



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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Abstract

Objective Acute respiratory distress syndrome (ARDS) leads to life-threatening acute hypoxemic respiratory failure and requires mechanical ventilation. However, there is a lack of certainty regarding recruitment maneuvers (RMs) and positive end-expiratory pressure (PEEP) levels. Therefore, we performed a network meta-analysis to identify the optimal RM and PEEP levels of patients with ARDS.

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

Results Thirteen RCTs comprising 4410 patients were included in the network meta-analysis. In terms of death at 28 days, inconsistencies were found globally and locally in the tests. None of the ventilation strategies was significantly superior to the others on any outcomes. According to the relative rank probabilities, RM + lower PEEP levels showed the highest probability of reducing the risk of in-hospital death and reducing ventilator-free days. Lower PEEP levels showed the highest probability of benefitting barotrauma. The overall quality of the evidence per grade was moderate to low.

Conclusions The no ventilation strategy is significantly superior to the other strategies. RM + lower PEEP levels has the highest probability of benefitting survival. The evidence has low overall quality and should be further studied.

Keywords Acute respiratory distress syndrome · Ventilation strategies · Recruitment maneuver · Positive end-expiratory pressure · Network meta-analysis

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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1 Introduction

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury characterized by damaged pulmonary capillary endothelial cells, damaged alveolar epithelial cells and increased vascular permeability, leading to life-threatening acute hypoxemic respiratory failure in the clinic [1]. ARDS was first reported 50 years ago [2], and a number of positive clinical trials have been conducted over the past decades to examine treatment strategies, such as

mechanical ventilation with a low tidal volume [3], neuromuscular blockers in early ARDS [4], and prone positioning [5]. Approximately 40.1% of patients with ARDS need invasive ventilation. To date, mechanical ventilation is the firstline therapy for ARDS. On the basis of clinical research, guidelines endorsed by multiple professional societies recommend lowering the tidal volume and airway pressure as the basic strategies for ventilation [6, 7]. In addition to tidal volume, other parameters of mechanical ventilation, such as positive end-expiratory pressure (PEEP) levels and lung recruitment maneuvers, can affect the outcomes of patients with ARDS. In previous studies, higher PEEP levels for patients with ARDS responded to increased PEEP through improved oxygenation and reduced mortality [8]; additionally, some studies have shown that lung recruitment maneuvers (RMs) with higher PEEP levels may reduce mortality [9], while other studies have reached a different conclusion [10]. 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. 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 to compare multiple mechanical ventilation strategies. We compared different PEEP levels with or without lung recruitment maneuvers in terms of low tidal volume ventilation to identify the optimal ventilation strategy for ARDS.

2 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 [11].

2.1 Eligibility Criteria

The inclusion criteria of the studies were randomized controlled trials (RCTs) that were used to compare different mechanical ventilation strategies for adult patients with moderate to severe ARDS. The inclusion criteria of patients were adults with moderate to severe ARDS who received mechanical ventilation with low tidal volume mechanical ventilation strategies.

The types of mechanical strategies included lower PEEP, higher PEEP, RM + higher PEEP, RM + lower PEEP, and RM + PEEP titration. A lower PEEP level is defined as the minimum PEEP levels reaching the clinical goals, including the ARDSNet PEEP/FiO₂ protocol [12] or minimum PEEP to maintain PaO₂ > 60 mmHg and FiO₂ < 0.6. A higher PEEP level is defined as the maximum PEEP without increasing the maximal inspiratory plateau pressure above 28–30 cm

H₂O or initial PEEP levels higher than a comparator strategy used to determine PEEP, including the high PEEP/FiO₂ protocol. PEEP titration included PEEP titration according to the best respiratory-system static compliance, maximum SaO₂, or esophageal pressure. RM is defined as the application of transient elevations to airway pressure during mechanical ventilation to open, including collapsed lung units and an increase in the number of alveoli participating in tidal ventilation, including extended sigh, staircase incremental PEEP levels or continuous positive airway pressure.

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

2.2 Data Sources and Searches

We searched the PubMed, OVID, and Cochrane Central Register of Controlled Trials (Central) databases to find relevant articles up to 30 December 2019 in all languages without limitations concerning publication dates and languages. We used 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”). The electronic search strategy for the 4 databases is shown in the supplemental file.

2.3 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 were extracted, and the study quality was 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 and the first and third quartiles were recorded in clinical trial studies, then the equation ($X \approx (0.7 + 0.39/n)(q1 + q3)/2 + (0.3 - 0.39/n) m$) [13] was used to transform information to the sample mean, and the equation ($SD \approx (q3 - q1)/1.35$) was used to transform information to standard deviation [14] to avoid data loss.

