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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 cmH_2O was applied in the higher PEEP groups and 1.9±2.6 cmH_2O 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 < 0.00001), 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.

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
RCT	randomized controlled trial
FiO2	fraction of inspiration O2
PaO2	partial pressure of oxygen in arterial blood
HR	heart rate
SVRI	systemic vascular resistance index
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
P-V	pressure-volume
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 tends 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 O_2 (FiO_2) 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 $3cmH_2O$ [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 (PaO_2) / fractional inspired oxygen ($FiO_{2)}$ ratio, blood pressure, heart rate (HR), cardiac index, systemic vascular resistance index (SCRI). 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 H_2O versus ≥10 cm H_2O) [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 $I^2 \geq 50\%$, 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

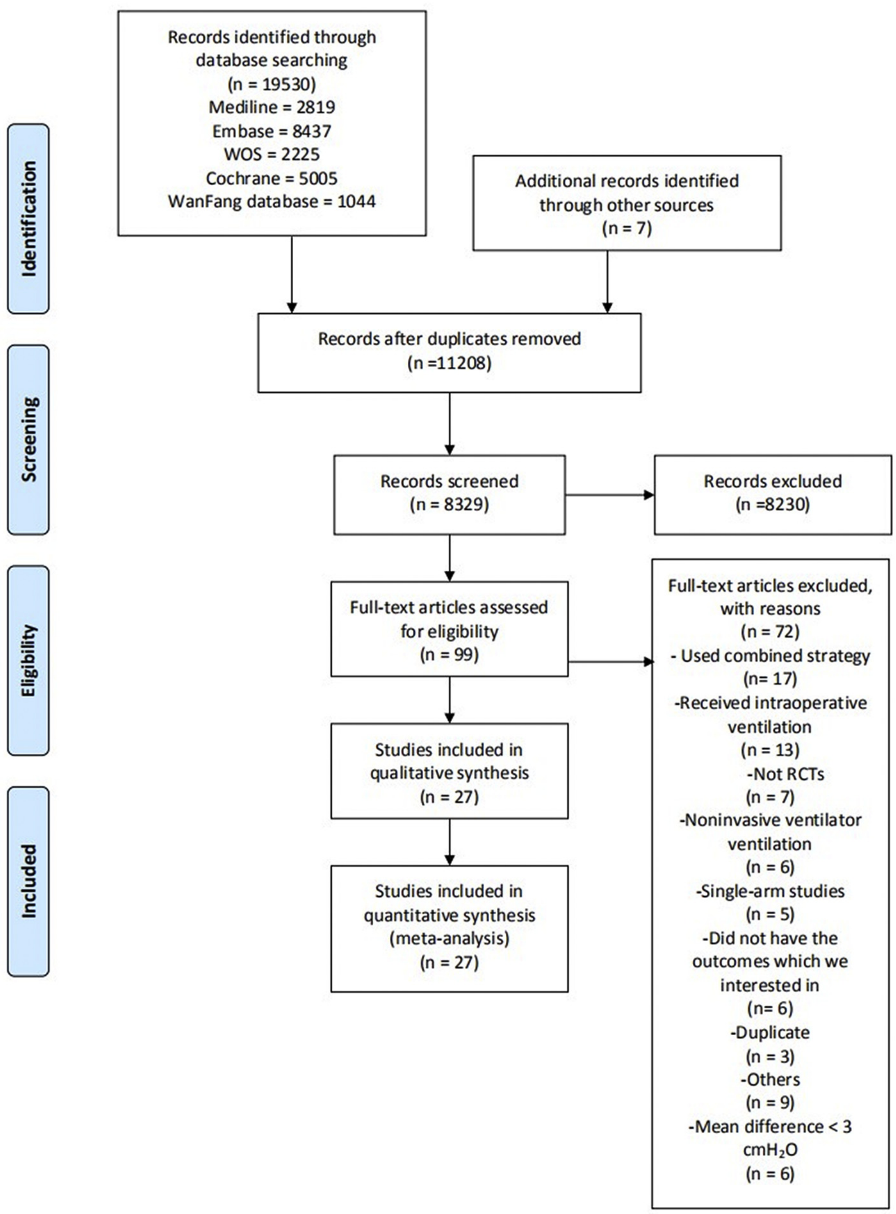

Fig. 1. Flow chart of the search process and study selection.

Table 1
The characteristics of the included articles.

