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Effect of different levels of PEEP on mortality in ICU patients without acute respiratory distress syndrome: systematic review and meta-analysis with trial sequential analysis

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Abstract

Objective: To determine whether higher positive end-expiratory pressure (PEEP) could provide a survival advantage for patients without acute respiratory distress syndrome (ARDS) compared with lower PEEP.

Methods: Eligible studies were identified through searches of Embase, Cochrane Library, Web of Science, Medline, and Wanfang database from inception up to 1 June 2021. Trial sequential analysis (TSA) was used in this meta-analysis.

Data synthesis: Twenty-seven randomized controlled trials (RCTs) were identified for further evaluation. Higher and lower PEEP arms included 1330 patients and 1650 patients, respectively. A mean level of 9.6±3.4 cmH2O was applied in the higher PEEP groups and 1.9±2.6 cmH2O was used in the lower PEEP groups. Higher PEEP, compared with lower PEEP, was not associated with reduction of all-cause mortality (RR 1.03; 95% CI 0.91–1.18; P =0.627), and 28-day mortality (RR 1.07; 95% CI 0.92–1.24; P =0.365). In terms of risk of ARDS (RR 0.43; 95% CI 0.24–0.78; P =0.005), duration of intensive care unit (MD -1.04; 95%CI-1.36 to –0.73; P < 0.0001), and oxygenation (MD 40.30; 95%CI 0.94 to 79.65; P = 0.045), higher PEEP was superior to lower PEEP. Besides, the pooled analysis showed no significant differences between groups both in the duration of mechanical ventilation (MD 0.00; 95%CI-0.13 to 0.13; P = 0.996) and hospital stay (MD -0.66; 95%CI-1.94 to 0.61; P = 0.309). More importantly, lower PEEP did not increase the risk of pneumonia, atelectasis, barotrauma, hypoxemia, or hypotension among patients compared with higher PEEP. The TSA analysis showed that the results of all-cause mortality and 28-day mortality might be false-negative results.

Conclusions: Our results suggest that a lower PEEP ventilation strategy was non-inferior to a higher PEEP ventilation strategy in ICU patients without ARDS, with no increased risk of all-cause mortality and 28-day mortality. Further high-quality RCTs should be performed to confirm these findings.

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List of abbreviations

IMV invasive mechanical ventilation
ICU intensive care unit
VILI ventilator–induced lung injury
LPV lung-protective ventilation
PEEP positive end-expiratory pressure
VT tidal volume
ARDS acute respiratory distress syndrome
CO cardiac output
SD standard deviation
RRs risk ratios
GRADE Grading of Recommendations Assessment, Development, and Evaluation
RRR relative risk reduction
PBW predicted body weight
BMI Body Mass Index
IQR interquartile range
P/F ratio oxygenation index
LIP lower inflection point
EIT electrical impedance tomography
ΔP driving pressure
CRs respiratory system compliance
CI confidence interval

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1. Introduction

Invasive mechanical ventilation (IMV) is recognized as one of the most frequently applied lifesaving strategies among critically ill patients in intensive care unit (ICU). However, inappropriate IMV can aggravate or even initiate ventilator–induced lung injury (VILI), such as atelectasis and barotrauma [1-3]. VILI is a common complication in ICU patients receiving MV and could increase morbidity and mortality [4]. Although the protective role of low tidal volume (VT) has been proven even in patients with normal lungs [5-7], there are still many uncertainties regarding positive end-expiratory pressure (PEEP) setting among ICU patients receiving MV, especially in those without acute respiratory distress syndrome (ARDS) [8].

PEEP is applied to keep alveolar pressure above the closing pressure of alveoli, which could maintain end-expiratory lung volume (EELV) and improve patient oxygenation [9]. Based on previous studies, patients with ARDS can benefit from ventilation with a higher PEEP due to their pathophysiological characteristics [3,10]. For non-ARDS patients, the benefit of PEEP may be diminished because they receive spontaneous ventilation more frequently and have less atelectasis than patients with ARDS. Because patients are usually extubated at lower PEEP, the application of higher PEEP may theoretically increase the duration of MV [11]. A recent study reported that non-ARDS patients had higher ICU and in-hospital mortality than expected [12]. There is less evidence for ventilation strategies for non-ARDS patients in the ICU than strategies for patients with ARDS [3,13], which causes ventilation strategies for non-ARDS patients to be inevitably influenced by PEEP used in ARDS patients. Although there is a paucity of studies to confirm the relationship between different levels of PEEP and mortality in patients without ARDS, the PEEP settings for these patients tend to be elevated [14-16]. A previous study demonstrated that although a higher PEEP was associated with a lower risk of hypoxemia and a higher oxygenation index among non-ARDS patients than a lower PEEP, there was no significant reduction in in-hospital mortality [17]. Similarly, the latest randomized controlled trial (RCT) showed no difference between the higher and lower PEEP groups in 28-day mortality [8]. In addition, several animal studies revealed that ventilation with higher PEEP among healthy animals could induce a more severe inflammatory response and hyperinflation but reduce tidal reaeration with a decrease in normally aerated areas [18-20].

