Higher versus lower positive end-expiratory pressure in patients without acute respiratory distress syndrome: a meta-analysis of randomized controlled trials

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Online Resource 1. Methods

Participants, Interventions, Comparisons, Outcomes, and Study design question

- Participants: adult patients in the intensive care unit (ICU) undergoing invasive mechanical ventilation
- Interventions: higher positive end-expiratory pressure (PEEP)
- Comparisons: lower PEEP
- Outcomes:
 - Primary outcome: hospital mortality
 - Secondary outcomes:
 - Arterial partial pressure of oxygen to fraction of inspired oxygen ratio
 - Alveolar-arterial oxygen pressure difference
 - Hypoxemia
 - Respiratory system compliance
 - Atelectasis
 - Barotrauma
 - Development of acute respiratory distress syndrome (ARDS)
 - Ventilator-associated pneumonia
 - Cardiac index
 - Central venous pressure
 - Hypotension
 - Postoperative bleeding and transfusion
 - Duration of ventilation
 - ICU length of stay
 - Hospital length of stay
 - ICU mortality
 - 28-day mortality
- Study design: randomized controlled trials.

Database Search Strategies

MEDLINE search strategy (744 citations):

Ovid MEDLINE(R) 1946 to June Week 3 2021

Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations June 16, 2021

- 1. positive end expiratory pressure.mp,kw.
- 2. positive end-expiratory pressure.mp,kw.
- 3. PEEP.mp,kw.
- 4. or/1-3 [PEEP]
- 5. randomized controlled trial.pt.
- 6. RCT.mp,kw.
- 7. random*.mp,kw.
- 8. or/5-7 [RCT]
- 9. 4 and 8 [PEEP + RCT]

EMBASE search strategy (3635 citations): see MEDLINE search strategy

Scopus search strategy (5511 citations):

((POSITIVE END-EXPIRATORY PRESSURE) OR PEEP) AND ((RANDOMIZED CONTROLLED TRIAL*) OR RCT)

Cochrane Central Register of Controlled Trials search strategy (2942 citations): see Scopus search strategy

CINAHL search strategy (404 citations): see Scopus search strategy

Web of Science search strategy (672 citations): see Scopus search strategy

OpenGrey search strategy (22 citations): (POSITIVE END-EXPIRATORY PRESSURE) OR PEEP

Risk of Bias Assessment

The risk of bias (ROB) of the included studies was independently assessed by three authors (TP, PP, FZ) according to the revised Cochrane ROB tool for randomized trials (RoB 2) [S1]. RoB2 examines 5 domains of bias: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported results. The overall RoB judgment for each domain was attributed according to the criteria specified in the RoB 2 tool. The study was considered at low risk of bias when it was judged to be at low risk of bias for all domains; the study was considered to raise some concern when it was judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain; the study was considered at high risk of bias when it was judged to be at high risk of bias in at least one domain or it was judged to have some concerns for multiple domains in a way that substantially lowered confidence in the result. The risk of bias of individual studies was examined at the study level. All disagreements were resolved by discussion or referral to a third author (LP) if necessary.