	Source/Year	Country	Centre (s)	Type of patients	Sample size	Higher PEEP					Lower PEEP					Quality score	Main findings
						N	PEEP, cm H_2O	Vt, mL/kg PBW	FiO2	RM	N	PEEP, cm H_2O	Vt, mL/kg PBW	FiO_2	RM		
Surgical patients																	
1.	Carroll/1988	USA	1 ICU	Surgical ICU patients without ARDS	50	22	10	12	≥0.5	Yes	28	4	12	≥0.5	Yes	Unclear	Higher PEEP was associated with more hypotension, barotrauma, and death and higher duration of ventilation.
2.	Celebi/2007	Turkey	1 ICU	Post-CS	60[a]	20	10	7	0.4	Yes	20	5	7	0.4	Yes	Low	Higher PEEP could increase oxygenation and decreased atelectasis equally.
3.	Good/1979	USA	1 ICU	Post-CS	24	10	6	11	NA	NO	14	0	11	NA	NO	High	No differences were found in the rate of atelectasis, P/F ratio and arterial–alveolar ratio.
4.	Holland/2007	Germany	1 ICU	Post-CS	28	14	10	6–8	NA	NO	14	5	6–8	NA	NO	High	Higher PEEP does not compromise liver function and gastric mucosal perfusion
5.	Lago/2014	Brazil	1 ICU	Post-CS	136[b]	44	10	8	≤0.4	NO	45	5	8	≤0.4	NO	Unclear	Higher PEEP could decrease the duration of ventilation.
6.	Marvel/1986	USA	1 ICU	Post-CS	44[c]	12	10	12	0.4	NO	15	5	12	0.4	NO	Low	Higher PEEP could decrease alveolar–arterial oxygen tension gradient. No differences regarding atelectasis, and hospital length of stay
7.	Zurick/1982	Britain	1 ICU	Post-CS	83	41	10	NA	NA	NO	42	0	NA	NA	NO	High	No differences were found in the amount of blood loss, need for re-exploration or blood requirement.
8.	Dyhr/2002	Danmark	1 ICU	Post-CS	16	8	15	6	1.0	Yes	8	0	6	1.0	Yes	High	Higher PEEP is required after a lung recruitment maneuver in patients ventilated with high FiO2 after cardiac surgery to keep lung volumes and the improved oxygenation.
9.	Murphy/1983	USA	1 ICU	Post-CS	139	94	10	NA	NA	NO	45	0	NA	NA	NO	Unclear	Higher PEEP could not decrease the mean blood loss among cardiac surgery patients.
10.	Michalopoulos/1996	Greece	1 ICU	Post-CS	67[d]	21	10	NA	NA	NO	22	0	NA	NA	NO	Unclear	No differences were found in the OI, CI, and duration of MV.
11.	Borges/2013	Brazil	1 ICU	Post-CS	136[e]	44	10	8	≤0.4	NO	45	5	8	≤0.4	NO	Low	Higher PEEP could decrease the risk of compliance and improve the OI.
12.	Schmidt/1976	USA	1 ICU	Post abdominal surgery	112	56	8	12–15	NA	NO	56	0	12–15	NA	NO	High	Higher PEEP could decrease the risk of compliance and improve the OI.
13.	Berenjestanaki/2018	Iran	1 ICU	Post-CS	240[f]	60	10	NA	NA	NO	60	5	NA	NA	NO	Low	Higher PEEP could decrease rate of atelectasis, the duration of intubation in ICU, length of hospital and ICU.
Medical patients																	
14.	Feeley/1975	USA	1 ICU	ARF patients	25	12	5	15	NA	No	13	0	15	NA	No	High	The use of PEEP. during weaning may be helpful in patients who fail to wean.
15.	Nelson/1987	USA	1 ICU	Patients with early, moderate arterial hypoxemia	38	20	15	NA	0.45	No	18	8	NA	0.45	No	High	No differences between different levels of PEEP in duration of ventilation, ICU and hospital length of stay, barotrauma, and mortality.
16 .	Manzano/2008	Spain	2 ICU s	Nonhypoxemic patients without lung injury	127	64	5–8	8	NA	NO	63	0	8	NA	NA	High	Higher PEEP in nonhypoxemic ventilated patients reduces the number of hypoxemia episodes and the incidence of ventilator-associated pneumonia.
17.	Cujec/1993	Canada	1 ICU	ARF	46	NA	10	NA	NA	NA	NA	0	NA	NA	NA	High	In patients with a patent foramen ovale, the right-to-left shunt is usually increased by using higher PEEP.
18.	Lesur/2010	Canada	1 ICU	ARF	63	30	5	8	NA	NO	33	0	7	NA	NO	Low	No differences were found in the rate of hypotension, duration of ventilation and