To date, there is no consensus on the selection of appropriate PEEP levels for patients without ARDS in the ICU. To provide doctors with suggestions for the application of PEEP in patients without ARDS, we performed a series of systematic reviews to compare the effects of different PEEP levels among patients without ARDS.

2. Material and method

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines published by the Equator Network, we reported this study to explore the effect of different PEEP levels on mortality in ICU patients without ARDS (Additional File 1). And this work has been registered on the website of INPLASY (DOI number: 10.37766/inplasy2021.2.0052).

2.1. Search strategy

The search ran from inception to June 1, 2021 with regular alerts to update the search until the publication of the final study. And the systematic search was conducted using the Embase, Cochrane Library, Web of Science, Medline, and WanFang databases. Our search strategy combined concepts related to PEEP (i.e., ‘PEEP’ or ‘positive end-expiratory pressure’) and RCT (i.e., ‘RCT’ or ‘randomized controlled trial’) (Additional File 2). We applied no restrictions on the type of study and language.

2.2. Eligibility and excluded criteria

The inclusion criteria were as follows: (1) RCTs; (2) adult (age greater than 18 years old) patients without ARDS; (3) received MV in an ICU setting; (4) higher PEEP was applied in the intervention group; (5) a control group was needed, and lower PEEP should be used in the control group; (6) similar VT and fraction of inspiration O2 (FiO2) were used between these two groups; (7) other concomitant therapies should be comparable between these two groups; (8) the mean difference between the higher and the lower PEEP groups should be at least 3cmH2O [21]. Case reports, duplicates, observational studies, patients who received intraoperative ventilation or combined strategy (such as compared higher PEEP combined lower VT versus lower PEEP combined with higher VT), studies were comparing the effect of different levels of PEEP within single-arm patients, animal studies, and studies that did not report the outcomes which we interested in were excluded.

2.3. Study selection

Two authors (SS, YQW) screened the titles and abstracts of original studies, independently, to define eligible studies for further evaluation. Meanwhile, the citations of each eligible study were reviewed carefully to avoid omitting eligible studies. We e-mailed the corresponding authors of the eligible articles for further details, if available. We resolved eligibility discrepancy by further discussion with a third author (ZHT).

2.4. Data extraction and quality assessment

Two authors (SS and ZBQ) completed data extraction independently by using a double-entry procedure. Meanwhile, the results of data extraction were checked by a third author (HYJK). The abstracted data included publication year, country, first-author, the number of ICU, type of patients, sample size, ventilation strategies, and outcome data of each study. For each eligible RCT, the risk of bias in the overall effect of different studies was assessed by the Cochrane Collaboration risk of bias tool [22].

2.5. Outcomes

The primary outcomes were all-cause mortality and 28-day mortality. Secondary outcomes included duration of MV, duration of hospital stay, duration of ICU, complications (ARDS, pneumonia, atelectasis, barotrauma, hypotension, and hypoxemia), arterial blood gas (PaO2 / fractional inspired oxygen (FiO2) ratio, blood pressure, heart rate (HR), cardiac index, systemic vascular resistance index (SVRI). We accepted the wide spectrum definitions of complications in each study (Additional File 3).

2.6. Statistical synthesis and analysis

We generated summary estimates of mean and standard deviation (SD) for continuous outcomes. Values for dichotomous results were given as the risk ratios (RRs) with 95% confidence intervals (CIs). Random-effect models was used to preform meta-analysis. The estimation of the effect was summarized by the forest plot. The correction factor of 1.0 was added to each cell of the contingency table when no events occurred in the exposed groups to enforce the effect of RR [23]. Outcomes with a two-tailed value of \(P < 0.05\) were considered statistically significant. We used \(I^2\) that derived from Chi [2] tests to judge the heterogeneity between studies (\(I^2 > 50\%\) is regarded as substantial heterogeneity). Meta-regression was performed using a random-effects model analysis to find the potential sources of heterogeneity. Meta-regression was performed by using the following covariates: publication year (<2000 year and ≥2000 year) [17], the proportion of males, mean age, race, including acute respiratory failure (ARF) patients or not [24]. The funnel plot and Egger’s test were applied to reveal the
outcome's publication bias, which included more than five studies [25]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to judge the quality of evidence for the primary and secondary outcomes. In terms of trial sequential analysis (TSA), we applied the analysis in the mortality of RCTs. The required information size was calculated using relative risk reduction (RRR) for falls calculated from eligible studies. O'Brien-Fleming alpha was chosen to construct adjusted significance trial sequential monitoring boundaries. The type I errors and type II errors were limited by a two-sided alpha of 0.05 and a beta of 0.20 (power:80%). The statistical analyses were finished by GRADE Profiler version 3.6, Stata version 15.1, Review Manager Version 5.3, and TSA 0.9.5.10 Beta.

