD(95%CI)	*p*-value
Death in hospital						
Lower PEEP *vs*	RM+PEEP titration	5	0.0%	0.547	1.044(0.934,1.167)	0.445
Lower PEEP vs	Higher PEEP	2	0.0%	0.906	0.929(0.825,1.046)	0.222
Lower PEEP vs	RM+higher PEEP	1	-	-	0.917(0.801,1.050)	0.21
Lower PEEP vs	RM+lower PEEP	1	-	-	0.745(0.508,1.094)	0.133
Higher PEEP *vs*	RM+higher PEEP	1	-	-	0.647(0.417,1.004)	0.052
Higher PEEP vs	RM+lower PEEP	1	-	-	0.654(0.418,1.023)	0.063
RM+lower PEEP *vs*	RM+PEEP titration	1	-	-	1.04 (0.780,1.387)	0.79
RM+lower PEEP vs	RM+higher PEEP	1	-	-	0.95 (0.515,1.751)	0.95
Death in 28 day						
RM+PEEP titration *vs*	Lower PEEP	5	0.0%	0.651	1.097(0.986,1.220)	0.09
RM+PEEP titration vs	RM+lower PEEP	2	**64.5%**	0.093	0.806(0.412,1.578)	0.53
Lower PEEP *vs*	RM+higher PEEP	1	-	-	0.908(0.785,1.051)	0.196
Lower PEEP vs	RM+lower PEEP	1	-	-	0.718(0.466,1.107)	0.134
Lower PEEP vs	higher PEEP	1	-	-	0.921(0.785,1.081)	0.316
Ventilator-free days						
RM+PEEP titration *vs*	lower PEEP	3	**56.8%**	0.099	-0.001(-0.214,0.211)	0.989
RM+PEEP titration *vs*	RM+lower PEEP	2	0.0%	0.476	0.013(-0.229,0.256)	0.914
Higher PEEP *vs*	Lower PEEP	2	**71.3%**	0.062	0.043(-0.162,0.247)	0.682
RM+lower PEEP *vs*	Lower PEEP	1	-	-	0.338(-0.038,0.715)	0.078
Barotrauma						
RM+PEEP titration *vs*	lower PEEP	5	**55.5%**	0.061	1.136(0.763,1.753)	**0.013**
higher PEEP *vs*	lower PEEP	2	0	0.879	1.072(0.854,1.345)	0.548
RM+PEEP titration *vs*	RM+lower PEEP	1	-	-	1.074(0.615,1.875)	0.802
RM+higher PEEP *vs*	lower PEEP	1	-	-	1.109(0.911,1.350)	0.303
Significant values *($p < 0.05$)* or I^2>50% are in bold and underlined, indicating a significant heterogeneity, and the random-effects model was chose.						

Table 3 Comparisons of the fit of consistency and inconsistency models in Bayesian framework

model	Death in 28 day Median(95%Crl)	Death in hospital Median(95%Crl)	Ventilator-free days Median(95%Crl)	Barotrauma Median(95%Crl)
consistency	0.36 (0.04, 0.94)	0.19 (0.01, 0.69)	1.62 (0.22, 3.25)	0.60 (0.12, 1.21)
Inconsistency	0.32 (0.04, 1.06)	0.19 (0.02, 0.71)	1.57 (0.17, 3.21)	0.56 (0.04, 1.19)
The DIC is a Bayesian model evaluation criterion that measures model fit adjusted with complexity of the model; smaller DIC values correspond to more preferable models.				

Table 4 Node-splitting analysis for Death in hospital, Death in 28 day, Ventilator-free days and Barotrauma in Bayesian framework

Ventilation strategy	Direct Effect (95%CI)	Indirect Effect ((95%CI))	Overall ((95%CI))	*p*-Value
Death in 28 day				
RM+PEEP titration vs RM+lower PEEP	0.27 (-0.46, 1.24)	-0.69 (-1.95, 0.65)	0.02 (-0.65, 0.80)	0.20
RM+PEEP titration vs lower PEEP	-0.04 (-0.52, 0.57)	0.92 (-0.46, 2.51)	0.08 (-0.39, 0.71)	0.18
RM+lower PEEP vs lower PEEP	0.68 (-0.53, 1.85)	-0.33 (-1.42, 0.66)	0.07 (-0.70, 0.86)	0.17
Death in hospital				
RM+PEEP titration vs RM+lower PEEP	-0.08 (-0.89, 0.77)	-0.65 (-1.48, 0.26)	-0.29 (-0.93, 0.26)	0.33
RM+PEEP titration vs lower PEEP	-0.05 (-0.37, 0.45)	0.53 (-0.62, 1.66)	0.03 (-0.30, 0.47)	0.31
RM+higher PEEP vs RM+lower PEEP	-0.26 (-1.64, 1.14)	-0.05 (-0.89, 1.10)	-0.07 (-0.78, 0.67)	0.75
RM+higher PEEP vs higher PEEP	2.28 (0.14, 5.17)	0.07 (-0.60, 0.74)	0.16 (-0.39, 1.11)	0.05
RM+higher PEEP vs lower PEEP	0.18 (-0.55, 0.91)	0.93 (-0.41, 2.37)	0.24 (-0.23, 0.96)	0.34
RM+lower PEEP vs higher PEEP	2.25 (0.08, 6.04)	0.10 (-0.56, 0.88)	0.27 (-0.34, 1.14)	0.06
RM+lower PEEP vs lower PEEP	0.60 (-0.37, 1.58)	0.22 (-0.47, 1.08)	0.35 (-0.18, 0.99)	0.55
higher PEEP vs lower PEEP	0.15 (-0.27, 0.59)	-1.97 (-5.06, 0.26)	0.07 (-0.49, 0.47)	0.07
Ventilator-free days				
RM+PEEP titration *vs* RM+lower PEEP	-0.51 (-5.14, 4.27)	3.80 (-2.41, 9.36)	1.28 (-2.67, 4.83)	0.26
RM+PEEP titration *vs* lower PEEP	0.41 (-2.73, 2.80)	-3.90 (-11.14, 2.86)	-0.14 (-3.17, 2.15)	0.25
RM+lower PEEP *vs* lower PEEP	-3.41 (-8.60, 1.71)	0.75 (-4.68, 6.09)	-1.42 (-5.37, 2.38)	0.29
Barotrauma				
RM+PEEP titration *vs* RM+lower PEEP	-0.19 (-2.05, 1.67)	-9.01 (-35.46, 11.46)	-0.19 (-2.07, 1.56)	0.45
RM+PEEP titration *vs* lower PEEP	-0.32 (-1.18, 0.76)	8.50 (-9.60, 45.55)	-0.30 (-1.15, 0.75)	0.38
RM+lower PEEP *vs* lower PEEP	5.73 (-15.99, 38.53)	-0.13 (-2.13, 2.07)	-0.10 (-2.00, 2.11)	0.63
Significant values ($p \leq 0.05$) are in bold and underlined, indicating a significant inconsistency between the direct effect and indirect effects				

