Higher PEEP versus Lower PEEP Strategies for Patients in ICU without Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: The application of high PEEP remains to be a controversial issue when it comes to ICU patients underwent ventilation. There are studies supporting the usage of high PEEP in patients with ARDS, while for those without ARDS, the conclusion is of great ambiguity. We performed this systematic review and meta-analysis to compare the effects of high and low level of PEEP on ICU patients without ARDS.

Methods: We searched public databases (including PubMed, EMBASE, Cochrane Library and Clinicaltrial.gov) to find eligible randomized controlled trials (RCTs). The primary outcomes included in this meta-analysis were in-hospital mortality, 28-day mortality and the duration of ventilation, ICU stay, and hospital stay. We used the Cochrane risk of bias assessment tool to evaluate risk of bias. Trial Sequential Analysis (TSA) was conducted.

Results: We included 2307 patients from 24 trials using high and low PEEP. Although no significant difference was found between high and low PEEP applications in in-hospital mortality (risk ratio[RR] 0.98, 95% confidence interval[CI] [0.81, 1.19], P=0.87), 28-day mortality (RR 0.68, 95% CI [0.33, 1.40], P=0.30) and the duration of ventilation (mean difference[MD] -0.30, 95% CI [-0.64, 0.04], P=0.09), ICU stay (MD -0.38, 95% CI [-1.03, 0.27], P=0.25), and hospital stay (MD -0.56, 95% CI [-1.44, 0.32], P=0.22), high PEEP indeed increased the level of PaO_2/FIO_2 (MD 32.39, 95% CI [13.06, 51.72], P=0.001), and therefore decreased the incidences of ARDS (RR 0.57, 95% CI [0.37, 0.89], P=0.01) and hypoxaemia (RR 0.60, 95% CI [0.41, 0.88], P=0.009). In addition, although total results did not reveal the advantage of high PEEP on other secondary outcomes regarding atelectasis, barotrauma, ventilator associated pneumonia (VAP), hypotension, mean arterial pressure (MAP), SaO_2 and lactate, subgroup analysis seemed to obtain different results. The TSA results suggested more RCTs were needed.

Conclusion: Ventilation with high PEEP in ICU patients without ARDS may improve the level of oxygenation (PaO_2/FIO_2) resulting in low incidences of ARDS and hypoxaemia. Nevertheless, other clinical outcomes including in-hospital and 28-day mortality, duration of ventilation, ICU stay and hospital stay, pulmonary complications, hemodynamics and post-operative fluid balance did not show any significant difference.

1 Introduction

The wide application of high positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) has been thought to be one of the best ventilation strategies for patients to reduce mortality and improve other clinical outcomes[1]. However, there is no definitive conclusion regarding the benefits of PEEP usage in patients without ARDS. Post-operative patients admitted to ICU often receive mechanical ventilation to prevent insufficient oxygenation and improve the gas exchange[2], especially those underwent open heart surgery[3]. According to several studies, coronary artery bypass grafting (CABG) is closely associated with impaired lung function, resulting in high risk of postoperative pulmonary complications such as atelectasis, pneumonia, ARDS, pneumothorax and so forth[4]. Similarly, for patients suffering from acute respiratory failure (ARF), hypoxaemia and even brain diseases[5], adequate respiratory support therapy is also required.

To prevent or dispose of pulmonary complications and hypoxic conditions of ICU patients, various ventilation strategies have been performed, including intermittent positive pressure breathing (IPPB), continuous positive

h[6]. But none of them produced obvious effectiveness.

High level of PEEP, combined with the low tidal volume ($V_T \le$ 6 ml/kg and adjusted according to body weight), plateau pressure $\le$ 30 cm H_2O and permissive hypercapnia, was called the lung-protective ventilation strategy and may lead to the improvement in oxygenation[7, 8]. However, in one meta-analysis incorporating eight RCTs (randomized controlled trials), patients with ARDS did not obtain benefits from high PEEP in regard to 28-day mortality, barotrauma, and organ failure[9]. In addition, RCTs focused on patients without ARDS using high PEEP versus low PEEP drew different conclusions. Dyhr et al.[8] and Celebi et al.[10] reported that the usage of high PEEP might decreased the incidence of atelectasis while eased the hypoxaemia via increasing the level of PaO2. Similarly, Borges et al.[11] found high PEEP could increase the level of PaO_2/FIO_2 resulting in decreased hypoxaemia in post-operative patients underwent cardiac surgery. However, several studies did not verify the possible effect of high PEEP on pulmonary complications and even reported the increased risk of ARDS in trauma patients received high PEEP[12]. In terms of hemodynamics, ventilation with high PEEP might reduce the level of mean arterial pressure (MAP) and raised the development of hypotension in patients without ARDS[13].

Furthermore, a recently RCT did not find evidence to support the application of high PEEP in ICU patients without ARDS[14]. Although these is already a systematic review published in 2016 comparing the effectiveness between high and low PEEP in non-ARDS patients[15], the conclusions were insufficient and did not include some recent studies. For these reasons, we conducted this systemic review and meta-analysis to update the existing evidence and find more factors to evaluate the efficacy of high and low level of PEEP performed in ICU patients without ARDS.