2.4 Risk of Bias in Individual Studies

The risk of bias in individual studies was classified into three levels: low risk of bias, unclear risk of bias, and high risk of bias. Risk of bias analysis was performed using Review Manager® Version 5.3 for Windows (RevMan, The Cochrane Collaboration, Oxford, UK).

2.5 Statistical Analysis

Traditional pairwise meta-analysis was used 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).

Risk ratios (RRs) were used to estimate the relative effect sizes for binary variables, while the 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 I^2 statistics and p values. Statistical significance was set at a p value of 0.05. Heterogeneity was considered low, moderate, or high for the estimated I^2 values under 25%, between 25 and 50%, and over 50%, respectively. If $p < 0.05$ or $I^2 > 50%$, the random effects model was used for pairwise meta-analyses; otherwise, the 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 significant heterogeneity. The random effects model was used to calculate the 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 a basis for selecting alternatives. For each ventilation strategy, the 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 the curves was calculated. The SUCRA can be used to estimate the priority of the strategy. SUCRA was calculated using a previously reported equation [13]. The ranking probabilities were calculated using the Bayesian framework, and cumulative ranking probability curves were drawn using GraphPad Prism 5.

3 Results

3.1 Characteristics of Enrolled Studies

A total of 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 a low tidal volume ventilation strategy in the control groups. Ultimately, 13 randomized controlled trials including 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 Fig. 1A. The main characteristics of all studies are reported in Table 1.

3.2 Risk of Bias Within Studies

The risk of bias within studies is shown in Fig. 1B. An article [15] did not describe randomization methods. Three articles had a high risk of other bias, and one of them [12] 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 study [26] was caused by different treatments between focal ARDS and nonfocal ARDS.

3.3 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 was 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 55.5%. The comparisons of other strategies show low heterogeneity. The results of the pairwise meta-analyses are shown in Supplemental file 1.

The fit of the consistency model for all outcomes was similar to that of the inconsistency model (Supplemental file 2), suggesting low global inconsistency. The node-splitting analysis for death in 28 days, RM + PEEP titration versus RM + lower PEEP and RM + lower PEEP versus lower PEEP had local inconsistency ($p < 0.05$). The other outcomes showed no significant inconsistency between the direct effects and indirect effects (Supplemental file 3).

3.4 Network Structure and Geometry

The network plot for all outcomes is shown in Fig. 2. 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