Table 5 Node-splitting analysis for Death in hospital, Death in 28 day, Ventilator-free days and Barotrauma in Frequentist framework

Ventilation strategy	Direct Effect (Std.Err)	Indirect Effect (Std.Err)	Difference (Std.Err)	*p*-Value
Death in 28 day				
RM+PEEP titration vs RM+lower PEEP	0.36 (0.75)	0.16 (1.16)	0.20 (1.38)	0.887
RM+PEEP titration vs lower PEEP	0.57 (0.52)	0.76 (1.28)	-0.19 (1.38)	0.888
RM+lower PEEP vs lower PEEP	0.41 (1.04)	0.21 (0.91)	0.20 (1.38)	0.887
Death in hospital				
RM+PEEP titration vs RM+lower PEEP	-0.06 (0.22)	-0.39 (0.20)	0.34 (0.29)	0.246
RM+PEEP titration vs lower PEEP	-0.04 (0.11)	0.30 (0.27)	-0.34 (0.29)	0.246
RM+higher PEEP vs RM+lower PEEP	0.04 (0.33)	-0.12 (0.21)	0.16 (0.39)	0.685
RM+higher PEEP vs higher PEEP	0.59 (0.25)	0.005 (0.11)	0.59 (0.28)	**0.036**
RM+higher PEEP vs lower PEEP	0.10 (0.09)	0.54 (0.27)	-0.43 (0.29)	0.129
RM+lower PEEP vs higher PEEP	0.57 (0.25)	0.03 (0.16)	0.54 (0.29)	0.067
RM+lower PEEP vs lower PEEP	0.30 (0.23)	0.22 (0.19)	0.08 (0.30)	0.778
higher PEEP vs lower PEEP	0.10 (0.08)	-0.41 (0.22)	0.51 (0.23)	**0.031**
Ventilator-free days				
RM+PEEP titration *vs* RM+lower PEEP	-0.02 (0.15)	0.038 (0.24)	-0.40 (0.28)	0.149
RM+PEEP titration *vs* lower PEEP	0.04 (0.10)	-0.36 (0.26)	0.40 (0.28)	0.149
RM+lower PEEP *vs* lower PEEP	-0.34 (0.22)	0.06 (0.17)	-0.40 (0.28)	0.149
Barotrauma				
RM+PEEP titration *vs* RM+lower PEEP	-0.14 (0.79)	-0.28 (2.11)	0.14 (2.25)	0.952
RM+PEEP titration *vs* lower PEEP	-0.25 (0.46)	-0.14 (2.20)	-0.14 (2.25)	0.952
RM+lower PEEP *vs* lower PEEP	-5.9e-11 (2.06)	-0.14 (0.91)	0.14 (2.25)	0.952
Significant values ($p \leq 0.05$) are in bold and underlined, indicating a significant inconsistency between the direct effect and indirect effects				

Network structure and geometry

The network plot for all outcomes is shown in Figure 3. The size of the node is proportional to the number of patients randomized to receive the treatment. The width of each line is proportional to the number of trials comparing the connected treatments. The most common comparison was RM+PEEP titration versus lower PEEP, and the most common subjects were RM+PEEP titration versus lower PEEP. The network plots for death in 28 days (Figure 3A) and barotrauma (Figure 3D) were similar. The difference is mainly the number of studies comparing the two strategies.

Network meta-analysis for outcomes

For the primary outcomes in terms of death in 28 days, five ventilation strategies were included. None of the ventilation strategies were significantly superior to others, and the 95% CI included 1 in the Bayesian (Fig. 4A) and the frequentist frameworks (Fig. 4C)

For the secondary outcomes, the ventilation strategies were compared except the RM+higher PEEP in terms of ventilator-free day. The result of network meta-analysis indicated that the differences among the strategies were not significant in either Bayesian (Fig. 4B) or Frequentist framework (Fig.4D) with 95% CI of 0. In terms of the other two secondary outcomes, the results of the two frameworks suggested that no strategy was superior in terms of hospital deaths and barotrauma.