2.7. Subgroup and sensitivity analysis

Subgroup analysis was conducted for outcomes that had significant heterogeneity. The predefined subgroup analysis was performed according to the risk of bias, type of patients (medical versus surgical), PEEP gradient of the control group (high PEEP versus no PEEP), PEEP gradient of the intervention group (< 10 cm H2O versus ≥10 cm H2O) [17], VT gradient (≤ 8 ml/kg predicted body weight (PBW) versus >8 ml/kg PBW), publication year (before 2004 versus after 2004) and sample size (≥ 150 patients or < 150 patients). The differences in treatment effect across these subgroups were assessed by a test of interaction [26-28]. When I² ≥ 50%, we performed sensitivity analyses by sequentially removing one study each time to address the methodological quality of the studies.

3. Results

3.1. Study selection and characteristics

The flowchart of the study search and selection is shown in Fig. 1. We identified 19,530 original articles, of which 11,208 were duplicates. After screening the abstracts, 99 articles were eligible for the full-text review process. Ultimately, the literature pieces were
| Source/Year   | Country | Centre          | Type of patients | Sample size | Higher PEEP | Lower PEEP | Quality score | Sample size | Higher PEEP | Lower PEEP | Quality score | Main findings                                                                                           |
|--------------|---------|-----------------|------------------|-------------|--------------|-------------|---------------|-------------|--------------|-------------|---------------|---------------------------------------------------------------------------------------------------------|
| 1. Carroll/1988 | USA     | 1 ICU   | Surgical patients without ARDS | 50 | 22 | 10 | NA | 12 | ≥0.5 | Yes | 28 | 4 | Low | Higher PEEP was associated with more hypotension, barotrauma and death. Higher PEEP could increase oxygenation and decreased the rate of atelectasis. Higher PEEP does not compromise liver function and gastric mucosal perfusion. Higher PEEP could decrease the duration of ventilation. No differences were found in the rate of atelectasis, and hospital length of stay.
| 2. Celebi/2007 | Turkey  | 1 ICU   | Surgical ICU | 60 | 20 | 10 | 7 | 0.4 | Yes | 20 | 5 | Low | Higher PEEP could increase oxygenation and decreased atelectasis equally. Higher PEEP could decrease the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease rate of atelectasis, the duration of intubation in ICU, length of hospital and ICU.
| 3. Good/1979  | USA     | 1 ICU   | Post-CS | 24 | 10 | 6 | NA | 11 | NA | 0.5 | No | High | No differences were found in the OI, CI, and duration of MV. Higher PEEP could decrease rate of atelectasis and improve the OI. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 4. Holland/2007 | Germany | 1 ICU | Post-CS | 28 | 14 | 10 | 6-8 | NA | 14 | 5 | No | High | Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 5. Lago/2014  | Brazil  | 1 ICU   | 136 | 44 | 10 | 8 | ≤0.4 | 8 | ≤0.4 | No | Unclear | Higher PEEP could decrease the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 6. Marvel/1986 | USA     | 1 ICU   | Post-CS | 44 | 12 | 10 | 12 | 0.4 | NO | 15 | 5 | Low | Higher PEEP could decrease the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 7. Zurick/1982 | USA     | 1 ICU   | Post-CS | 83 | 41 | 10 | NA | 42 | 0 | NA | High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 8. Dyhr/2002  | Denmark | 1 ICU   | 16 | 8 | 15 | 6 | 1.0 | Yes | 8 | 0 | 6 | Low | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 9. Murphy/1983 | USA     | 1 ICU   | ARF patients | 25 | 12 | 5 | 15 | NA | 13 | 0 | NA | High | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 10. Michalopoulos/1996 | Greece | 1 ICU | ARF patients | 38 | 20 | 15 | NA | 0.45 | No | 18 | 8 | NA | High | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 11. Borges/2013 | Brazil  | 1 ICU   | 136 | 44 | 10 | 8 | ≤0.4 | 8 | ≤0.4 | No | Unclear | Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 12. Schmidt/1976 | USA     | 1 ICU   | Post-abdominal surgery | 112 | 56 | 8 | 12-15 | NA | 56 | 0 | NA | Low | No Low | Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 13. Cujec/1993 | Canada  | 1 ICU   | ARF patients | 63 | 30 | 5 | 8 | NA | 33 | 0 | 7 | NA | High | No Low | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 14. Manzano/2008 | Spain   | 2 ICU   | Nonhypoxemic patients | 27 | 12 | 5 | 15 | NA | 13 | 0 | NA | High | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 15. Nelson/1987 | USA     | 1 ICU | Early moderate arterial hypertension | 38 | 20 | 15 | NA | 0.45 | No | 18 | 8 | NA | High | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 16. Zurick/1982 | USA     | 1 ICU | ARF patients | 25 | 12 | 5 | 15 | NA | 13 | 0 | NA | High | No High | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 17. Cujec/1993 | Canada  | 1 ICU | ARF patients | 63 | 30 | 5 | 8 | NA | 33 | 0 | 7 | NA | High | No Low | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| 18. Lavo/2010 | Canada  | 1 ICU | ARF patients | 63 | 30 | 5 | 8 | NA | 33 | 0 | 7 | NA | High | No Low | The use of PEEP during weaning may be helpful in patients who fail to wean. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation. No differences were found in the amount of blood loss, need for re-exploration or blood requirement. Higher PEEP could decrease the risk of atelectasis, and the duration of ventilation.