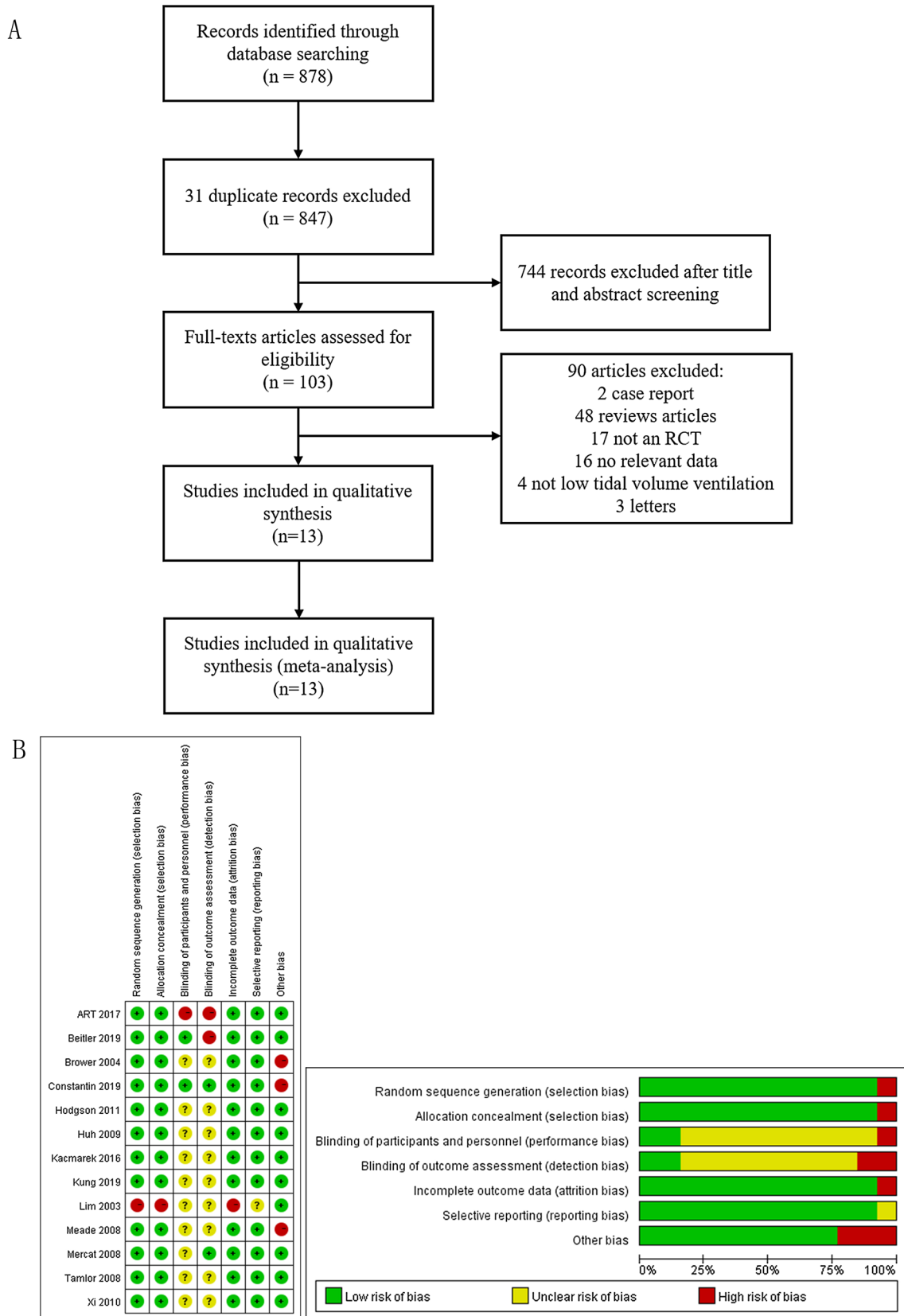


Fig. 1 Flow diagram of the literature search and risk of bias graph. **A** Flow chart of the different phases of the literature search. **B** Cochrane risk of bias assessment for enrolled studies

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 (cmH ₂ O) | APACHEII score | Plateau pressure (cmH ₂ O) | Pulmonary pressure (%) | ARDS | PEEP levels on day 1 (mmHg) |
|-----------------------------|---------------------------|------------------------|------------|---|----------------|---------------------------------------|------------------------|------|-----------------------------|
| Lim et al. [15] | 20 (60) | RM + higher PEEP | 10% | | | | 75 | | 15 |
| | 19 (61) | RM + lower PEEP | 10.5% | | | | 78.9 | | 10 |
| | 8 (60) | Higher PEEP | 12.5% | | | | 87.5 | | 15 |
| Brower et al. [12] | 276 (49) | Higher PEEP | 43% | 151 ± 67 | | 27 ± 6 | 58 | | 14.7 ± 3.5 |
| | 273 (54) | Lower PEEP | 47% | 165 ± 77 | | 24 ± 7 | 53 | | 8.9 ± 3.5 |
| Meade et al. [16] | 475 (54.5) | RM + higher PEEP | 40.6% | 144.8 ± 47.9 | 24.8 ± 7.8 | 30.4 ± 5.5 | 69 | | 15.6 ± 3.9 |
| | 508 (56.9) | Lower PEEP | 39.6% | 144.6 ± 49.2 | 25.9 ± 7.7 | 29.3 ± 6.0 | 75.9 | | 10.1 ± 3.0 |
| Mercat et al. [17] | 385 (60) | Higher PEEP | 32% | 144 ± 58 | | 23.7 ± 4.9 | 70 | | 14.6 ± 3.2 |
| | 382 (60) | Lower PEEP | 33% | 143 ± 57 | | 22.9 ± 5.3 | 75 | | 7.1 ± 1.8 |
| Talmor et al. [18] | 30 (54.5) | RM + PEEP titration | 37% | 147 ± 56 | 26.3 ± 6.4 | 29 ± 7 | 23.3 | | 17 ± 6 |
| | 31 (51.2) | RM + lower PEEP | 45% | 145 ± 57 | 26.8 ± 6.5 | 29 ± 5 | 16.1 | | 10 ± 4 |
| Huh et al. [19] | 30 (55) | RM + PEEP titration | 37% | 115.0 ± 8.5 | 22.0 ± 1.1 | | 66.7 | | 10 |
| | 27 (62) | Lower PEEP | 40% | 110.8 ± 6.3 | 20.0 ± 1.4 | | 66.7 | | 9.5 |
| Xi et al. [20] | 55 (62.2) | RM + lower PEEP | 30.9% | 104.8 ± 60.2 ^a | 21.5 ± 6.7 | 24.2 ± 5.3 | 45.4 | | 10.5 ± 3.2 |
| | 55 (65.5) | Lower PEEP | 27.3% | 115.9 ± 38.3 ^a | 23.1 ± 8.6 | 23.4 ± 5.3 | 38.2 | | 9.7 ± 2.4 |
| Hodgson et al. [21] | 10 (60) | RM + PEEP titration | 30% | 155 ± 8 | 20.1 ± 3 | 28.9 ± 1.2 | 50 | | 15 ± 1 |
| | 10 (58) | Lower PEEP | 40% | 149 ± 12 | 20.1 ± 2 | 27.1 ± 1.2 | 60 | | 10 ± 0.5 |
| Kacmarek et al. [22] | 99 (52.2) | RM + PEEP titration | 42.4% | 121 ± 37 | 18 ± 10 | 27 ± 5 | 68 | | 15.8 ± 3.8 |
| | 101 (53.4) | Lower PEEP | 33.7% | 114 ± 33 | 17 ± 6 | 27 ± 5 | 66 | | 11.6 ± 2.5 |
| ART 2017 [23] | 501 (51.3) | RM + PEEP titration | 37.5% | 119.5 ± 43.5 | | 25.8 ± 4.7 | 62.5 | | 16.2 ± 0.5 ^a |
| | 509 (50.6) | Lower PEEP | 37.5% | 117.2 ± 41.9 | | 26.2 ± 5.2 | 61.5 | | 12.0 ± 0.4 ^a |
| Beitler et al. [24] | 102 (58) | RM + PEEP titration | 37.3% | 99.2 ± 41.5 ^a | 27 ± 8 | 28.0 ± 5.9 ^a | 80.4 | | 17 ± 6 |
| | 98 (57.5) | RM + lower PEEP | 55.1% | 94.2 ± 40.0 ^a | 28 ± 7 | 27.4 ± 3.7 ^a | 89.8 | | 16 ± 4 |
| Kung et al. [25] | 60 (66.8) | RM + PEEP titration | 45/15 | 133.4 ± 47.0 | 20.4 ± 5.8 | 25.3 ± 3.9 | 86.7 | | 13 ± 3 |
| | 60 (63.7) | Lower PEEP | 44/16 | 129.7 ± 42.0 | 21.5 ± 6 | 25.7 ± 4.6 | 76.7 | | 12 ± 3 |
| Constantin et al. [26] | 82 (63) | RM + PEEP titration | 21% | 121 ± 4 | | 26 ± 1 | 73 | | 14 ± 3 |
| | 204 (61) | Lower PEEP | 28% | 115 ± 4 | | 24 ± 1 | 73 | | 10 ± 2 |