2 Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) guidelines to perform this systematic review and meta-analysis[16]. We have prospectively registered this meta-analysis on PROSPERO database (Registration number: CRD42021229077).

2.1 Search strategy and selection of studies

We applied an electronic search of PubMed (1955 till December 2020), CENTRAL (the Cochrane Library till December 2020), Clinicaltrial.gov (till December 2020), and EMBASE(till December 2020)with no language restrictions. The search strategy combined with keywords and Medical Subject Headings (MeSH) is as follows: (“Positive End-Expiratory Pressure” OR “positive-end expiratory pressure” OR “PEEP” OR “positive end-expiratory pressure”) AND (“randomized controlled trial” OR “RCT”). To find out additional studies, we also checked the reference of studies included and other systematic reviews.

Two investigators (Hongyu Yi and Xiaoming Li) independently and blindly screened the possible studies identified by above databases. Any discrepancies were solved by discussion. Studies were selected if they met the following criteria: 1) Participants: adult patients who were not diagnosed with ARDS upon their admission to ICU; 2) Intervention and comparison intervention: patients randomized into two groups receiving different level of PEEP respectively, intervention group received higher level of PEEP, while comparison group received lower level of PEEP; 3) Outcomes: at least one of these following outcomes can be extracted: primary outcomes (including in-hospital mortality, 28-day mortality and the duration of ventilation, ICU stay and hospital stay) and

 modynamics index, gas exchange and oxygenation index); 4) Study design: randomized controlled trial. The exclusive criteria are as follows: 1) Observational and retrospective studies; 2) the differences of other ventilator parameters except for PEEP were enough to affect the outcomes; 3) patients not in ICU; 4) self-controlled studies that different levels of PEEP were applied within a single patient.

2.2 Data extraction and quality assessment of studies

The following items of date were extracted from studies by two authors (Hongyu Yi and Xiaoming Li) with further reviewed by a third author (Zhi Mao): first author, publication year, country, study design, simple size, male percentage, median age of each group, tidal volume, ventilation strategies, hemodynamics index, gas exchange and oxygenation index and clinical outcomes.

The Cochrane Risk of Bias Assessment tool was used to evaluate the quality of studies included. The items included: the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

The primary outcomes were in-hospital mortality, 28-day mortality and the duration of ventilation, ICU stay, and hospital stay. The secondary outcomes included 1) pulmonary complications such as ARDS, atelectasis, barotrauma and ventilator associated pneumonia (VAP); 2) hypotension and mean arterial pressure (MAP); 3) hypoxaemia, PaO_2/FIO_2, oxygen saturation (SaO_2) and lactate; 4) chest-tube drainage and red blood cell (RBC) usage after cardiac surgery.

2.3 Trial sequential analysis

We performed the trial sequential analysis to assess whether the studies in our meta-analysis were convincing and authentic. The cumulative Z curve was conducted using a random effect model. Parameters were set as follows: 1) a two-side α of 0.05; 2) power of 80% and 3) the anticipated relative risk reduction (RRR) of 20% with the adjustment based on the incidence of intervention and control group of our selected studies. Detailed process and assessment of TSA were carried out according to a previous study[17].

2.3 Statistical analysis

For dichotomous variables, we calculated the relative risks (RRs) with their 95% confidence intervals (CIs) using random effects model via Mantel and Haenszel method. In addition, we applied pooled mean differences (MDs) with a 95% CI for continuous outcomes. We graphically presented these pooled variables using forest plot graphs. Statistical heterogeneity of selected studies was assessed by I^2 that estimates the percentage of total variation across the studies due to heterogeneity rather than chance. I^2 was calculated as I^2 = 100% × (Q-*df*)/Q, where Q is the Cochran's heterogeneity statistic. I^2 values above 50% indicate considerable statistical heterogeneity. Publication bias was displayed using a funnel plot and if the value of *P* is less than 0.1, publication bias may exist. We also conducted subgroup analysis regarding the level of low PEEP (using zero end-expiratory pressure (ZEEP) or not), publication year (before or after 2000) and type of patients (postoperative or medical ones) of selected studies to further evaluate the potential impacts of these confounders.

All parametric data were presented as the mean ± standard deviation (SD) except for nonparametric ones expressed as the median (interquartile range). Under such condition, mean and SD were calculated via the

BoxCox approach[18]. Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and TSA 0.9.5.10 (Copenhagen Trial Unit, Copenhagen, Denmark) were used to perform statistical analyses. $P < 0.05$ were defined as statistically significant.

3 Results

3.1 Characteristics of selected studies

Our search strategies returned 16358 potential articles followed with the exclusion of 3696 duplicate studies (Fig. 1). According to inclusion and exclusion criteria mentioned before, we precluded 12599 results after screening titles and abstracts in detail. After carefully reading the full text of the remaining 63 articles, we found 39 of them inappropriate for the following reasons: 1) not ICU patients (n = 3); 2) disequilibrium of other ventilation parameters (n = 7); 3) not RCT (n = 3); 4) animal trials (n = 2); 5) receiving different PEEP within single patients (n = 15); 6) including patients with ARDS or age under 18 (n = 2); 7) retrospective studies (n = 4); 8) intra-operative studies (n = 2) and 9) full article unavailable. Therefore, we finally analyzed 24 studies[5, 8, 10–14, 19–35].