Rank probabilities

The relative ranking of the ventilation strategies was estimated using SUCRA. The Bayesian and the Frequentist frameworks were used to calculate the ranking probability and SURCA. The Bayesian framework indicates that the lower the SUCRA, the more superior the strategy in terms of the outcome of death in 28 days, death in hospital, and barotrauma. The outcomes of ventilator-free days indicate that the higher the SUCRA, the more superior the strategy. The frequentist framework indicates that for all outcomes, the higher the SUCRA, the more superior the strategy. The ranking results in both frameworks are shown in Table 6 and Table 7, respectively, and the SUCRA in both frameworks are shown in Figure 5.

In terms of death in 28 days, the lower PEEP was the worst strategy in the Bayesian and frequentist frameworks. However, the superior strategy was different in the two frameworks. Higher PEEP was the best strategy in the Bayesian framework, whereas RM+PEEP titration was the best one in the frequentist framework.

In terms of hospital deaths, the results were the same for the Bayesian framework and the frequentist framework, that is, RM+lower PEEP was the superior strategy and lower PEEP was the worst strategy.

In terms of ventilator-free days, the results were similar to the results of hospital death. RM+lower PEEP had the highest SUCRA value in the Bayesian framework and the frequentist framework, whereas lower PEEP strategy had the lowest SUCRA value in the two frameworks.

In terms of barotrauma, the relative ranking was consistent in the Bayesian framework and the frequentist framework. Lower PEEP was the superior mechanical ventilation strategy and RM+PEEP titration was the worst mechanical ventilation strategy.

Table 6. Bayesian ranking results of network meta-analysis

Strategy	Rank of possibility					SUCRA
	1	2	3	4	5	
Death in 28d (Rank 1 is worst, rank N is best)						
RM+PEEP titration	0.13	0.2	0.23	0.27	0.16	0.571
RM+higher PEEP	0.29	0.18	0.17	0.18	0.18	0.644
RM+lower PEEP	0.24	0.16	0.16	0.21	0.23	0.588
higher PEEP	0.2	0.13	0.12	0.17	0.39	<u>**0.5**</u>
lower PEEP	0.14	0.34	0.32	0.17	0.04	0.705
Death in hospital (Rank 1 is worst, rank N is best)						
RM+PEEP titration	0.3	0.27	0.25	0.14	0.04	0.75
RM+higher PEEP	0.07	0.08	0.15	0.34	0.36	0.406
RM+lower PEEP	0.05	0.05	0.14	0.25	0.52	<u>**0.339**</u>
higher PEEP	0.25	0.17	0.27	0.23	0.07	0.639
lower PEEP	0.33	0.43	0.19	0.04	0	0.844
Ventilator-free days (Rank 1 is best, rank N is worst)						
RM+PEEP titration	0.12	0.29	0.25	0.34		0.543
RM+lower PEEP	0.56	0.19	0.12	0.13		<u>**0.8**</u>
higher PEEP	0.28	0.29	0.21	0.23		0.663
lower PEEP	0.04	0.22	0.43	0.3		0.49
Barotrauma (Rank 1 is worst, rank N is best)						
RM+PEEP titration	0.22	0.32	0.22	0.17	0.07	0.71
RM+higher PEEP	0.27	0.21	0.2	0.17	0.15	0.661
RM+lower PEEP	0.28	0.14	0.11	0.12	0.36	0.56
higher PEEP	0.19	0.19	0.2	0.2	0.21	0.584
lower PEEP	0.02	0.13	0.28	0.35	0.21	<u>**0.468**</u>
The number in each cell represents the probability of each ventilation strategy. The value of SUCRA with biggest probability of ranking best is in bold and underlined.						

Table 7 Frequentist ranking results of network meta-analysis

Strategy	Rank of possibility					SUCRA
	1	2	3	4	5	
Death in 28d (Rank 1 is best, rank N is worst)						
RM+PEEP titration	0.36	0.38	0.18	0.07	0.01	0.749
RM+higher PEEP	0.23	0.15	0.14	0.17	0.31	0.453
RM+lower PEEP	0.18	0.25	0.23	0.18	0.16	0.529
higher PEEP	0.22	0.15	0.14	0.17	0.32	0.445
lower PEEP	0.01	0.08	0.3	0.42	0.19	0.323
Death in hospital (Rank 1 is best, rank N is worst)						
RM+PEEP titration	0.01	0.11	0.3	0.21	0.37	0.296
RM+higher PEEP	0.31	0.45	0.15	0.06	0.04	0.736
RM+lower PEEP	0.64	0.26	0.07	0.02	0.01	0.871
higher PEEP	0.04	0.15	0.28	0.21	0.32	0.345
lower PEEP	0	0.03	0.21	0.49	0.27	0.252
Ventilator-free days (Rank 1 is best, rank N is worst)						
RM+PEEP titration	0.12	0.3	0.27	0.31		0.409
RM+lower PEEP	0.52	0.21	0.13	0.14		0.704
higher PEEP	0.3	0.26	0.2	0.24		0.542
lower PEEP	0.06	0.23	0.4	0.31		0.345
Barotrauma (Rank 1 is best, rank N is worst)						
RM+PEEP titration	0.07	0.16	0.22	0.31	0.24	0.382
RM+higher PEEP	0.16	0.15	0.19	0.22	0.28	0.423
RM+lower PEEP	0.33	0.12	0.11	0.16	0.29	0.512
higher PEEP	0.22	0.21	0.2	0.19	0.18	0.521
lower PEEP	0.22	0.37	0.28	0.12	0.02	0.663
The number in each cell represents the probability of each ventilation strategy. The value of SUCRA with biggest probability of ranking best is in bold and underlined.						