| Source/Year | Country   | Centre(s) | Type of patients | Sample size | Higher PEEP | Lower PEEP | Quality score | Main findings |
|-------------|-----------|-----------|------------------|-------------|-------------|-------------|---------------|---------------|
|             |           |           |                  |             | N          | PEEP, cm H₂O | Vt, mL/kg PBW | FiO₂ | RM | N          | PEEP, cm H₂O | Vt, mL/kg PBW | FiO₂ | RM |               |
| 19. Weigelt/1979 | USA       | 1 ICU     | Risk of ARDS     | 79          | 45          | 5           | 15 ±0.5       | NO    | 34  | 0           | 15          | ±0.5               | NO    | Unear | Mortality. Higher PEEP could decrease the rate of ARDS and pulmonary mortality. But higher PEEP is associated with higher incidence of pulmonary dysfunction. |
| 20. Pepe/1984 | USA       | 1 ICU     | Risk of ARDS     | 92          | 44          | 8           | 12 ±1.0 or ≤0.5 | NO    | 48  | 0           | 12          | 1.0 or ≤0.5               | NO    | Unear | No differences were found in the risk of incidence of ARDS, atelectasis, pneumonia, and barotrauma, as was mortality. Higher PEEP could improve the oxygenation, CO, and cardiac function. |
| 21. Yan/2016  | China     | 1 ICU     | NPE              | 50          | 25          | 5–15        | 6–8 NA       | NO    | 25  | 0           | 6–8         | NA                     | NO    | Unear | No differences were found in the risk of incidence of ARDS, atelectasis, pneumonia, and barotrauma, as was mortality. Higher PEEP could improve the oxygenation, CO, and cardiac function. |
| 22. Zeng/2009 | China     | 1 ICU     | COPD patients with ARF | 75          | 38          | 4–10        | 400–550 m l–600 m l | NA    | 37  | 0           | 400–550 m l–600 m l | NA                     | NO    | High | Higher PEEP might lower urinary volume, urea excretion ratio, creatinine clearance rate of patients. |
| 23. He/2018   | China     | 1 ICU     | ARF              | 100         | 50          | 4–10        | 400–600 m l  | NA    | 50  | 0           | 400–600 m l  | NA                     | NO    | High | Higher PEEP might lower urinary volume, urea excretion ratio, creatinine clearance rate of patients. |
| 24. PROVEnt/2020 | Netherlands | 8 ICUs   | ICU patients without ARDS | 969         | 467         | 7.0 (5.0–8.0) | 6.9 (6.1–8.0) | Yes   | 493 | 5.0 (5.0–8.0) | 7.0 (6.1–8.0) | 0.50 (0.40–0.65) | Yes   | Low  | A lower PEEP strategy was not inferior to a higher PEEP strategy regarding the number of ventilator-free days at day 28. Although higher PEEP could improve the oxygenation, it might damage the indexes of hemodynamics in COPD patients (HR, MAP, CI, SVRI). |
| 25. Yi/2009   | China     | 1 ICU     | ARF              | 40          | 20          | 10          | 6 ±0.4       | NO    | 20  | 5           | 6          | 0.4                     | NO    | High | Higher PEEP could decrease the rate of ARDS and pulmonary mortality. But higher PEEP is associated with higher incidence of pulmonary dysfunction. |
| Abbreviations: ICU intensive care unit; N number of patients; PEEP positive end-expiratory pressure; Vt Tidal volume; PBW, predicted body weight; FiO₂, fraction of inspired oxygen; P/F ratio oxygenation ratio; RM: recruitment maneuvers; ARDS Acute respiratory distress syndrome; Data was expressed as median (IQR) or exact value; USA the United States of America; sLMA, LMA Supreme™, ARF, acute respiratory failure; CPAP, Continuous Positive Airway Pressure; OI, oxygenation index, CO, cardiac output; CI, cardiac index, Post-CS, Post cardiac surgery; COPD, chronic obstructive pulmonary disease; NPE, Neurological pulmonary edema; HR, heart rate, MAP, mean arterial pressure; SVRI, systemic vascular resistance index; VD/VT, dead space to tidal volume ratio; NA not available; |
| a One group containing 20 patients was excluded (They only received CPAP). |
| b One group containing 47 patients was excluded (The median PEEP group [8 cmH₂O]). |
| c One group containing 17 patients was excluded (exhaled to ambient pressure). |
| d One group containing 24 patients was excluded (The median PEEP group [5 cmH₂O]). |
| e One group containing 47 patients was excluded (The median PEEP group [8 cmH₂O]). |
| f One group containing 78 patients was excluded (The median PEEP group [8 cmH₂O]). |
| g Four groups containing 68 patients was excluded (The median PEEP group [5/10/15 cmH₂O] and patients who received different tidal volume [tidal volume = 10 mL/kg PBW]). |
3.3. Synthesis of results

All of the clinical outcomes are presented in Table 3.