The main characteristics of selected studies are shown in Table 1 and Additional file 1. These RCTs were conducted among different countries in the world and most of them were published in English except one in Chinese[5]. There was a wide range of publication year among studies and 10 of them published 20 years ago. Among studies presented in Table 1, high PEEP groups applied PEEP ranging from 5 to 30 cm H_2O, while the range of PEEP in low PEEP groups was from 0 to 10 cm H_2O. Ten studies used ZEEP (defined as 0 cm H_2O PEEP) as comparative group and most of them published earlier[8, 12, 19, 21–26, 31]. Patients in ICU requiring PEEP were either medical ones (including ARF, trauma, NPE, etc.), postoperative ones (most of them underwent cardiac surgery) or mixed ones (containing medical and postoperative patients), and the number of participants ranged from 15 to 969. Although the strategy and the duration of ventilation varied among studies, the levels of tidal volumes of each study were quite similar.

Table 1
Characteristics of selected studies

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Medical ICU patients									
Feeley et al. 1975	ARF	25	12	5	NO	13	0	NO	High PEEP increased inspiratory force and vital capacity in patients during weaning
Weigelt et al. 1979	At risk of ARDS	79	45	5	NO	34	0	NO	High PEEP reduced pulmonary mortality, ARDS, and the duration of ventilation and ICU stay while increased pulmonary dysfunction. No differences in in-hospital mortality
Pepe et al. 1984	At risk of ARDS	92	44	8	NO	48	0	NO	No differences in in-hospital mortality, ARDS, atelectasis, and pneumonia
Nelson et al. 1987	Hypoxaemia (PaO_2/FIO_2 < 250, not ARDS)	38	20	15	NO	18	8	NO	No differences in in-hospital and ICU mortality, pulmonary barotrauma and the duration of ventilation, ICU stay, and hospital stay

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Vigil et al. 1996	Trauma	39	20	5	NO	19	0	NO	High PEEP increased ARDS and the duration of hospital stay. No differences in in-hospital mortality, the duration of ventilation, the physiologic shunt, V_D/V_T and PaO2/FIO2
Koutsoukou et at.2006	Brain-damaged	21	11	8	NO	10	0	NO	High PEEP kept static elastance and minimal resistance stable which may prevented low lung volume injury
Lesur et al.2010	ARF	63	30	5	NO	33	0	NO	No differences in in-hospital and 28-day mortality, the duration of ventilation, hypotension, and MAP
Ma et al. 2014	NPE	120	60	11–30	NO	60	3–10	NO	High PEEP increased PaO2/FIO2 while decreased MAP, lactate and 28-day mortality
Postoperative ICU patients									
Good Jr et al. 1979	Post-cardiac surgery	24	10	8	NO	14	0	NO	No differences in alveolar-arterial oxygen ratio, PaO2/FIO2 and atelectasis

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Zurick et al. 1982	Post-cardiac surgery	83	41	10	NO	42	0	NO	No differences in the amount of chest-tube drainage and blood administered, and the level of hematocrit
Marvel et al. 1986	Post-cardiac surgery	44[a]	12	10	NO	15	5	NO	No differences in alveolar-arterial oxygen ratio, atelectasis and the duration of ICU stay
Michalopoulos et al.1998	Post-cardiac surgery	67[b]	21	10	NO	24	5	NO	No differences in in-hospital mortality, pneumothorax, atelectasis, the duration of ventilation, the amount of transfusion requirements (RBC, crystalloid and albumin), PaO2/FIO2, and SvO2
Carroll et al. 1988	Post-cardiac surgery (PaO2/FIO2 < 200)	50	22	15	NO	28	4	NO	High PEEP increased hypotension, pulmonary complications, the duration of ventilation and in-hospital mortality

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Collier et al. 2002	Post-cardiac surgery	84	40	10	NO	44	5	NO	No differences in in-hospital mortality, the duration of ventilation and hospital stay, and the amount of chest-tube drainage and transfusion requirements (RBC, crystalloid and albumin)
Dyhr et al. 2002	Post-cardiac surgery	15	7	15	YES	8	0	YES	High PEEP increased PaO2 and EELV while decreased atelectasis. No differences in hemodynamics
Celebi et al. 2007	Post-cardiac surgery	60	20	10	YES	20	5	YES	High PEEP increased PaO2 while decreased atelectasis. No differences in the duration of ventilation, ICU stay and hospital stay
Holland et al. 2007	Post-cardiac surgery	28	14	10	NO	14	5	NO	No differences in liver function, gastric mucosal perfusion, and hemodynamics
Borges et al. 2013	Post-cardiac surgery	136[d]	45	10	NO	44	5	NO	High PEEP increased PaO2/FIO2 resulting in decreased hypoxaemia. No differences in hemodynamics