Discussion

In our systematic review and network meta-analysis, we summarized mechanical ventilation strategies based on the low tidal volume among patients with severe ARDS. To the best of our knowledge, this study is the first to use network meta-analysis to compare different mechanical ventilation strategies. The major findings from our present analysis are as follows: i) No ventilation strategy was significant superior to others in terms of death in 28 days, hospital death, ventilator-free days, and barotrauma. ii) For the relative ranking of death in 28 days, higher PEEP was the first choice in Bayesian framework, while RM+PEEP titration was the first choice in the frequentist framework. Lower PEEP was the worst in the two frameworks. iii) For relative ranking of death in hospital, ventilator-free days, and barotrauma, the results were consistent in the Bayesian framework and in the frequentist framework. In terms of Death in hospital and Ventilator-free days, RM+PEEP titration may be the first choice, and lower PEEP was the worst. In terms of barotrauma, lower PEEP was the safest strategy, whereas RM+PEEP titration posed the highest risk for barotrauma. Given that the use of ventilator should be monitored at any time and the parameters are adjusted by the clinician according to the condition of the patients, the blind method is not suitable for these random clinical trials. Thus, the overall quality of the evidence is moderate-to-low or low for the primary and secondary outcomes.

The Bayesian and the frequentist frameworks are two typical models for performing network meta-analysis. In our network meta-analysis, we used the two frameworks to compare different ventilation strategies among patients with ARDS. The global and local inconsistencies in the two frameworks were low, suggesting that the direct and indirect comparisons of interventions were reliable.

In the past 50 years, considerable progress has been made in understanding ARDS. However, no effective pharmacological therapies have been developed for the treatment of ARDS. The incidence of ARDS is nearly 34/100,000 per year[30]. ARDS also represents 10.4% of total ICU admissions and 23.4% of all patients requiring mechanical ventilation constituting 0.42 cases/ICU bed over 4 weeks[7]. Ventilation- to-perfusion mismatch leads to hypoxia and impaired excretion of carbon dioxide, including endothelial damage, VE- cadherin disruption, immune cell recruitment to the lung, and epithelial injury and repair[31]. Respiratory support is the most important management for ARDS. Slutsky et al. summarized the progress in mechanical ventilation[32]; low tidal volume, neuromuscular block, and prone position ventilation are the most important progress in the past 20 years. However, lung recruitment maneuvers and PEEP remain controversial. Recruitment maneuver can open up the collapsed lung and PEEP can maintain alveolar stability; a recent study suggested that the total amount of lung recruitment tissue increased with ARDS severity[33]. A recent two pairwise meta-analysis suggested that RM had no advantageous effect on mortality[13, 34]. Higher PEEP reduced mortality in the subgroup for patients with ARDS who responded to increased PEEP by improved oxygenation; overall, higher PEEP was not an advantageous for patients with ARDS[11]. The negative result may be caused by studies that did not take into account the combined effects of RM and PEEP levels.

Lung protective ventilation is now universally accepted, and low tidal volume ventilation is the basis of lung protection. In our study, RCTs in which subjects did not receive low tidal volume were excluded. In our network meta-analysis, five combinations of RM and PEEP levels were enrolled, and RM+PEEP titration versus low-PEEP were the most common points of comparison. The lower PEEP strategy was mainly based on the lower PEEP/FiO2 chart described in the ARDS Clinical Trials Network[15]. Higher PEEP strategy was mainly based on the plateau pressure. The results of RCTs suggest that RM+PEEP titration cannot improve 28-day mortality and ICU mortality among patients with moderate-to-severe ARDS[33]. Conventional pairwise meta-analysis failed to reveal any superior ventilation strategy. As such, we used network meta-analysis to provide relative efficacy estimates among all interventions; however, some techniques have never been compared head to head[35].

In this study, the differences among death in 28 days, hospital death, ventilator-free days, and barotrauma were not significant. This finding is consistent with previous conventional pairwise meta-analyses. Relative ranking possibility results suggested that higher PEEP strategy was best for death in 28 days in the Bayesian framework, whereas RM+PEEP titration was best in the frequentist framework. In terms of death in hospital and ventilator-free days, RM+lower PEEP was the best strategy in both

Bayesian and frequentist frameworks. These results achieved were beyond our expectations. PEEP titration is a personalized treatment for obtaining the optimal PEEP; several methods have been proposed for PEEP titration in an individual patient with ARDS, including gas change, compliance, pressure–volume curve, and esophageal pressure[36]. PEEP should be selected as a balance between alveolar recruitment and overdistention, and PEEP titration is a good method for balancing alveolar recruitment and overdistention. However, RM+PEEP is not the best recommended strategy in our network meta-analysis. PEEP titration failed to establish the best balance between the alveolar recruitment and overdistention. Krebs showed that PEEP titrated in accordance with the minimal static elastance of the respiratory system did not prevent negative end-expiratory transpulmonary pressure[37]. Among the studies enrolled in our analysis, PEEP titration strategy based on respiratory-system compliance (Hug 2009, Kacmarek 2016, Art 2017), saturation of oxygen (Hodgson 2011, Constantin 2019), and esophageal pressure (Tamlor 2008, Beitler 2019) were conducted. Although the decrease in driving pressure is strongly associated with increased survival, no studies used this parameter as the PEEP titrated strategy [38]. This factor may explain why RM+PEEP titration was not the first choice in our analysis.

RM+lower PEEP is the combination that may likely result in hospital death and ventilator-free days; this result is consistent with previous results to some extent[26]. A recent finding showed that the open lung strategy is not satisfactory using PEEP up to 15 cmH2O and plateau pressure up to 30 cmH2O; high pressures are required for opening the lung[39]. This result is attributed to the heterogeneity of pulmonary lesions among patients with severe ARDS; maximum compliance was determined by overdistending the normal tissue, thereby resulting in adverse effects than that of recruitment collapse alveolar.