(continued on next page)

Table 1 (*continued*)

	Source/Year	Country	Centre (s)	Type of patients	Sample size	Higher PEEP					Lower PEEP					Quality score	Main findings
						N	PEEP, cm H_2O	Vt, mL/kg PBW	FiO2	RM	N	PEEP, cm H_2O	Vt, mL/kg PBW	FiO_2	RM		
																	mortality.
19.	Weigelt/1979	USA	1 ICU	Risk of ARDS	79	45	5	15	≤0.5	NO	34	0	15	≤0.5	NO	Unclear	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	Unclear	No differences were found in the risk of incidence of ARDS, atelectasis, pneumonia, and barotrauma, as was mortality.
21.	Yao/2016	China	1 ICU	NPE	50	25	5–15	6–8	NA	NO	25	0	6–8	NA	NO	Unclear	Higher PEEP could improve the oxygenation, CO, and cardiac function.
22.	Zeng/2009	China	1 ICU	NPE	102[g]	17	20	5	NA	NO	17	0	5	NA	NO	High	Serious effect in hemodynamics was observed in the condition of higher PEEP.
23.	Shen/2012	China	1 ICU	COPD patients with ARF	75	38	4–10	400 ml–550 ml	NA	NO	37	0	400 ml–550 ml	NA	NO	High	Higher PEEP might lower urinary volume, urea excretion ratio, creatinine clearance rate of patients.
24.	He/2018	China	1 ICU	ARF	100	50	4–10	400 ml–600 ml	NA	NO	50	0	400 ml–600 ml	NA	NO	High	Although no differences were found in the rate of mortality, higher PEEP might damage kidney function of COPD patients.
25.	PROVEnet/2020	Netherlands	8 ICUs	ICU patients without ARDS	969	467	7.0 (5.0–8.0)	6.9 (6.1–8.0)	0.50 (0.40–0.70)	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 noninferior to a higher PEEP strategy regarding the number of ventilator-free days at day 28.
26.	Yi/2009	China	1 ICU	COPD	40	20	10	6	0.4	NO	20	5	6	0.4	NO	High	Although higher PEEP could improve the oxygenation, it might damage the indexes of hemodynamics in COPD patients (HR, MAP, CI, SVRI)
27.	Vigil/1996	Mexico	1 ICU	Trauma	39	20	5	12	NA	NO	19	0	12	NA	NO	High	The PEEP group showed significantly higher VD/VT and poorer P/F ratios. Higher PEEP is not necessary for patients without ARDS.

Abbreviations: ICU intensive care unit; N number of patients; PEEP positive end-expiratory pressure; Vt Tidal volume; PBW, predicted body weight; FiO_2, 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 cmH_2O]).
[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 cmH_2O]).
[e] One group containing 47 patients was excluded (The median PEEP group [8 cmH_2O]).
[f] One group containing 78 patients was excluded (The median PEEP group [8 cmH_2O]).
[g] Four groups containing 68 patients was excluded (The median PEEP group [5/10/15 cmH_2O] and patients who received different tidal volume [tidal volume = 10 mL/kg PBW]).

subsequently refined to 27 eligible RCTs involving a total of 2980 participants for further consideration [8,29-54]. The eligible studies recruited in this study were performed between 1975 and 2020. Thirteen of the RCTs came from surgical ICU [29-41], and the rest were extracted from medical ICU [8,42-54]. Eleven RCTs applied low Vt among intervention group [8,30,32,33,36,39,44,46,49,50,53] (Vt ≤ 8 cmH_2O). Seventeen RCTs applied zero PEEP among control group [31,35-38,40,42,44-52,54] (Table 1). Six of them included patients after surgery [31,35-38,40], and the rest of the RCTs included patients from the medical ward with severe brain injury, ARF, trauma, or patients who were at risk of acute respiratory distress syndrome. The level of PEEP was 9.6 ± 3.4 (inter-quartile range (IQR) (25th and 75th percentiles) 8 cmH_2O and 10 cmH_2O) cmH_2O and 1.9 ± 2.6 (IQR 0cmH_2O and 5cmH_2O) cmH_2O in the higher and lower PEEP arms of eligible studies, respectively. The median age of mean age of each study in our meta-analysis was 56.7 years old, and IQR was 47.2 years old and 62.3 years old (Table 2). One RCT used lower inflection point (LIP) on the lung pressure-volume (P-V) curve to set PEEP in the intervention and control groups [36]. And eight of twenty-seven RCTs used P/F ratio or $SpaO_2$ to set PEEP between these two groups [8,29,30,43,44,47,48,53]. The rest of studies set PEEP according to predefined protocol [31-35,37-42,45,46,49-52,54].