^aData were transformed from the median (interquartile range) to mean (SD)

common subjects were RM + PEEP titration versus lower PEEP.

3.5 Network Meta-analysis for Outcomes

For the primary outcomes in terms of death at 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 analysis (Fig. 3A).

For the secondary outcomes, the ventilation strategies were compared in terms of ventilator-free days. The results of the network meta-analysis indicated that the differences among the strategies were not significant (Fig. 3B) with a 95% CI of 0. In terms of the other two secondary outcomes, the results suggested that no strategy was superior in terms of hospital deaths (Fig. 3A) and barotrauma (Fig. 3B).

3.6 Rank Probabilities

The relative ranking of the ventilation strategies was estimated using SUCRA. In our study, the results indicate that the higher the SUCRA is, the more superior the strategy. The ranking results are shown in Table 2, and the SUCRA values are shown in Fig. 4.

In terms of death at 28 days, higher PEEP had the highest SUCRA value (0.701), and RM + lower PEEP had the lowest SUCRA value (0.546). RM + lower PEEP had the highest SUCRA value in terms of hospital deaths (0.925) and ventilator-free days (0.759). Higher PEEP had the lowest SUCRA value (0.410) in terms of hospital deaths. The lower PEEP strategy had the lowest SUCRA value (0.470) in terms of ventilator-free days. In terms of barotrauma, lower PEEP had the highest SUCRA value (0.734), whereas RM + PEEP titration had the lowest SUCRA value (0.435).

4 Discussion

In our systematic review and network meta-analysis, we summarized mechanical ventilation strategies based on the low tidal volume among patients with moderate to 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. (1) No ventilation strategy was significantly superior to other strategies in terms of in-hospital death, ventilator-free days, and barotrauma. (2) This technique is not applicable to studies involving deaths in 28 days because of the considerable inconsistency found in global and local inconsistency tests. (3) The overall quality of the evidence is moderate-to-low or low for the primary and secondary outcomes. Given that the use of ventilators should be monitored at all times and the parameters should be adjusted

by the clinician according to the condition of the patients, blinding is not suitable for these random clinical trials. Thus, it is difficult to improve the overall quality of RCTs. The research population in our meta-analysis was mainly European and American, and 4 RCTs were conducted in Asia [15, 19, 20, 25]. The sample size was 334, accounting for 7.57% of the total. We analyzed 9 RCTs conducted in European and American countries, and the results were the same as before. The heterogeneous study population did not influence the results.