3.3.1. Primary outcomes

Eleven articles with a total of 1669 patients clearly provided the all-cause mortality [8,29,38,43,44,48-51,52,54] (Fig. 2A). The risk of all-cause mortality did not differ significantly between the higher PEEP and lower PEEP groups (RR 1.03; 95% CI 0.91–1.18; I² 0%; P = 0.627) (Table 3). Besides, no statistically significant difference could be found in the primary outcome regarding 28-day mortality which containing two RCTs [8,46] (RR 1.07; 95% CI 0.92–1.24; I² 0%; P = 0.365) (Fig. 2B).

3.3.2. Secondary outcomes

Regarding the outcomes of complications, higher PEEP was associated with a lower risk of ARDS compared to control arm [8,40,44,47,48] (RR 0.43; 95% CI 0.24–0.78; I² 44.0%; P = 0.005) (Additional File 7). In terms of the other pulmonary complications (pneumonia, atelectasis, barotrauma, hypotension and hypoxemia), no statistically significant difference could be found in the higher PEEP compared with lower PEEP. The pooled data extracted from RCTs demonstrated that the higher PEEP, compared with lower PEEP, was associated with a significant difference in duration of ICU [8,41] (mean difference (MD) -1.04; 95% CI -1.36 to -0.73; I² 0%; P < 0.00001) (Additional File 7). Four studies reported P/F ratio [32,36,39,44], and higher P/F ratio (MD 40.30; 95% CI 0.94 to 79.65; I² 64.9%; P = 0.045) could be found in the higher PEEP arm versus lower PEEP arm (Table 3). Removing the RCT published in 2007 lowered the heterogeneity in P/F ratio (Additional File 8). There were no differences in the others secondary outcomes (duration of MV [8,31,33,41,43,46] (MD 0.00; 95% CI -0.13 to 0.13; I² 84.7%; P = 0.996), duration of hospital stay [8,34,41] (MD 0.66; 95% CI -1.94 to 0.61; I² 93%; P = 0.309), blood pressure [32,36,53] (MD 0.78; I² 44.0%; P = 0.005) (Additional File 7).

### Table 2

**Characteristics of patients at inclusion.**

| Source/Year | Mean males (%) | Mean age (years) | APACHE II scores | SOFA scores | Mean BMI (kg/m²) | Smoking (%) | Hypertension (%) | Diabetes mellitus (%) |
|-------------|---------------|-----------------|-----------------|------------|-----------------|-------------|-----------------|---------------------|
| 1. Carroll/1988 | 46.04          | 63.3            | –               | –          | –               | –           | –               | –                   |
| 2. Celline/2007 | 85.0           | 54.5            | –               | –          | –               | 27.5        | 70.0            | –                   |
| 3. Good/1979   | –              | 54.5            | –               | –          | –               | –           | –               | –                   |
| 4. Holland/2007 | 75.0           | 65.5            | 23              | 8          | 41.75           | –           | –               | –                   |
| 5. Lago/2014   | 71.9           | 56.2% patients elder than 60 years old | – | – | 64.0% patients are overweight or obese | 36.0 | 75.3 | 50.6 |
| 6. Marvel/1986 | –              | 58.6            | –               | –          | –               | –           | –               | –                   |
| 7. Zurick/1982 | 85.5           | 56.5            | –               | –          | –               | –           | –               | –                   |
| 8. Dyhr/2002   | 75             | 62.5            | –               | –          | –               | –           | –               | –                   |
| 9. Murphy/1981 | 83.5           | –               | –               | –          | –               | –           | –               | –                   |
| 10. Michalopoulos/1996 | 79.1 | 61.5 | – | – | – | 39.5 | – | – |
| 11. Borges/2013 | 71.9           | 56.2% patients elder than 60 years old | – | – | 64.0% patients are overweight or obese | 36.0 | 75.3 | 50.6 |
| 12. Schmidt/1976 | –              | ≥65             | –               | –          | –               | –           | –               | –                   |
| 13. Berengerstani/2018 | 59.2 | 55.63 | – | – | 26.6 | 8.3 | – | – |
| 14. Feeley/1975 | 44.0           | 61.6            | –               | –          | –               | –           | –               | –                   |
| 15. Nelson/1987 | –              | 53.9            | –               | –          | –               | –           | –               | –                   |
| 16. Manzano/2008 | 71             | 45              | 57             | 7.3        | –               | –           | –               | –                   |
| 17. Cujec/1993 | 67.4           | 59.1            | 20              | –          | –               | –           | –               | –                   |
| 18. Lesur/2010 | 60.3           | 64.5            | 19.0            | –          | 6.3% patients are overweight, whose BMI >40 kg/m² | 38.1 | 22.2 | – |
| 19. Weigelt/1979 | 72.4           | 45.0            | –               | –          | –               | –           | –               | –                   |
| 20. Pepe/1984   | 71.7           | 43.9            | –               | –          | –               | 38.5        | –               | –                   |
| 21. Yao/2016    | 66.0           | 38.6            | –               | –          | –               | –           | –               | –                   |
| 22. Zeng/2009  | 73.5           | 32.4            | –               | –          | –               | 23.0        | –               | 0                   |
| 23. Shen/2012  | 53.8           | 65.8            | –               | –          | –               | –           | –               | –                   |
| 24. He/2018     | 64.0           | 56.87           | –               | –          | –               | –           | –               | –                   |
| 25. PROVetNet/2020 | 64.3         | 65.8            | 23.5            | 9.5        | 26.0            | 60.8        | –               | –                   |
| 26. Yi/2009    | 55.0           | –               | –               | –          | –               | –           | –               | –                   |
| 27. Vigil/1966  | –              | 33.8            | –               | –          | –               | –           | –               | –                   |