3.2. Risk of bias and quality assessment

Regarding the risk of bias of individual RCTs, six studies were judged as low risk of bias [8,30,34,39,41,46]. The other seven studies were categorized as having an unclear risk of bias [29,33,37,38,47-49] (Additional File 4 and Additional File 5). The rest studies were assessed as high risk of bias because of some blind or random method defects. More details are shown in Additional File 6.

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 [8,29,38,43,44,46-48,51,52,54] (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; I^2 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; I^2 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; I^2 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; I^2 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; I^2 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; I^2 84.7%; $P = 0.996$), duration of hospital stay [8,34,41] (MD -0.66; 95% CI -1.94 to 0.61; I^2 93%; $P = 0.309$), blood pressure [32,36,53] (MD

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.	Celibe/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	–	–	41.4	–	–	–
8.	Dyhr/2002	75	62.5	–	–	–	–	–	–
9.	Murphy/1983	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.	Berenjestanaki/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[a]	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/m 2	–	38.1	22.2
19.	Weigelt/1979	72.4	45.0	–	–	–	–	–	–
20.	Pepe/1984	71.7	43.9	–	–	–	–	–	–
21.	Yao/2016	66.0	38.6	–	–	–	–	0	0
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.	PROVEnet/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 venitlation; SOFA, Sequential Organ Failure Assessment; BMI, Body Mass Index; — not available.
[a] 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)	I^2	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, 79.65)	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	[32,36,53]	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 51.82; 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; I^2 0%; $P \leq 0.00001$). 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. 4 A). Similarly, the TSA analysis showed the result of 28-day mortality might also be a 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. 4 B).

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 mate-regressions were conducted to control confounding factors such as publication year, to ensure the robustness of the results.