The optimal lung recruitment maneuvers and PEEP levels for patients with ARDS remain unclear. Sarina et al. summarized approaches to setting PEEP, but the optimal approach to setting PEEP has not yet been firmly established [27]. A pairwise meta-analysis suggested that the use of higher PEEP is unlikely to improve clinical outcomes among unselected patients with ARDS [28]. Our network meta-analysis also showed that no approaches to setting PEEP were significantly superior to others. The reason may be that the theoretical beneficial effects of higher PEEP on oxygenation can be offset by heart–lung interactions. Therefore, the approach to find the optimal PEEP needs more study. The recruitment maneuver can open up the collapsed lung, and PEEP can maintain alveolar stability, but a recent study suggested that RM + PEEP titration and RM + lower PEEP had no difference in terms of 28-day mortality and ICU mortality in patients with moderate–severe ARDS [29], and another two pairwise meta-analyses suggested that RM had no advantageous effect on mortality [10, 30]. These results were consistent with the results of our network meta-analysis. The negative result may be caused by studies that did not take into account the lung recruitability. ARDS patients enrolled in the RCTs were randomized, and they did not receive an assessment of lung recruitability, which influences the effect of RM and PEEP. In these RCTs, more pneumonia patients were recruited, except two RCTs [18, 20]. Pneumonia patients have low lung recruitability, which may cause negative results. Guo et al. found that high PEEP reduced mortality in a subgroup of patients with ARDS who responded to increased PEEP by improved oxygenation [8]. This study demonstrated that lung recruitability is important for the effect of RM and PEEP level. Lung recruitability should be considered for further RCTs.

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. In our study, the PEEP level in the lower PEEP group was 7.1 ± 1.8 mmHg [17] to 12 ± 3 mmHg [25] on day 1, which was lower than that in the control groups. The high PEEP-FIO₂ strategy proposed by the ALVEOLI trial was included in the higher PEEP group. The PEEP level in the higher PEEP group was 14.6 ± 3.2 mmHg [17] to 16 ± 4 mmHg [24] on day 1. The PEEP level in the PEEP