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Lima et al. 2015	Post-cardiac surgery	78[e]	20	10	NO	32	5	NO	No differences in PaO2/FIO2 and SaO2 in the first 6 h after extubation
Cordeiro et al. 2017	Post-cardiac surgery	30[f]	10	15	NO	10	10	NO	No differences in PaO2/FIO2, SaO2 and hemodynamics during the NIV in the first day after surgery
Setak-Berenjestan-aki et al. 2017	Post-cardiac surgery	180[g]	60	10	NO	60	5	NO	High PEEP decreased atelectasis, the duration of ventilation, ICU stay, and hospital stay
Cordeiro et al. 2019	Post-cardiac surgery	60[h]	18	15	NO	19	10	NO	High PEEP increased PaO2/FIO2. No differences in hemodynamics and SaO2
Mixed ICU patients									
Manzano et at. 2008	Not hypoxaemia (PaO2/FIO2 > 200)	127	64	5/8[C]	NO	63	0	NO	High PEEP decreased hypoxaemia and VAP. No differences in PaO2/FIO2, in-hospital mortality, pulmonary barotrauma, ARDS atelectasis and the duration of ventilation, ICU stay and hospital stay

Studies	Patient type	Total Number	High PEEP			Low PEEP			Main conclusions
			N	PEEP	RM	N	PEEP	RM	
Algera et al. 2020	Mixed	969	493	8	39/ 493	476	5	62/ 476	No differences in in-hospital, ICU and 28-day mortality, ARDS, atelectasis, hypoxaemia, pneumothorax, VAP and the duration of ventilation, ICU stay, and hospital stay

Definition of abbreviations: V_T: tidal volume; CV: controlled ventilation; IPPV: intermittent positive-pressure ventilation; Qsp/Qt: physiologic shunt; SIMV: synchronous intermittent mandatory ventilation; $Q\bar{V}_A/Q_T$: calculated venoarterial admixture. A/C: assist-control(A/C) ventilation; PSV: pressure support ventilation; VCV: volume-control ventilation; PSV: pressure support ventilation; CMV: controlled mechanical ventilation; PCV: pressure controlled ventilation; NIV: noninvasive ventilation; PSM: pressure support mode; V_D/V_T: represents ventilatory dead space; EELV: end-expiratory lung volume; MAP: mean arterial pressure; VAP: ventilator associated pneumonia.

a. minus 17 patients using 0 cmH2O PEEP, the calculated number is 27

b. minus 22 patients using 0 cmH2O PEEP, the calculated number is 45

c. 5 cm H2O PEEP was applied when abdomen pressure below chest pressure, otherwise 8 cm H2O applied

d. minus 47 patients using intermediate 8 cm H2O PEEP, the calculated number is 89

e. minus 26 patients using intermediate 8 cm H2O PEEP, the calculated number is 52

f. minus 10 patients using intermediate 12 cm H2O PEEP, the calculated number is 20

g. minus 60 patients using intermediate 8 cm H2O PEEP, the calculated number is 120

h. minus 23 patients using intermediate 12 cm H2O PEEP, the calculated number is 37

The quality and publication bias of selected studies were shown in Additional file 4. For the majority of RCTs, the risk of bias was unclear or high due to the incompleteness of information, especially those published before 2000. The high risk of bias was mainly the blinding of participants and personnel as well as outcome evaluation.

3.2 Primary outcomes

Nine studies reported in-hospital mortality. Two hundred and eight of patients (36.1%) received high PEEP (n = 775) and 260 of patients (34.0%) received low PEEP (n = 764) died during hospitalization. The pooled RR was 0.98 (95% CI 0.81–1.19; P = 0.87; Fig. 2) and the heterogeneity was minimal (I^2 = 14%). The TSA analysis found

each the required information size (RIS, n = 3026), the cumulative Z-curve indeed crossed the futility boundary, which means that the cumulative evidence of in-hospital mortality was conclusive and sufficient.

Three studies reported 28-day mortality and the pooled RR was 0.68 (95% CI 0.33–1.40, P = 0.30, Fig. 2). The heterogeneity may be considerable (I^2 = 89%). However, TSA results suggested further evidence was needed to get firm conclusions (Fig. 3A,B).

In terms of the duration of ventilation, ICU stay and hospital stay, there are seven, six and six studies reported respectively (Fig. 2) and their heterogeneity seemed quite high (81%, 76% and 70%, respectively). None of these outcomes acquired statistically significant differences (P = 0.09, 0.25 and 0.22, respectively). In addition, the publication bias evaluated by funnel plots indicated the risk may exist (Additional file 7).

Subgroup analysis regarding the level of low PEEP (ZEEP or not), publication year (before or after 2000) and patient type (medical or postoperative ones) were presented in Additional file 2. Subgroup results did not affect the pooled RR or MD of in-hospital mortality, the duration of ventilation, ICU stay, and hospital stay.

3.3 Secondary outcomes

Only four articles reported the incidence of ARDS within non-ARDS patients received PEEP treatment and found the potential preventive effects of high PEEP application (Additional file 5). Similarly, the incidence of hypoxaemia was also decreased in high PEEP group (RR 0.60, 95% CI 0.41–0.88, Additional file 5). TSA analysis regarding hypoxaemia confirmed benefits of high PEEP application while the evidence of ARDS was still insufficient (Fig. 3C,D). Moreover, the usage of high PEEP did not obtained benefits regarding the incidences of other pulmonary complications such as atelectasis, barotrauma and VAP (P = 0.28, 0.76 and 0.17, respectively, Additional file 5).