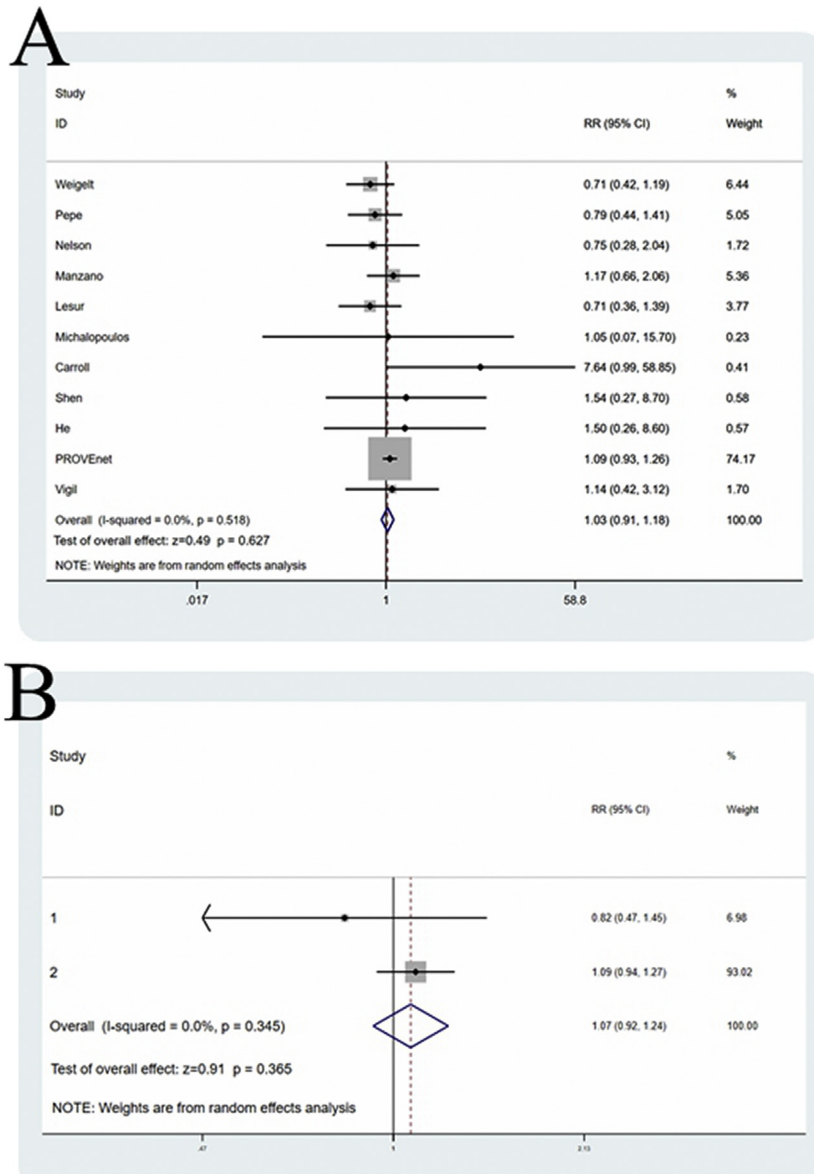

Fig. 2. Forest plot of primary outcome:
A All-cause mortality.
B 28-day mortality.

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

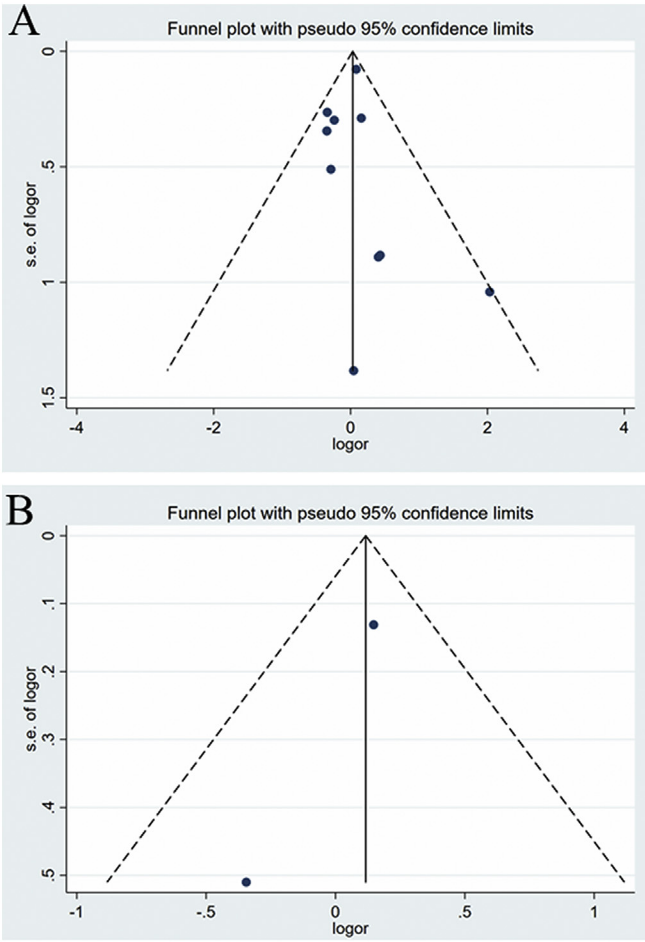

Fig. 3. Funnel plot of primary outcome:
A All-cause mortality.
B 28-day mortality.

atelectasis, may be nullified by coinciding overdistension of lung tissue, which could result in increased dynamic and end-inspiratory lung stress [8]. Therefore, the pooled benefits or harm from PEEP depend on the balance between the beneficial and harmful physiological effects, and when adverse effects are dominant, the clinical outcomes for patients cannot be improved.

This meta-analysis showed that a higher PEEP was associated with a lower risk of ARDS compared to a lower PEEP. However, the application of PEEP and recruitment maneuvers could significantly affect PaO_2 / FiO_2 during MV [65,66], which might affect the diagnosis of ARDS. The publication of the Berlin definition improved the limitations of American-European Consensus Conference (AECC) diagnosis by requiring PEEP ≥5 cmH2O. However, the Berlin definition does not consider the nonlinear relationship between PaO_2 and FiO_2 [67] and its prediction accuracy is limited [68-70]. Compared with the AECC diagnosis criteria, the minimum PEEP of 5 cmH_2O did not significantly improve prediction for the Berlin definition [71]. Although, our results were similar to previous meta-analyses with respect to the reduction in ARDS [17], four of five eligible studies in this endpoint were published before 2011, which might cause risk of bias due to the different diagnostic criteria used in each study. It is difficult to obtain an accurate conclusion as to whether higher PEEP is a therapy to prevent the development of ARDS or a method to mask the diagnosis of ARDS in this study. How to improve the validity and reliability of ARDS diagnosis should be considered in the future.