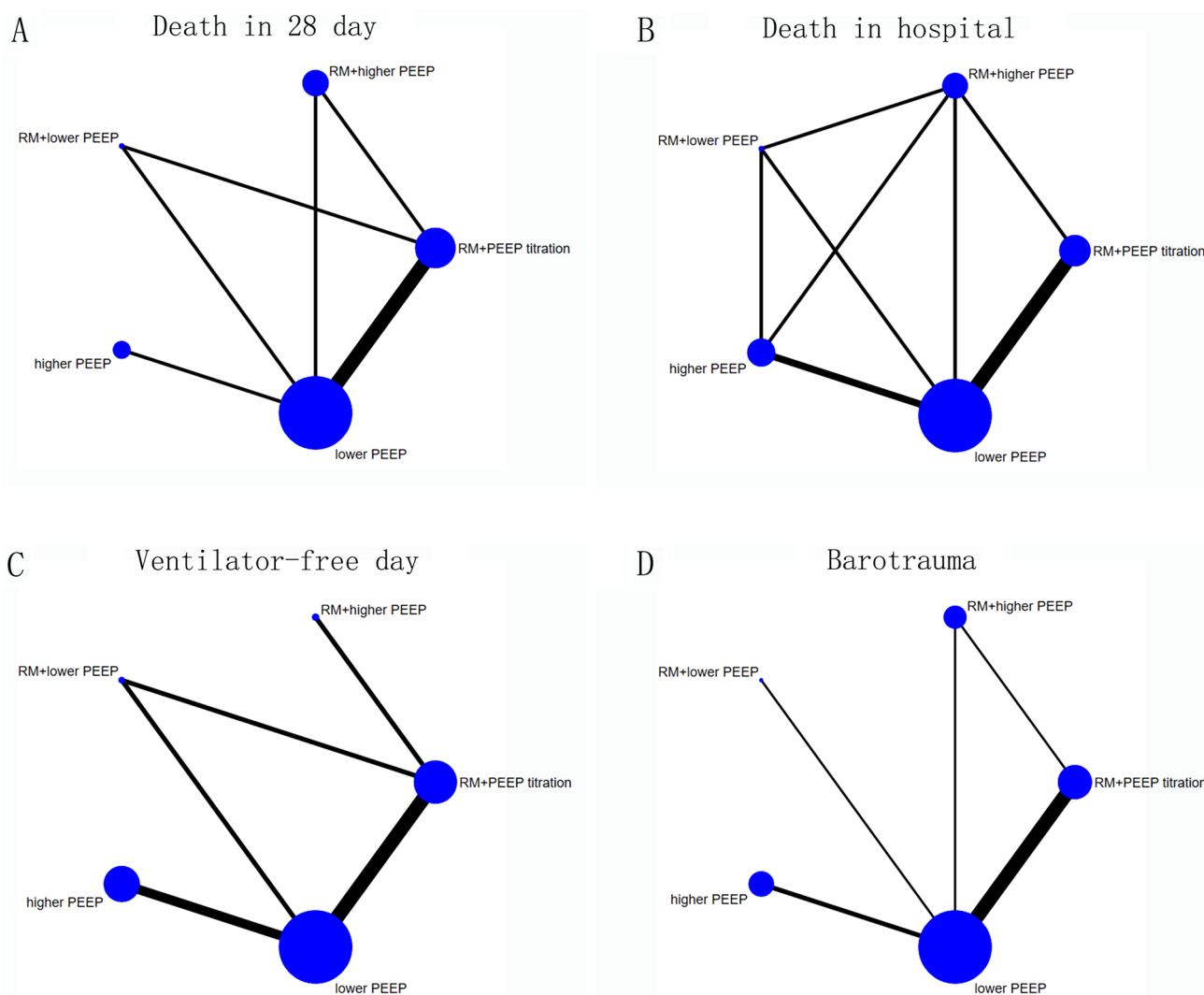


Fig. 2 Network plots for all outcomes. **A** Network plots for death in 28 days. **B** Network plots for death in hospital. **C** Network plots for ventilator-free days. **D** Network plots for barotrauma. Treatments are

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

titration group was 13 ± 3 mmHg [25] to 17 ± 6 mmHg [24] on day 1. In Beitler's research, the PEEP level in the higher group was lower than that in the titration group, which may be caused by the inconsistent baseline PEEP between the two groups.

Network meta-analysis is a technique to meta-analyze more than two treatments at the same time. The advantage of network meta-analysis is that it can be used to estimate the probability that a particular treatment is the best, the second best, etc. [31]. As such, we used network meta-analysis to provide relative efficacy estimates among all interventions; however, some techniques have never been directly compared. In this study, the differences among in-hospital death, ventilator-free days, and barotrauma were not significant. This finding is consistent with previous conventional

pairwise meta-analyses. In terms of death at 28 days, an inconsistency was found globally and locally in the tests, so the network meta-analysis was improper for death at 28 days. For ranking probabilities, in terms of in-hospital death and ventilator-free days, RM + lower PEEP had the highest SUCRA and the highest Rank 1 possibility. These results 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 [32]. However, RM + PEEP titration was not the best recommended strategy in our network meta-analysis. Among the studies enrolled in our analysis, a PEEP titration strategy based on respiratory-system compliance [19, 22, 23], oxygen saturation

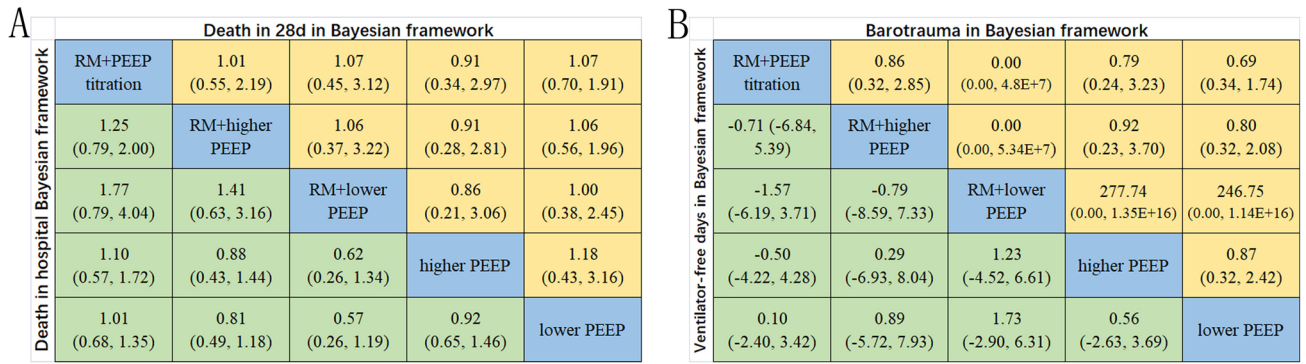


Fig. 3 Pooled estimates of network meta-analysis. **A** Risk ratios (95% credible intervals) for death in 28 days (upper triangle) and death in the hospital (lower triangle) in the Bayesian framework. **B** Risk ratios (95% credible intervals) for barotrauma (upper triangle) and standard mean difference (95% credible intervals) for ventilator-free days