**APACHE, Acute Physiology and Chronic Health Evaluation; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment; BMI, Body Mass Index; — not available.**

* Used APACHE III to assess the condition of patients.
Table 3
Outcomes or subgroup analysis of included studies.

| Outcomes or subgroup analysis or sensitive analysis | Number of studies | Study reference number | Patients | RR/MD (95% CI) | P | P |
|-----------------------------------------------------|-------------------|------------------------|----------|----------------|---|---|
| **Primary outcomes**                               |                   |                        |          |                |   |   |
| All-cause mortality                                 | 11                | [8,29,38,43-44,46-48,51-52,54] | 1669     | 1.03 (0.91, 1.18) | 0.0% | 0.627 |
| 28-day mortality                                    | 2                 | [8,46]                 | 1032     | 1.07 (0.92, 1.24) | 0.0% | 0.365 |
| **Secondary outcomes**                             |                   |                        |          |                |   |   |
| ARDS                                                | 5                 | [8,40,44,47,48]        | 1379     | 0.43 (0.24, 0.78) | 44.0% | 0.005 |
| Pneumonia                                           | 4                 | [8,40,44,48]          | 1300     | 0.66 (0.38, 1.16) | 44.7% | 0.152 |
| Atelectasis                                         | 6                 | [8,34,40,41,44,48]    | 1447     | 0.72 (0.46, 1.14) | 63.3% | 0.161 |
| Barotrauma                                          | 8                 | [8,29,30,38,40,43,44,48] | 1513     | 0.86 (0.53, 1.40) | 3.6% | 0.545 |
| Hypoxemia                                           | 5                 | [8,29,34,38,44]       | 1218     | 1.16 (0.44, 3.03) | 82% | 0.768 |
| Hypotension                                         | 2                 | [29,46]               | 147      | 3.87 (0.11, 138.03) | 92.2% | 0.459 |
| Duration of MV                                      | 6                 | [8,31,33,41,43,46]    | 913      | 0.00 (~0.13, 0.13) | 84.7% | 0.996 |
| P/F ratio                                           | 4                 | [32,36,39,44]         | 240      | 40.30 (0.94, 79.05) | 64.9% | 0.045 |
| Blood pressure                                      | 3                 | [32,36,53]           | 64       | 2.52 (~0.73, 5.76) | 0.0% | 0.128 |
| Duration of hospital stay                           | 3                 | [8,34,41]           | 1116     | ~0.66 (~1.94, 0.61) | 93.0% | 0.309 |
| Duration of ICU                                     | 2                 | [8,41]               | 1089     | ~1.04 (~1.36, ~0.73) | 0.0% | <0.00001 |
| HR                                                  | 4                 | [36,49,50,53]        | 120      | ~9.54 (~22.30, 3.22) | 80.9% | 0.143 |
| Cardiac index                                       | 3                 | [32,46,53]          | 84       | ~0.19 (~0.44, 0.05) | 7.7% | 0.118 |
| SVRI                                                 | 3                 | [30,50,53]          | 94       | 51.82 (~231.51, 335.16) | 53.4% | 0.720 |

*Values of test of interaction between subgroups. RR: Risk ratio; CI: confidence interval; MD: mean difference; ARDS: acute respiratory distress syndrome; P/F ratio: oxygenation index; HR: heart rate; SVRI: systemic vascular resistance index; ICU intensive care unit; MV mechanical ventilation.

2.52; 95%CI -0.73 to 5.76; \( I^2 \) 0.0%; \( P = 0.128 \)), cardiac index [32,36,53] (MD -0.19; 95%CI -0.44 to 0.05; \( I^2 \) 7.7%; \( P = 0.118 \)), HR [36,49,50,53] (MD -9.54; 95%CI -22.30 to 3.22; \( I^2 \) 80.9%; \( P = 0.143 \)), and SVRI [30,50,53] (MD 1.82; 95%CI -231.51 to 335.16; \( I^2 \) 53.4%; \( P = 0.720 \)) between these two groups. Based on sensitive analysis, after exclude the RCT published in 1979 [31], the result of duration of MV reversed and the heterogeneity decreased from 85% to 0% (RR ~0.10; 95% CI ~0.13 to ~0.07; \( P \) 0.0%; \( P \) ≤0.000001). Therefore, the outcome of duration of MV may be more reliable after excluding this study. Similarly, we could found the potential source of heterogeneity in the results of ARDS, atelectasis, P/F ratio, duration of hospital, HR, and SVRI according to sensitive analyses (Additional File 8), there was no certain RCT could eliminate the heterogeneity in hypoxemia.