The level of PaO_2/FIO_2 was higher in high PEEP group (MD = 32.39; 95% CI 13.1–51.7; Additional file 6), while the level of SaO2 and lactate did not show the difference (Additional file 6). In terms of hemodynamics index, neither of the incidence of hypotension and MAP exhibited statistically significant differences between high and low PEEP arms (Additional file 6). For patients underwent cardiac surgery, the pooled MD of postoperative chest-tube drainage and RBC usage were 32.1 (95% CI -97.8-162.1) and 0.02 (95% CI -0.48-0.53), respectively (Additional file 6). The application of high PEEP did not affect the postoperative fluid balance of patients. Moreover, funnel plots indicated that the bias of publication may exist (Additional file 7).

Subgroup analysis concerning the incidence of ARDS, atelectasis and hypoxaemia confirmed the benefits of high PEEP application in studies published after 2000 (Additional file 3). In addition, subtype analysis regarding the level of low PEEP (ZEEP or not) also obtained different results from the overall analysis, including PaO_2/FIO_2, the incidence of atelectasis, hypotension and VAP (Additional file 3). Similarly, PaO_2/FIO_2 and the incidence of hypoxaemia and hypotension seemed to be different between medical and postoperative patients (Additional file 3). However, some subgroups only contained one trial, indicating the insufficiency of studies.

4 Discussion

In this systemic review and meta-analysis, twenty-four RCTs were selected and different level of PEEP were compared in total 2307 ICU patients without ARDS. We indeed found the advantages of high PEEP usage in respect to the improvement of pulmonary oxygenation (PaO_2/FIO_2) and the prevention of ARDS and hypoxaemia. Nonetheless, in terms of primary outcomes, including in-hospital and 28-day mortality and the duration of ventilation, ICU stay and hospital stay, and secondary outcomes such as 1) atelectasis, barotrauma and VAP; 2) hypotension and MAP; 3) SaO_2 and lactate; 4) chest-tube drainage and RBC usage in post-operative patients, no significant differences were detected between two arms of PEEP.

Heterogeneity may exist because of the differences in publication year (before or after 2000), level of low PEEP (ZEEP or not) and patients type (medical or postoperative ones). We conducted subgroup analysis but did not identify differences from overall analysis, except for several secondary outcomes including PaO_2/FIO_2 and the incidence of atelectasis, hypotension, hypoxaemia and VAP. Unfortunately, some discrepancies between subgroup and total derived from only one single study, indicating that more evidence are needed in the future.

Although there was one meta-analysis published in 2016 investigating the possible effect of high PEEP, the quality of evidence was low and insufficient[15]. In our present meta-analysis, we added four recent RCTs[33–35] including one largest RCT concerning high PEEP usage in non-ARDS patients[14]. Moreover, given that most of the selected patients underwent operations, especially cardiac ones, we also assessed the impact of high PEEP on postoperative chest-tube drainage and RBC usage, with no significant difference found.

The application of high PEEP in ICU patients has long been controversial. According to one meta-analysis, ARDS patients received high PEEP therapy acquired more benefits with respect to hospital survival compared with low PEEP group[36]. A study investigated both ARDS patients and animal models depicted that high PEEP may remit lung injuries via lowering the level of spontaneous efforts as well as uniformly distributing negative pleural pressure (Ppl)[37]. In our meta-analysis, high PEEP did not affect the mortality of patients without ARDS but reduced the incidence of hypoxaemia resulting in the prevention of ARDS. Another meta-analysis in animals without injured lung found that the advantages of high PEEP were uncertain and may even cause adverse impacts on hemodynamics[38].

Increased inspiratory efforts among postoperative patients and medical ones, especially patients with ARF, may impair the oxygenation and hemodynamics, resulting in hypoxaemia, atelectasis and pneumonia. As depicted by recent studies, high PEEP was thought to increase end-expiratory lung volume, as well as the diaphragm radius of curvature, and therefore lower the efforts of inspiration. Besides, high PEEP resulted in decreased tidal recruitment and pulmonary barotrauma compared with low PEEP[39, 40]. On the contrary, animal studies also showed that ventilation with high PEEP may even adversely cause lung injuries among healthy animals [41, 42]. These findings indicated that high PEEP may result in different clinical outcomes based on the state of lung function.

The advantage of high PEEP in the improvement of oxygenation did not mean that we could set PEEP in a higher level without concerning the state of patients. The undue level of high PEEP may also be harmful to patients in ICU. However, the best level of PEEP is quite difficult to determine[43]. Four RCTs in our present meta-analysis titrated PEEP according to the level of $PaCO_2$, PaO_2 or pulse oximetry-measure oxygen saturation (SpO_2) to prevent from hypocapnia and hypoxaemia[10, 13, 14, 28], while PEEP level in the rest of studies were set arbitrarily. Usually, PEEP was set 2 cm H_2O above the lower inflection point of the volume-pressure curve (PV)[7],

 uced including the recruitment : inflation (R:I) ratio[44], electrical impedance tomography (EIT)[45], PEEP/FIO_2 table[46] and so forth. However, more RCTs still needed to further demonstrate the advantage of these methods.