(lower triangle) in the Bayesian framework. 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. For the outcomes, if the range of 95% CI of 1, the difference between the two strategies is not significant

Table 2 Ranking results of network meta-analysis

| Strategy | Rank of possibility | | | | | SUCRA |
|---|---------------------|------|------|------|------|---------------------|
| | 1 | 2 | 3 | 4 | 5 | |
| <i>Death in 28d (Rank 1 is best, rank N is worst)</i> | | | | | | |
| RM + PEEP titration | 0.12 | 0.22 | 0.24 | 0.23 | 0.18 | 0.573 |
| RM + higher PEEP | 0.19 | 0.25 | 0.21 | 0.19 | 0.17 | 0.631 |
| RM + lower PEEP | 0.25 | 0.15 | 0.11 | 0.14 | 0.35 | 0.546 |
| Higher PEEP | 0.39 | 0.2 | 0.11 | 0.12 | 0.17 | <u>0.701</u> |
| Lower PEEP | 0.05 | 0.18 | 0.34 | 0.32 | 0.12 | 0.554 |
| <i>Death in hospital (Rank 1 is best, rank N is worst)</i> | | | | | | |
| RM + PEEP titration | 0.02 | 0.12 | 0.29 | 0.25 | 0.32 | 0.440 |
| RM + higher PEEP | 0.18 | 0.59 | 0.12 | 0.06 | 0.05 | 0.800 |
| RM + lower PEEP | 0.78 | 0.12 | 0.04 | 0.03 | 0.03 | <u>0.925</u> |
| Higher PEEP | 0.02 | 0.12 | 0.26 | 0.19 | 0.42 | 0.410 |
| Lower PEEP | 0 | 0.06 | 0.29 | 0.47 | 0.18 | 0.432 |
| <i>Ventilator-free days (Rank 1 is best, rank N is worst)</i> | | | | | | |
| RM + PEEP titration | 0.06 | 0.19 | 0.26 | 0.28 | 0.22 | 0.520 |
| RM + higher PEEP | 0.34 | 0.17 | 0.1 | 0.09 | 0.3 | 0.623 |
| RM + lower PEEP | 0.43 | 0.23 | 0.12 | 0.1 | 0.11 | <u>0.759</u> |
| Higher PEEP | 0.15 | 0.28 | 0.22 | 0.18 | 0.17 | 0.621 |
| Lower PEEP | 0.02 | 0.12 | 0.3 | 0.35 | 0.2 | 0.470 |
| <i>Barotrauma (Rank 1 is best, rank N is worst)</i> | | | | | | |
| RM + PEEP titration | 0.04 | 0.12 | 0.2 | 0.34 | 0.31 | 0.435 |
| RM + higher PEEP | 0.06 | 0.2 | 0.25 | 0.3 | 0.19 | 0.528 |
| RM + lower PEEP | 0.67 | 0.01 | 0.01 | 0.01 | 0.31 | 0.726 |
| Higher PEEP | 0.1 | 0.27 | 0.22 | 0.23 | 0.17 | 0.580 |
| Lower PEEP | 0.13 | 0.4 | 0.32 | 0.12 | 0.02 | <u>0.734</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.

[21, 26], and esophageal pressure [18, 24] was conducted. The different approaches for RM and PEEP titration may be the reason. Although the decrease in driving pressure is strongly associated with increased survival, no studies

have used this parameter as the PEEP titration strategy [33]. These factors may explain why RM + PEEP titration was not the first choice in our analysis. The rank possibility of RM + lower PEEP is superior to RM + PEEP titration, and