In terms of Barotrauma, lower PEEP is the safest strategy in rank possibility, which is consistent with theoretical and clinical understanding. However RM+PEEP titration had the highest risk of barotrauma, and the rank was worse than that of RM+higher PEEP. This result is ascribed to that RM+higher PEEP strategy recruit more collapsed alveolar which can reduce shear stress[40] and improve ventilation- to-perfusion mismatch.

Limitation

This study has several limitations. First, the modes of ventilation are diverse. Ventilator models used in clinical trials are inconsistent, and we classified the mechanical ventilation strategies, which may cause bias. For example, PEEP titration strategy based on compliance, gas change, and esophageal Pressure were all classified to PEEP titration. Second, the ventilator parameters may change anytime according to patients, and the same strategy may include different parameters that may influence the judgement for outcomes. A few articles used the median, the first, and the third quartiles to describe the results. We used an equation to transform data, which may decrease the reliability of the results.

Conclusion

In this network meta-analysis, we classified the mechanical ventilation strategies to RM+PEEP titration, RM+higher PEEP, RM+lower PEEP, higher PEEP, and lower PEEP on the basis of recruitment maneuvers and different PEEP levels for mechanical ventilation among patients with ARDS. None of the strategies were significantly superior to others. According to the relative ranking recommended by the Bayesian and frequentist frameworks, lower PEEP showed the lowest probability of harming death after 28 days, whereas RM+lower PEEP showed the highest probability of benefitting death in hospital and ventilator-free days. Lower PEEP showed the highest probability of benefitting barotrauma. In general, RM+lower PEEP may benefit patients with ARDS. The overall quality of the evidence is low and should be further studied.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication：Not applicable

Availability of data and materials：

All data analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WH, PW and FJ searched the scientific literature , WH drafted the manuscript. WH, BH, XC and HS performed the statistical analyses and revised the manuscript. WH, HD and QL participated in data interpretation and drafted the report. QL and AZ conceived of the study and contributed data. AZ made important revisions to the draft report. QL and AZ contributed equally to this paper and are joint corresponding authors. WH is first author. All authors have read and approved the final version of the manuscript.

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Abbreviations

ARDS, acute respiratory distress syndrome; DIC, deviance information criterion; ICU, intensive care unit; PEEP, positive end-expiratory pressure; RM, recruitment maneuver; RR, Risk ratios; SMD, standard mean difference;

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Figures

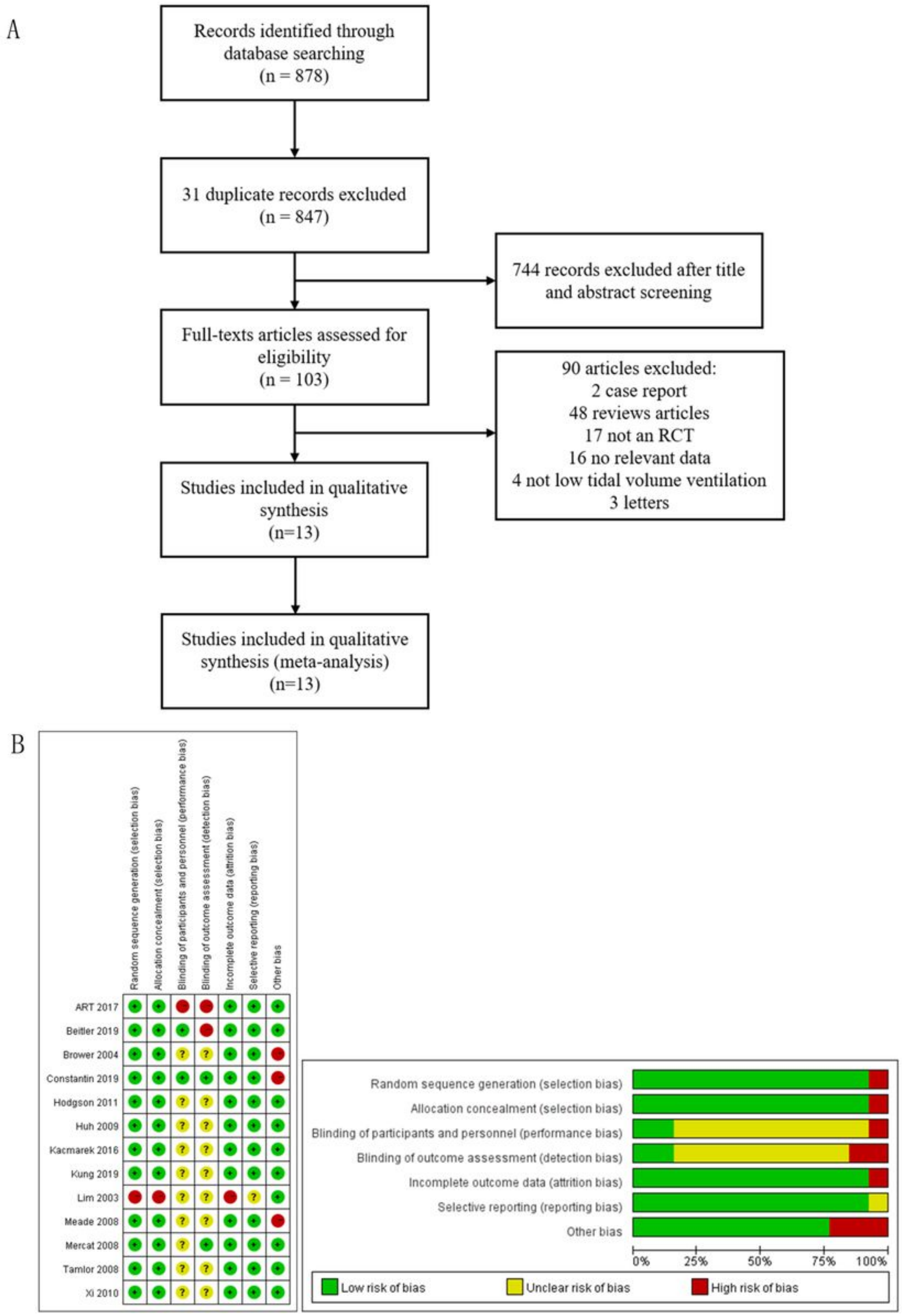

Figure 2

Flow diagram of the literature search and risk of bias graph. A. Flow chart of the different phases of the literature search. B. Cochrane risk of bias assessment for enrolled studies.