The strength of our meta-analysis lies in following aspects. Firstly, we added four recent RCTs including a largest trial compared with the former meta-analysis. Secondly, we divided patients of selected studies into three parts: postoperative, medical, and mixed ones (including postoperative and medical), and therefore performed subgroup analysis. Thirdly, TSA was conducted to further evaluate the quality and reliability of evidence. Finally, we applied a rigorous BoxCox method to estimate mean and SD of studies that only reported median and interquartile range. Nonetheless, these also exist several limitations. Firstly, ten RCTs of selected studies were published before 2000, resulting in the bias of study design and incompleteness of information. Secondly, the level of high and low PEEP varied among selected studies. Although most of studies defined PEEP under 5 cm H_2O as lower ones, some of them used a higher level of PEEP as comparison group. Thirdly, the baseline of ventilation strategies of including studies were quite different. Moreover, TSA results suggested that the power of several evidence was limited.

5 Conclusions

The present meta-analysis revealed that high PEEP improved lung oxygenation and therefore reduced the incidence of ARDS and hypoxaemia among non-ARDS patients received ventilation. However, there was no difference in mortality, duration of ventilation, ICU stay and hospital stay, pulmonary complications, hemodynamics, and postoperative fluid equilibrium. The quality of most selected RCTs was low. TSA results showed that more RCTs of high quality were needed to confirm these conclusions.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article [and its supplementary information files].

Competing interests

The authors declare no conflict of interests in this article.

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Author's contributions

HYY and XML contributed equally to this work. HYY and XML conceived the idea, conducted the collection of date and study design, performed statistical analyses, and wrote the manuscript. ZM and CL examined the data collection and offered advice of statistics. XH, RJS and SQ revised the manuscript. FHZ revised the whole manuscript and offered clinical recommendations. All authors approved the final manuscript.