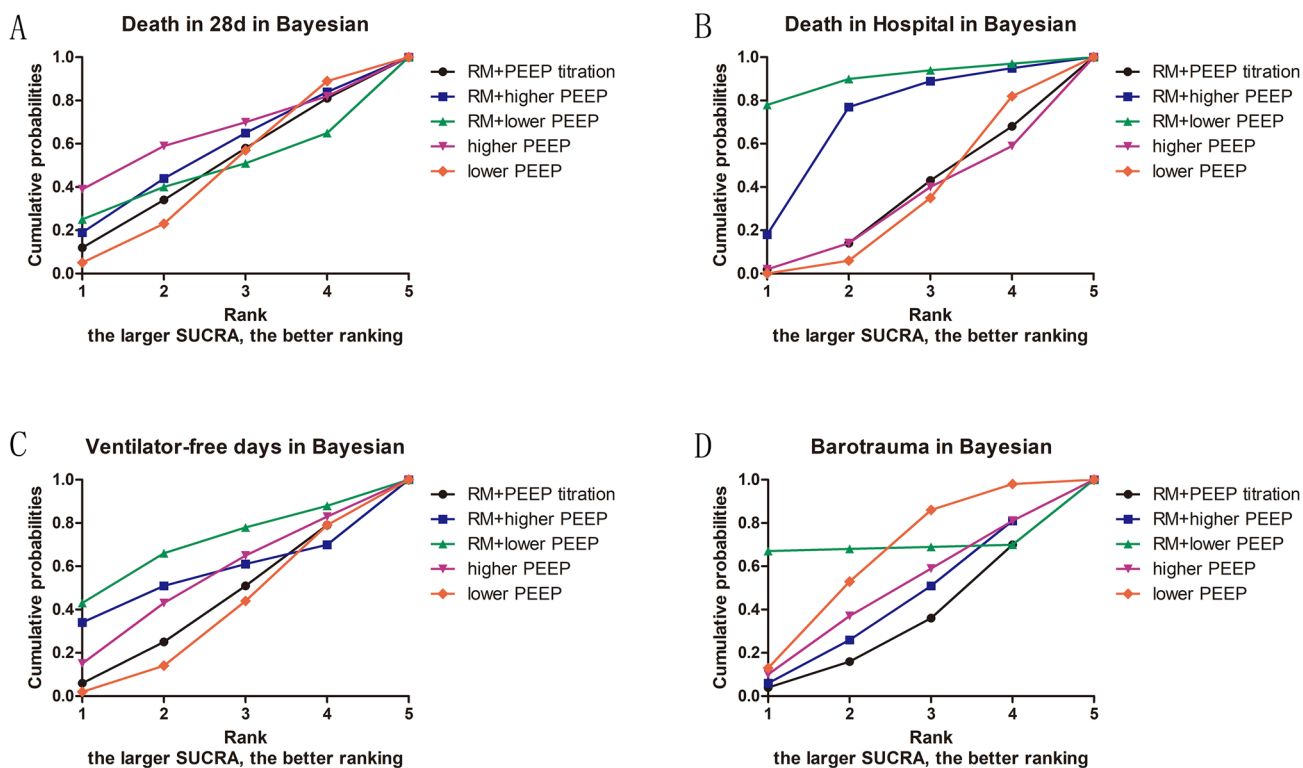


Fig. 4 Rankograms and the SUCRA for each ventilation strategy for **A** Death in 28 days in the Bayesian framework. **B** Death in the hospital in the Bayesian framework. **C** Ventilator-free days in the Bayes-

ian framework. **D** Barotrauma in the Bayesian framework. Horizontal axis shows possible ranks and vertical axis shows cumulative probability at each rank. The larger SUCRA, the better ranking

the low lung recruitability was the main reason. 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 pressure levels are required for opening the lung [34]. This result is attributed to the heterogeneity of pulmonary lesions among patients with severe ARDS; maximum compliance was determined by overdistingending the normal tissue, thereby resulting in adverse effects compared with alveolar recruitment.

In terms of barotrauma, lower PEEP is the safest strategy according to the SUCRA, which is consistent with theoretical and clinical understanding. However, RM + PEEP titration had the highest risk of barotrauma. One reason is that the baseline level of PEEP was higher in the titration group than in the higher group in Bietler's research. Another reason is ascribed to the RM + higher PEEP strategy recruiting more collapsed alveoli, which can reduce shear stress [35] and improve ventilation-to-perfusion mismatch.

5 Limitations

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. Second, ventilator parameters may change anytime according to patients, and the same strategy may include different parameters that may influence the judgment of outcomes. A few articles used the median and the first and third quartiles to describe the results. We used an equation to transform the data, which may decrease the reliability of the results.

6 Conclusion

In this network meta-analysis, we classified mechanical ventilation strategies 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 the others. According to the relative ranking recommended by the Bayesian frameworks, RM + lower PEEP showed the highest probability of reducing the risk of

in-hospital death and reducing ventilator-free days, whereas lower PEEP showed the highest probability of benefitting barotrauma. The overall quality of the evidence is low, and thus, further research should be conducted.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s44231-022-00015-2>.

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Availability of Data and Materials All data analysed during this study are included in this published article.

Declarations

Competing interests The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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