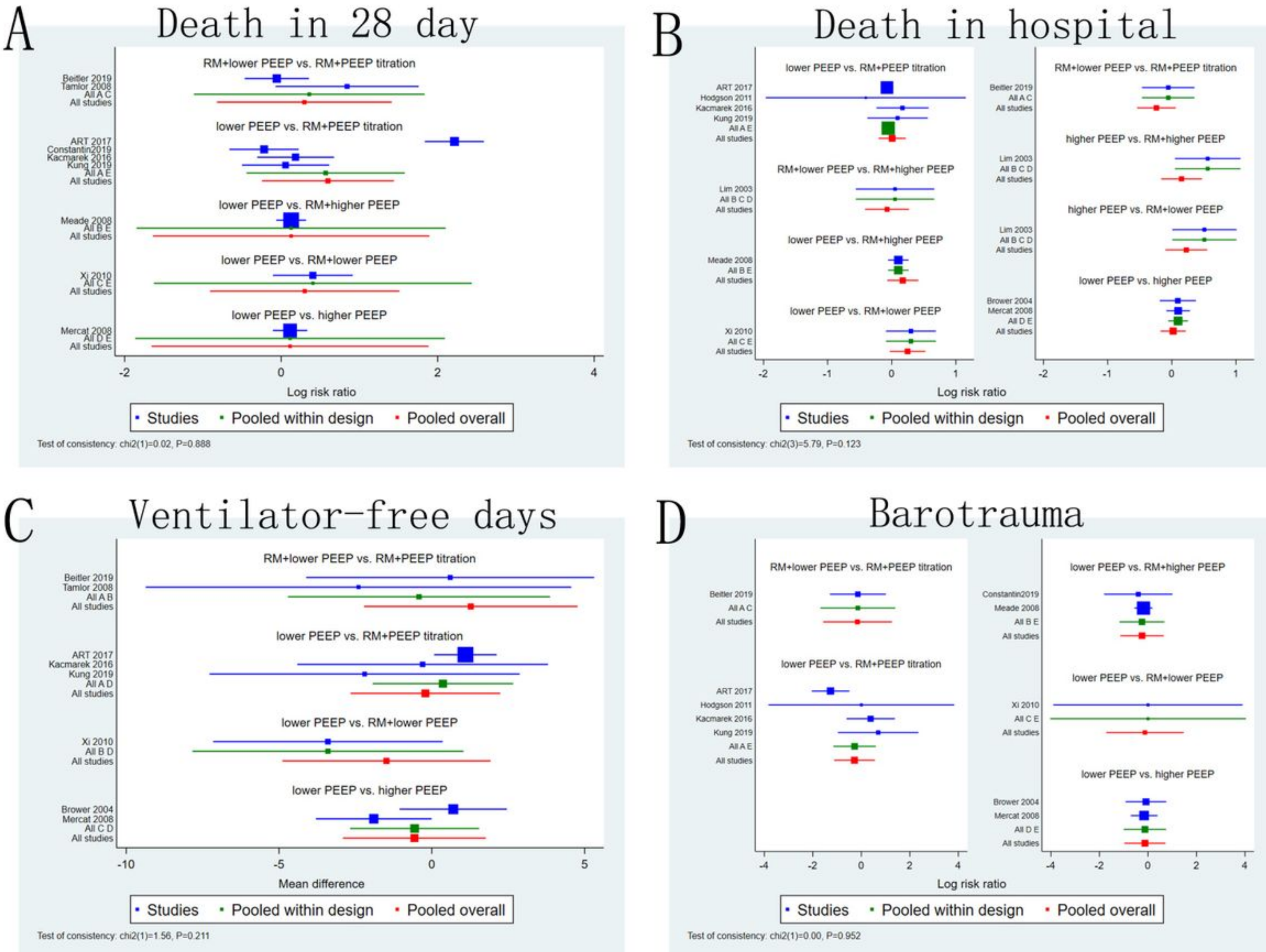

Figure 3

Forest plots of results with global inconsistency detection for all outcomes in the frequentist framework. A. Global inconsistency detection for death in 28 days. B. Global inconsistency detection for death in hospital. C. Global inconsistency detection for ventilator-free days. D. Global inconsistency detection for barotrauma. P value is shown at the bottom of the graph. p>0.05 indicates the absence of global inconsistency for the outcomes.