3.4. Subgroup analysis and meta-regression

First, we judged the source of heterogeneity in primary outcomes. None of the covariates mentioned above were the source of heterogeneity in all-cause mortality according to subgroup analyses. In addition, we did not find any possible sources of heterogeneity through a meta-regression on all-cause mortality. For 28-day mortality, neither meta-regression nor subgroup analysis was performed due to the limited number of RCTs. More details on the meta-regression can be found in Additional File 9. In addition, based on the subgroup analysis of secondary outcomes, the publication year (before 2004 versus after 2004) might be a potential source of heterogeneity in the duration of hospital stay. In addition, the PEEP gradient of the control group, risk of bias, and publication year (before 2004 versus after 2004) might be potential sources of heterogeneity in the duration of MV. The practice standard of ventilation might be affected by the studies published in 2000 and 2004 [13,55], and influence the results of RCTs published after that. More details on the subgroup analysis can be found in Additional File 10.

3.5. Publication bias

The funnel plot regarding all-cause mortality was absent near the bottom left. Egger's test was conducted to investigate publication bias; there was no evidence of potential publication bias (\( P = 0.957 \)) (Fig. 3A). Visual asymmetry could be found in the funnel plot of 28-day mortality (Fig. 3B). No visible asymmetry was detected for the secondary outcomes, and no evidence of potential publication bias was showed in light of the Egger linear regression test of secondary outcomes. The results of funnel plots of secondary outcomes are presented in Additional File 11.

3.6. Quality of the evidence in this meta-analysis

The evidence quality of sixteen outcomes ranged from very-low to moderate. The quality of all-cause mortality and 28-day mortality were assessed as low. More details for secondary outcomes are presented in Additional File 12.

3.7. TSA for primary outcomes

TSA was performed for all-cause mortality [8,29,38,43,44,46-48,51,52,54] and 28-day mortality [8,46]. Regarding the all-cause mortality, the Z-curve did not cross the conventional boundary as well as trial sequential monitoring boundary, which meant it may be a false negative result (Fig. 4A). Similarly, the TSA analysis showed the result of 28-day mortality might also be a false negative result and warranted more RCTs to judge the efficacy of different levels of PEEP in non-ARDS patients in the future (Fig. 4B).

4. Discussion

4.1. Main findings in this meta-analysis

Our study showed that a higher PEEP was not inferior to a lower PEEP with regard to the all-cause mortality, 28-day mortality, duration of both MV and hospital stay on patients without ARDS. Nevertheless, a higher PEEP could decrease the risk of ARDS and the duration of ICU stay compared to a lower PEEP. At the same time, a higher PEEP, compared with a lower PEEP, could increase the P/F ratio in patients. For other complications, no significant difference could be found between the groups.

4.2. Discussion of the most important differences in the present study

To our knowledge, this study recruited the largest number of eligible studies to date, including the latest RCT recruiting 980 patients. TSA software was used in the present meta-analysis to facilitate the robustness of the outcomes. At the same time, abundant subgroup analyses and meta-regressions were conducted to control confounding factors such as publication year, to ensure the robustness of the results.
Compared to previous meta-analyses [17, 56], we conducted a comprehensive study by recruiting RCTs published after 2016 [8, 41, 49, 52], and three RCTs published in Chinese [50, 51, 53]. And we evaluated the duration of ICU, duration of hospital stay, HR, cardiac index and SVRI for the first time. In addition, our inclusion criteria were more stringent than previous studies [17, 56]. Although our primary outcomes were similar to previous studies, our study showed that higher PEEP did not improve the risk of pneumonia [56] and hypoxemia [17], which was contrary to previous studies. At the same time, according to our subgroup analyses, publication year (before 2004 versus after 2004) might influence the results for the duration of hospital stay and MV.