Previous study showed that the prophylactic PEEP, compared with zero PEEP, could reduce the risk of ventilation-associated pneumonia (VAP) [72]. However, to date, whether prophylactic PEEP could improve the clinical prognosis of MV patients is still controversial [8,40,44,48]. Physicians seem to be hesitant about using no PEEP or using high PEEP (> 10 cmH_2O) 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 cmH_2O PEEP during MV, while only 3.2% patients received PEEP more than 10 cmH_2O [73,74]. In 2016, the median level of PEEP applied in ICU patients during MV increased from 5 cmH_2O to 7 cmH_2O [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 recruitability 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 cmH_2O 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/FiO_2 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/FiO_2 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.

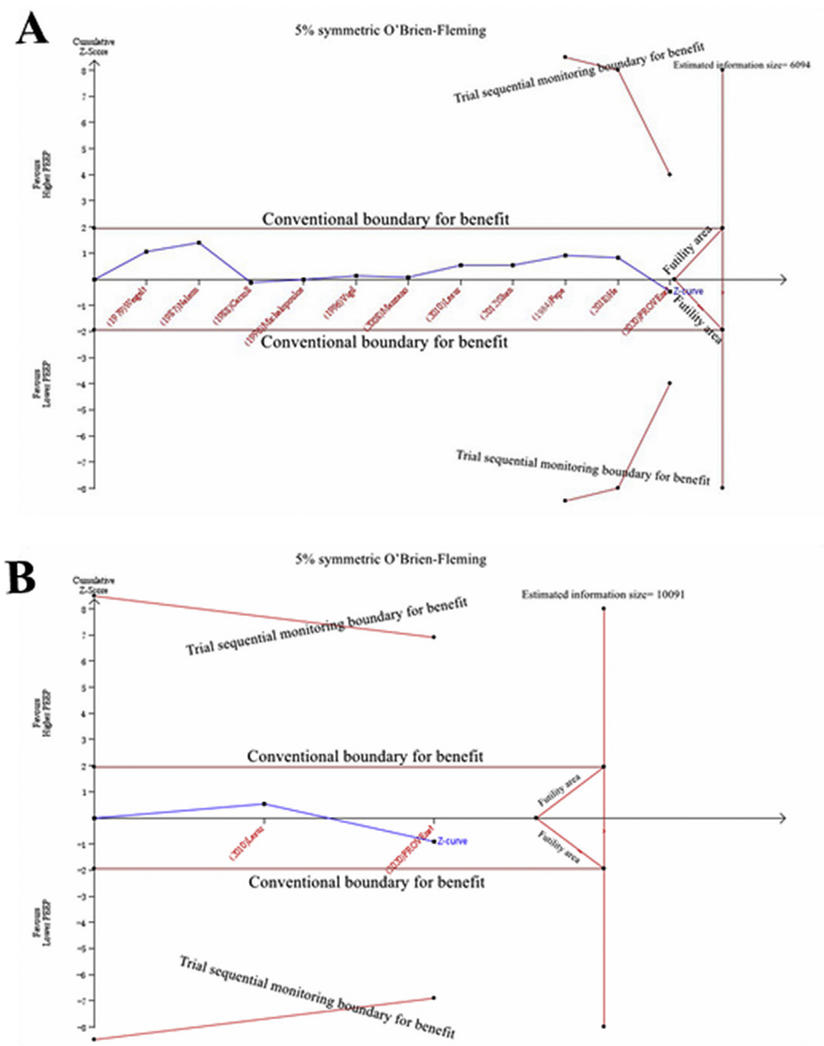

Fig. 4. TSA of primary outcomes.
A All-cause mortality.
B 28-day mortality.

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 radomization 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.

Code availability

Not applicable.

Author's Statements

Shuai Shao developed the initial idea of this study and conducted a comprehensive search of four databases. Shuai Shao and Quanying Wang took responsibility for selecting the study. Shuai Shao, Quanying Wang, Zhenbei Qian extracted data. All authors have made their contributions to research design, interpretation of results, and ideas for writing articles. Shuai Shao and Zhenbei Qian synthesized and analyzed the data and drafted the article. Hanyujie Kang and Zhaohui Tong reviewed this article and provided suggestion for it. All of the authors have carefully examined this manuscript and agreed with the ideas presented in the article.

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Declaration of Competing Interest

None of the authors has any competing interests.

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