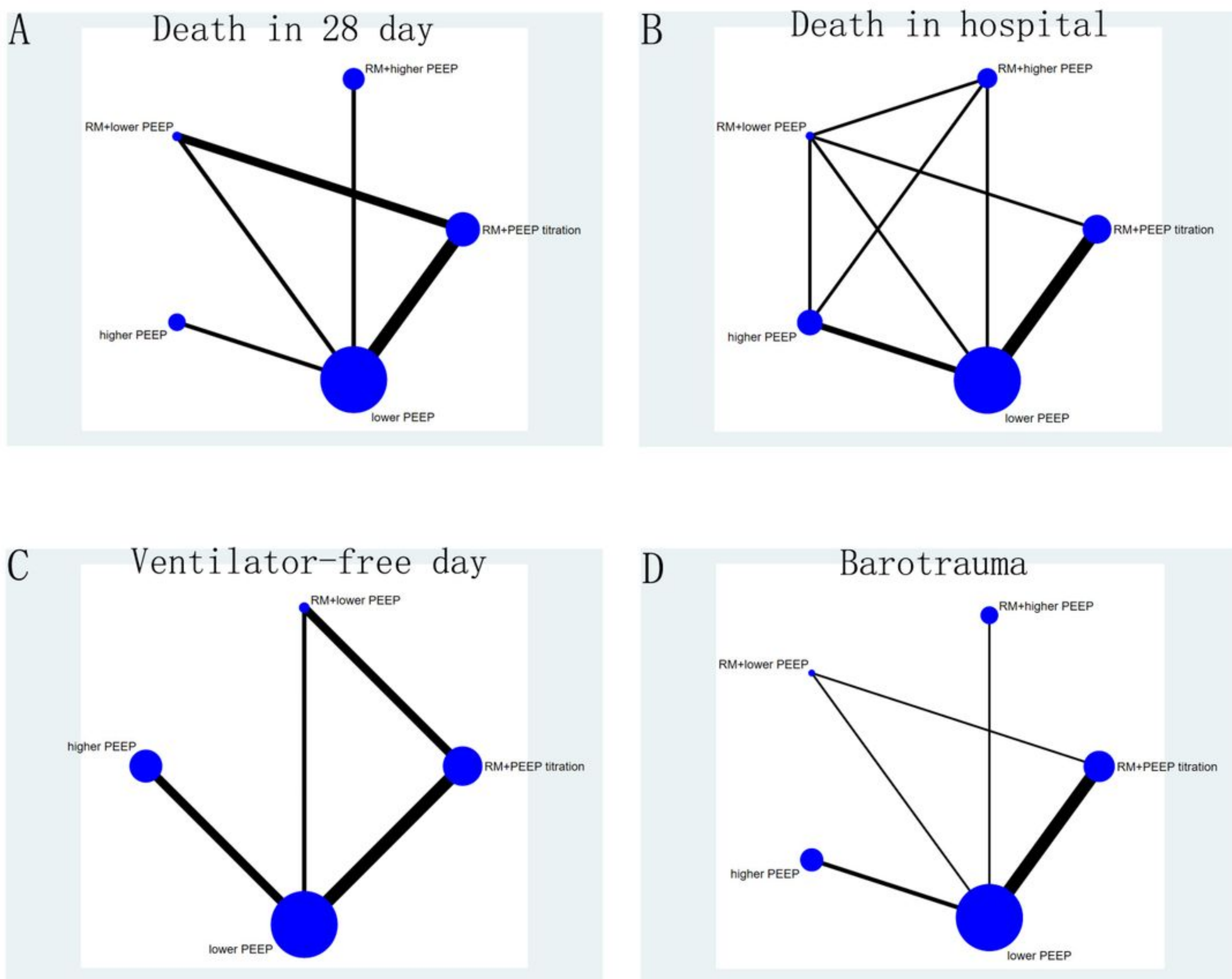

Figure 5

Network plots for all outcomes. A. Network plots for death in 28 days. B. Network plots for death in hospital. C. Network plots for ventilator-free days. D. Network plots for barotrauma. Treatments are represented by nodes and head-to-head comparisons with edges. The size of the nodes is proportional to the number of the patients, while the thickness of the edges is proportional to the number of studies.

A

Death in 28d in Bayesian framework (rows: Death in hospital Bayesian framework)

RM+PEEP titration	1.07 (0.48, 3.17)	1.02 (0.52, 2.23)	0.92 (0.32, 3.26)	1.08 (0.68, 2.04)
1.23 (0.65, 2.58)	RM+higher PEEP	0.95 (0.30, 2.62)	0.88 (0.23, 2.95)	1.01 (0.44, 2.07)
1.34 (0.77, 2.54)	1.07 (0.51, 2.19)	RM+lower PEEP	0.92 (0.26, 3.31)	1.07 (0.49, 2.35)
1.04 (0.49, 1.69)	0.85 (0.33, 1.47)	0.76 (0.32, 1.41)	higher PEEP	1.16 (0.43, 3.17)
0.97 (0.63, 1.35)	0.79 (0.38, 1.26)	0.71 (0.37, 1.20)	0.93 (0.62, 1.64)	lower PEEP

B

Barotrauma in Bayesian framework (rows: Ventilator-free days in Bayesian framework)

RM+PEEP titration	0.94 (0.24, 5.08)	0.82 (0.13, 4.77)	0.84 (0.22, 4.13)	0.74 (0.32, 2.12)
—	RM+higher PEEP	0.86 (0.07, 7.63)	0.89 (0.17, 4.67)	0.77 (0.23, 2.55)
-1.28 (-4.83, 2.67)	—	RM+lower PEEP	1.03 (0.12, 12.94)	0.90 (0.13, 8.24)
-0.43 (-4.02, 4.06)	—	0.86 (-3.88, 5.86)	higher PEEP	0.87 (0.28, 2.73)
0.14 (-2.15, 3.17)	—	1.42 (-2.38, 5.37)	0.55 (-2.43, 3.55)	lower PEEP

C

Death in 28d in Frequentist framework (rows: Death in hospital in Frequentist framework)