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Figures

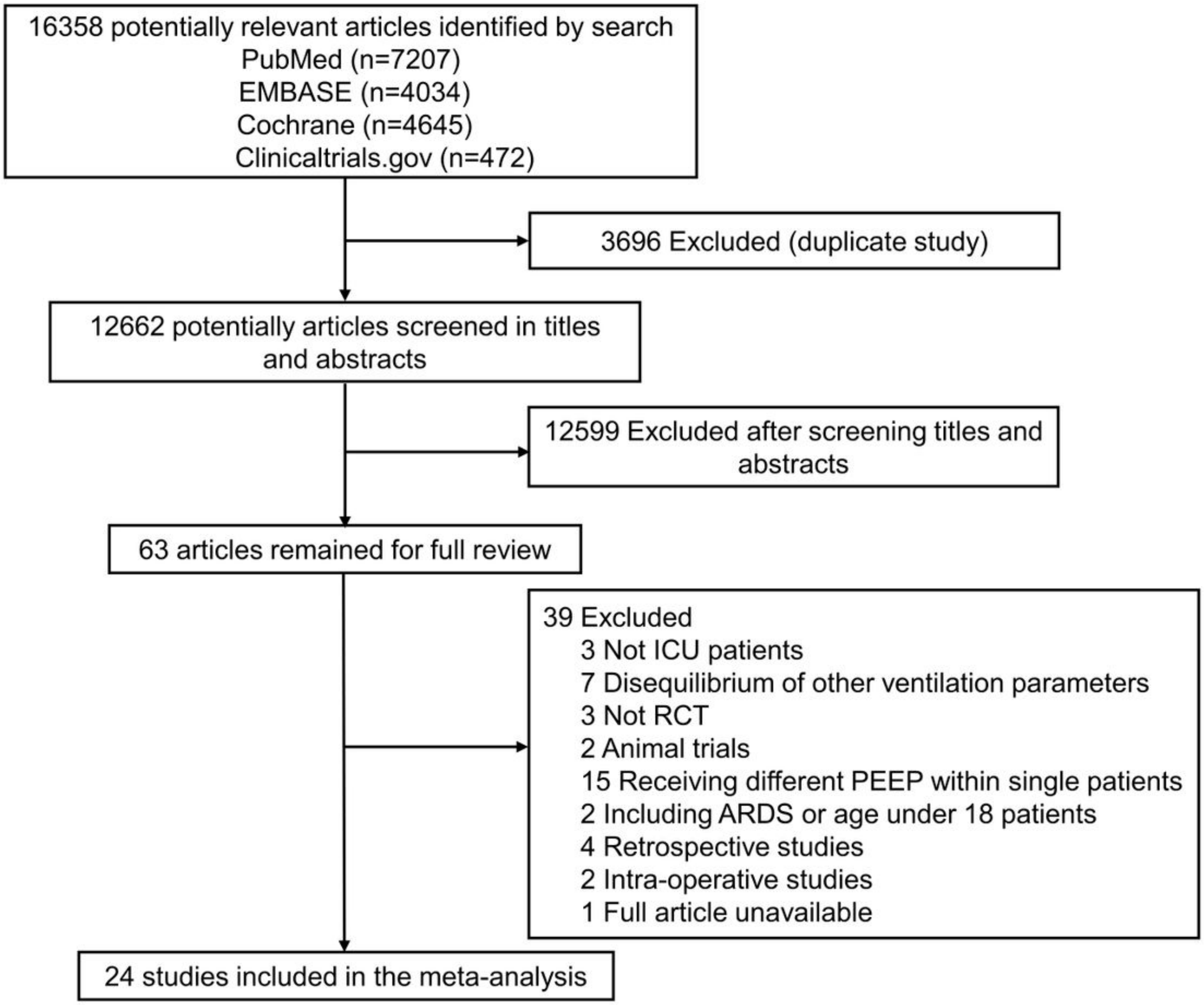

Figure 1

Flow diagram for the identification of selected studies

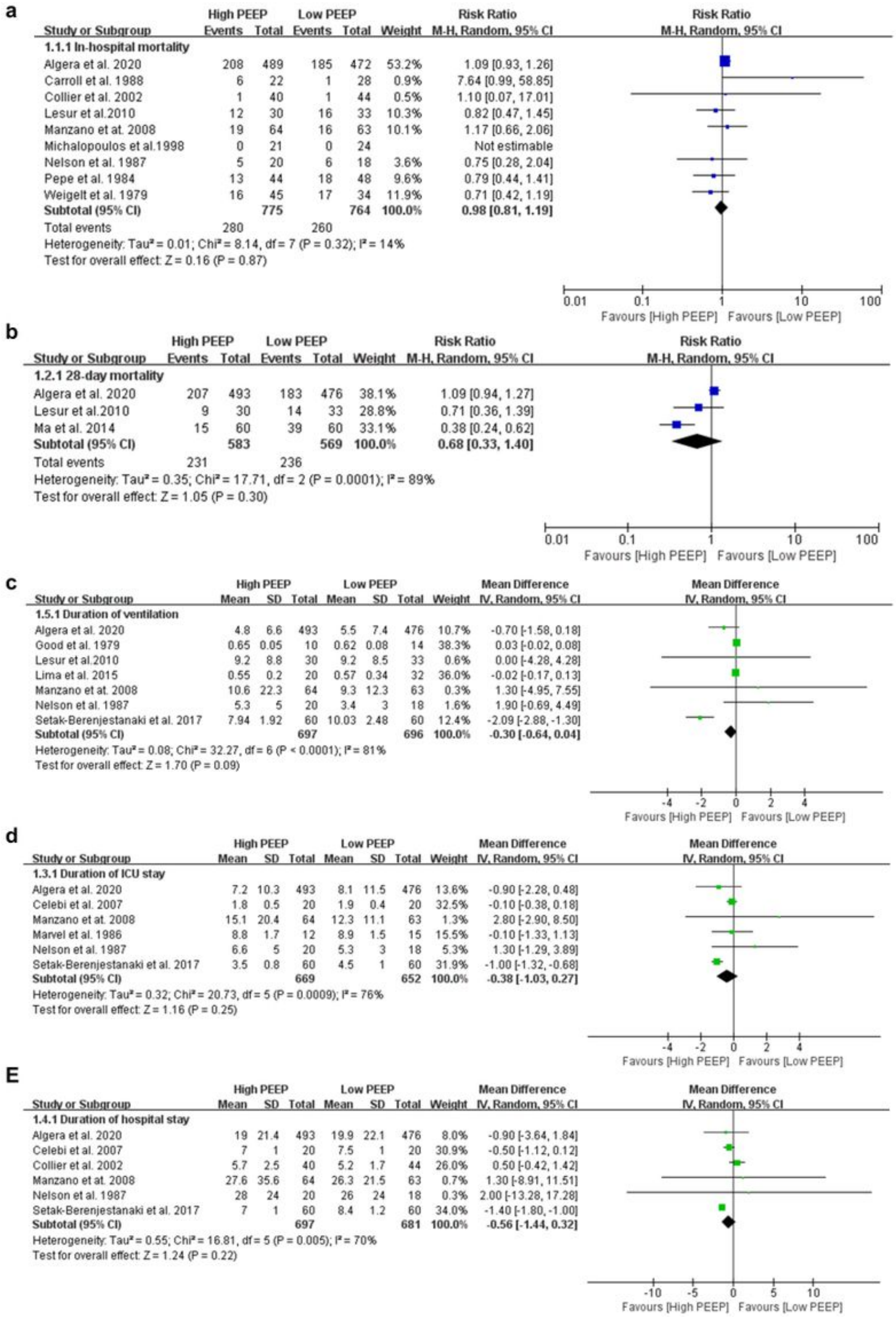

Figure 2

Forest plot of secondary outcomes: In-hospital mortality(a), 28-day mortality(b), Duration of ventilation(c), Duration of ICU stay(d) and Duration of hospital stay(e).