Our study revealed that higher PEEP did not decrease all-cause or 28-day mortality versus lower PEEP. However, higher PEEP could improve the P/F ratio and duration of ICU stay. For several years, the main goal of PEEP was to improve patients’ oxygenation and deliver oxygen [24]. But as time went on, this goal shifted to reduce VILI by limiting Vt and inspiratory pressure when sufficient PEEP was provided to avoid collapse of lung [3]. At the same time, PEEP is used to recruit collapsed lungs and decrease intrapulmonary shunts to improve the V/Q ratio [57, 58]. In addition, PEEP avoids cyclic lung opening and closing during MV, and allows Vt distribution over a larger and more homogeneously lung surface, which can reduce the risk of VILI and the stress and strain of the tidal lung [3, 57, 59, 60]. Additionally, because of ventricular interdependence, the reduction of volume of the right ventricular during MV will lead to movement of the interventricular septum, and left ventricular compliance and filling will increase, leading to increased CO [61, 62]. On the other hand, lower PEEP might cause atelectasis and hypoxemia, while excessive PEEP might increase pleural pressure, reduce venous return and raise pulmonary vascular resistance, eventually causing impaired hemodynamics [57, 63, 64]. In terms of the harmful effects of the lung parenchyma, higher PEEP may increase the stress and strain of the lung and cause VILI, while lower PEEP may cause atelectasis. Moreover, if PEEP could not recruit enough collapsed alveoli to participate in tidal ventilation, the advantages of PEEP, such as less
the clinical prognosis of MV patients is still controversial [8,40,44,49]. Physicians seem to be hesitant about using no PEEP or using high PEEP (> 10 cmH2O) among patients who need MV. Previous studies (over 95% of the patients did not have ARDS) revealed that 38.8% of ICU patients received no PEEP on day 7 and most patients received a median level of 5 cmH2O PEEP during MV, while only 3.2% patients received PEEP more than 10 cmH2O [73,74]. In 2016, the median level of PEEP applied in ICU patients during MV increased from 5 cmH2O to 7 cmH2O [14]. Up to date, much less effort has been made to define an adequate or optimum level of PEEP in patients without ARDS. If PEEP could provide clinical benefit to patients by markedly improving lung compliance through alveolar recruitment and the appropriate levels of PEEP are unclear, it is essential to identify the better level of PEEP for each individual patient [75]. However, considering that different diseases have different responses to PEEP, it is important to assess the lung recruitable of patients, which is the essential preliminary step to setting PEEP [76]. Lung recruitability may be assessed directly or indirectly by measuring actual changes in lung volume with the rise in PEEP [76,77]. Direct methods include spirometry, P-V curve, imaging (CT scan [78], lung ultrasound [79], and electrical impedance tomography [80]), and nitrogen washout [81-83], and indirect methods include PEEP test during inspiration or expiration and P/F ratio at five cmH2O PEEP according to Berlin classification [84-87]. Once the decision is made to apply PEEP for ICU patients, individual PEEP titration is necessary. Sella and coworkers compared the effects of titrating PEEP using higher and lower PEEP/FiO2 tables and electrical impedance tomography (EIT) in fifteen COVID-19 patients [88]. The results showed that the loss of lung compliance consequent to lung overdistension was significantly greater in patients who used higher PEEP/FiO2 tables to set PEEP than in those who used EIT. In addition, many other methods can guide PEEP titration, such as the lung P-V curve, esophageal pressure method [89], stress index method [90], and PEEP decreasing method [91].

At present, although there are various methods mentioned above that could help physicians titrate PEEP, the PEEP setting during the progression of disease could not be fully summarized in a table or a formula. Previous studies proposed using driving pressure (ΔP) to guide PEEP setting dynamically during MV [92]. In contrast, a recent study confirmed that transpulmonary pressure (pressure at the airway - pleural pressure), rather than ΔP, was considered an essential parameter to dynamically guide the PEEP settings [93]. An animal study demonstrated that, compared with maximum oxygenation-guided PEEP adjustment, transpulmonary pressure-guided PEEP titration was associated with improved pulmonary compliance, lower dead space ventilation, higher CO, and relieved VILI [94]. Similar results were found in a study that recruited 16 obese human patients [95]. But the value of these two methods to dynamically guide the PEEP settings needs further study in the future.

4.3. Limitations of this study

There are some limitations in this study. First, several RCTs contained very few patients, and the possibility of a “small sample effect” cannot be ignored. The results should be explained carefully [96]. In addition, we included several “older” RCTs that might suffer from bias due to the considerable change in standard ventilatory care over recent decades, which needs to be interpreted carefully. Moreover, the eligible RCTs recruited in this study used a broad spectrum of definitions for “higher” and “lower” PEEP, and relative values rather than exact data were reported. Because of the heterogeneity in our study, more high-quality RCTs with large sample sizes are warranted in the future.

4.4. Unanswered questions and future research

The evidence in this study suggests that higher PEEP should not be considered a regular treatment regimen for patients without ARDS.
However, the appropriate range of PEEP among non-ARDS patients with different baseline characteristics or diseases may be different. For non-ARDS patients not included in this study, such as obese patients or atelectasis patients in the ICU receiving MV, it is uncertain whether similar conclusions can be obtained. Further studies should judge the lung recruitability of patients before randomization rather than applying higher or lower PEEP uniformly to all ICU patients during MV. PEEP titration and dynamic monitoring are still essential for personalized PEEP settings among non-ARDS patients during MV. Moreover, people urgently need to know if there is a priority between different PEEP titration methods, especially in those without ARDS. At the same time, not a single ventilator parameter plays a dominant role in the prognosis of patients who received MV, perhaps further studies should attend to the overall physiological effects of combined ventilation strategies in patients with different disease.

5. Conclusion

Taken together, our results indicate that lower PEEP may be a feasible alternative to higher PEEP among patients without ARDS. If clinicians decide to use PEEP among patients without ARDS, it is important to evaluate lung recruitability and choose an appropriate PEEP titration method. Considering the heterogeneity and quality of the results in this study, more high-quality RCTs with larger sample sizes comparing higher PEEP with lower PEEP are needed in the future.

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Ethics approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The datasets generated and/or analyzed during the current study are available in the Medline, Embase, Cochrane Library, Web of Science, and Wanfang database.
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