RM+PEEP titration	1.60 (0.23,11.33)	1.34 (0.44,4.11)	1.62 (0.23,11.51)	1.82 (0.78, 4.22)
0.17 (-0.11,0.44)	RM+higher PEEP	0.84 (0.10,7.15)	1.01 (0.08,12.35)	1.14 (0.19,6.64)
0.24 (-0.06,0.54)	0.07 (-0.27,0.42)	RM+lower PEEP	1.21 (0.14,10.29)	1.35 (0.40,4.53)
0.01 (-0.30,0.33)	-0.15 (-0.47,0.17)	-0.23 (-0.55,0.10)	higher PEEP	1.12 (0.19,6.58)
-0.01 (-0.22,0.20)	-0.17 (-0.42,0.07)	-0.25 (-0.52,0.03)	-0.02 (-0.22,0.18)	lower PEEP

D

Barotrauma in in Frequentist framework (rows: Ventilator-free days in Frequentist framework)

RM+PEEP titration	0.96 (0.28,3.32)	0.85 (0.21,3.52)	0.86 (0.26,2.81)	0.75 (0.32,1.75)
—	RM+higher PEEP	0.89 (0.14,5.57)	0.89 (0.26,3.04)	0.78 (0.32,1.91)
0.92 (0.71,1.19)	—	RM+lower PEEP	1.04 (0.10, 14.01)	0.89 (0.13, 8.47)
0.97 (0.73,1.29)	—	1.06 (0.74,1.50)	higher PEEP	0.87 (0.26, 2.98)
1.01 (0.83,1.24)	—	1.10 (0.83,1.47)	1.04 (0.85,1.28)	lower PEEP

Figure 8

Pooled estimates of network meta-analysis. A. Risk ratios (95% credible intervals) for death in 28 days (upper triangle) and death in the hospital (lower triangle) in the Bayesian framework. B. Risk ratios (95% credible intervals) for barotrauma (upper triangle) and standard mean difference (95% credible intervals) for ventilator-free days (lower triangle) in the Bayesian framework. C. Risk ratios (95% credible intervals) for death in 28 days (upper triangle) and death in the hospital (lower triangle) in the frequentist framework. D. Risk ratios (95% credible intervals) for barotrauma (upper triangle) and standard mean difference (95% credible intervals) for ventilator-free days (lower triangle) in the frequentist framework. Result in each cell is presented as risk ratio or standard mean difference (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. In terms of death in 28 days, death in the hospital and barotrauma, if the range of 95% CIof 1, the difference between the two strategies is not significant. In terms of ventilator-free days, if the range of 95% CI of 0, the difference between the two strategies is not significant.

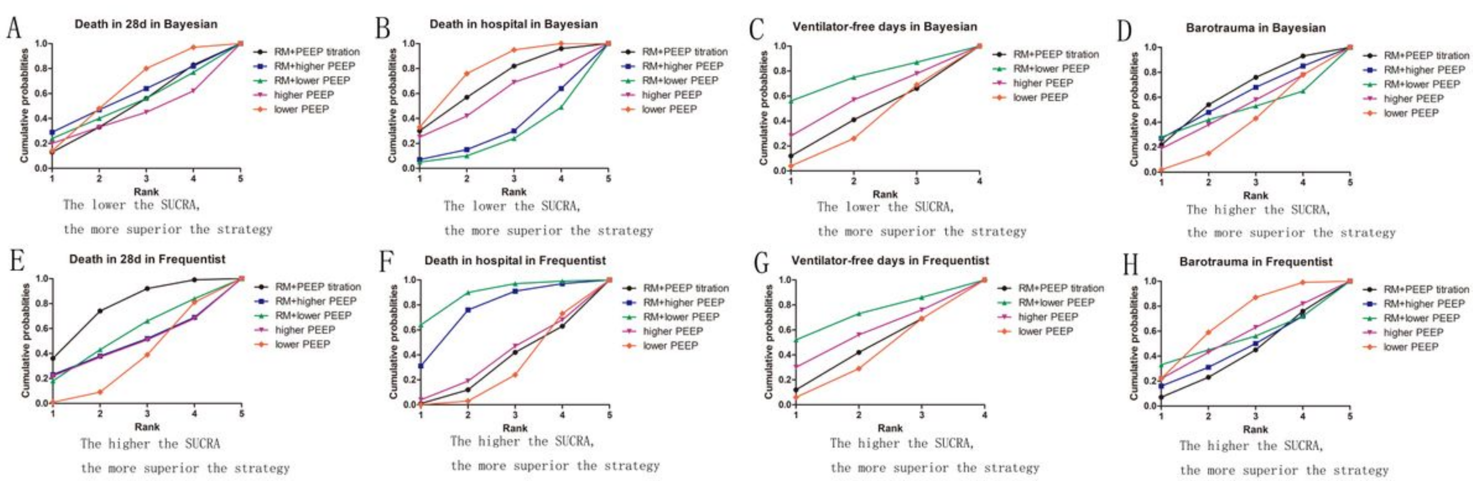

Figure 10

Rankograms and the SUCRA for each ventilation strategy for A. Death in 28 days in the Bayesian framework. B. Death in the hospital in the Bayesian framework. C. Ventilator-free days in the Bayesian framework. D. Barotrauma in the Bayesian framework. E. Death in 28 days in the frequentist framework. F. Death in the hospital in the frequentist framework . G. Ventilator-free days in the frequentist framework. H. Barotrauma in the frequentist framework. Horizontal axis shows possible ranks and vertical axis shows cumulative probability at each rank. In terms of death in 28 days, death in the hospital and barotrauma in Bayesian framework, the smaller SUCRA, the better the ranking. In terms of ventilator-free days in the Bayesian framework and all outcomes in the frequentist framework, the larger SUCRA, the better ranking.