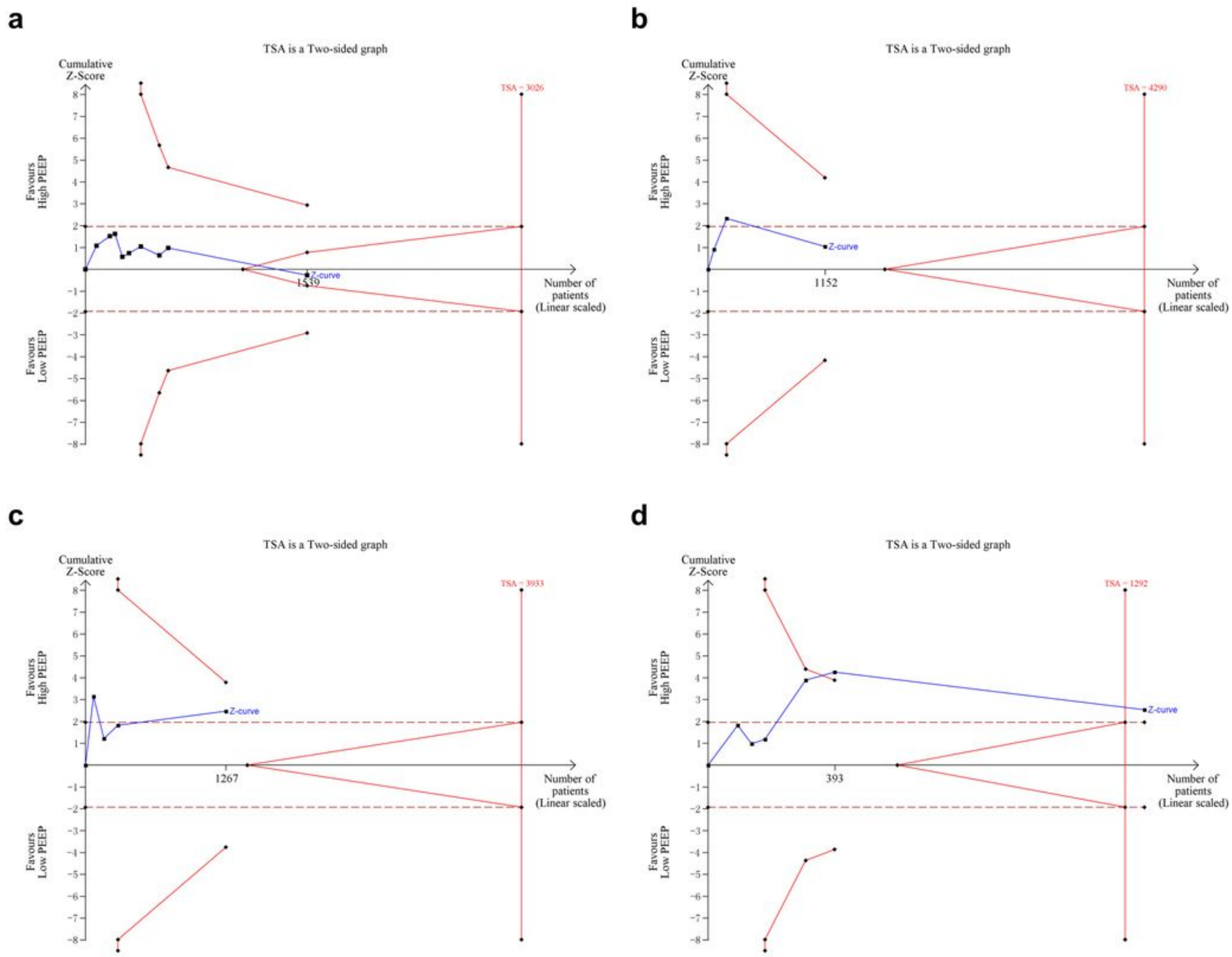

Figure 3

Trial sequential analysis. The cumulative Z curve (blue line) was conducted using a random effect model. Etched red line shows conventional test boundary. Complete red line represents the trial sequential monitoring boundary. a. TSA for in-hospital mortality. A diversity-adjusted information size of 3026 patients was calculated on the basis of using α =0.05 (two sided), β = 0.20 (power 80%), an anticipated relative risk reduction (RRR) of 15.0%, and a control event rate of 34.0%. The cumulative Z curve does not cross the conventional boundary as well as the trial sequential monitoring boundary, but reaches the futility boundary. b. TSA for 28-day mortality. A diversity-adjusted information size of 4290 patients was calculated on the basis of using α =0.05 (two sided), β = 0.20 (power 80%), an anticipated relative risk reduction (RRR) of 30.0%, and a control event rate of 41.0%. The cumulative Z curve does not cross the conventional boundary, the trial sequential monitoring boundary, and the futility boundary. c. TSA for ARDS. A diversity-adjusted information size of 3933 patients was calculated on the basis of using α =0.05 (two sided), β = 0.20 (power 80%), an anticipated relative risk reduction (RRR) of 30.0%, and a control event rate of 10.0%. The cumulative Z curve crosses the conventional bundary but not the trial sequential monitoring bonudary. d. TSA for hypoxaemia. A diversity-adjusted information size of 1292 patients was calculated on the basis of using α =0.05 (two sided), β = 0.20 (power 80%), an anticipated relative risk reduction (RRR) of 35.0%, and a control event rate of 25.0%. The cumulative Z curve crosses the convrntional boundary and the trial sequential monitoring boundary.

Supplementary Files

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