Online Resource 2. Included Studies and Major Exclusions

Studies included in both the qualitative and quantitative review

- Good JT Jr, Wolz JF, Anderson JT, Dreisin RB, Petty TL. The routine use of positive end-expiratory pressure after open heart surgery. Chest. 1979;76:397–400.
- Zurick AM, Urzua J, Ghattas M, Cosgrove DM, Estafanous FG, Greenstreet R. Failure of positive endexpiratory pressure to decrease postoperative bleeding after cardiac surgery. Ann Thorac Surg. 1982;34:608– 11.
- Marvel SL, Elliott CG, Tocino I, Greenway LW, Metcalf SM, Chapman RH. Positive end-expiratory pressure following coronary artery bypass graft- ing. Chest. 1986;90:537–41.
- Michalopoulos A, Anthi A, Rellos K, Geroulanos S. Effects of positive end-expiratory pressure (PEEP) in cardiac surgery patients. Respir Med. 1998;92:858–62.
- Collier B, Kolff J, Devineni R, Gonzalez LS. Prophylactic positive end-expiratory pressure and reduction of postoperative blood loss in open-heart surgery. Ann Thorac Surg. 2002;74(4):1191-1194.
- Dyhr T, Laursen N, Larsson A. Effects of lung recruitment maneuver and positive end-expiratory pressure on lung volume, respiratory mechanics and alveolar gas mixing in patients ventilated after cardiac surgery. Acta Anaesthesiol Scand. 2002;46:717–25.
- Koutsoukou A, Perraki H, Raftopoulou A, et al. Respiratory mechanics in brain-damaged patients. Intensive Care Med. 2006;32(12):1947-1954.
- Holland A, Thuemer O, Schelenz C, van Hout N, Sakka SG. Positive end-expiratory pressure does not affect indocyanine green plasma disap- pearance rate or gastric mucosal perfusion after cardiac surgery. Eur J Anaesthesiol. 2007;24:141–7.
- Korovesi I, Papadomichelakis E, Orfanos SE, et al. Exhaled breath condensate in mechanically ventilated brain-injured patients with no lung injury or sepsis. Anesthesiology. 2011;114(5):1118-1129.
- Korovesi I, Kotanidou A, Papadomichelakis E, et al. Exhaled nitric oxide and carbon monoxide in mechanically ventilated brain-injured patients. J Breath Res. 2016;10(1):017107.
- Lago Borges D, Nina VJ, Costa Mde A, Baldez TE, Santos NP, Lima IM, et al. Effects of different PEEP levels on respiratory mechanics and oxygena- tion after coronary artery bypass grafting. Rev Bras Cir Cardiovasc. 2013;28:380–5.

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- Feeley TW, Saumarez R, Klick JM, McNabb TG, Skillman JJ. Positive end- expiratory pressure in weaning patients from controlled ventilation. A prospective randomised trial. Lancet. 1975;2:725–9.
- Weigelt JA, Mitchell RA, Snyder WH 3rd. Early positive end-expiratory pressure in the adult respiratory distress syndrome. Arch Surg. 1979;114:497–501.
- Pepe PE, Hudson LD, Carrico CJ. Early application of positive end- expiratory pressure in patients at risk for the adult respiratory-distress syndrome. N Engl J Med. 1984;311:281–6.
- 16. Nelson LD, Civetta JM, Hudson-Civetta J. Titrating positive end-expiratory pressure therapy in patients with early, moderate arterial hypoxemia. Crit Care Med. 1987;15:14–9.
- Manzano F, Fernández-Mondéjar E, Colmenero M, Poyatos ME, Rivera R, Machado J, et al. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med. 2008;36:2225–31.
- Lesur O, Remillard MA, St-Pierre C, Falardeau S. Prophylactic positive end- expiratory pressure and postintubation hemodynamics: an interven- tional, randomized study. Can Respir J. 2010;17:e45–50.
- 19. Ma C, Liang D, Zheng F. Effect of high positive end-expiratory pressure for mechanical ventilation in the treatment of neurological pulmonary edema. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014;26:339–42.
- 20. Algera AG, Pisani L, Serpa Neto A, et al; Writing Committee and Steering Committee for the RELAx Collaborative Group. Effect of a lower vs. higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: a randomized clinical trial. JAMA. 2020;324(24):2509.

Studies included in the qualitative review only

- Murphy DA, Finlayson DC, Craver JM, Jones EL, Kopel M, Tobia V, et al. Effect of positive end-expiratory pressure on excessive mediastinal bleed- ing after cardiac operations. A controlled study. J Thorac Cardiovasc Surg. 1983;85:864–9.
- Vigil AR, Clevenger FW. The effects of positive end-expiratory pressure of intrapulmonary shunt and ventilatory deadspace in nonhypoxic trauma patients. J Trauma. 1996;40:618–22.

Studies on non-invasive mechanical ventilation

- Carroll GC, Tuman KJ, Braverman B, et al. Minimal positive end-expiratory pressure (PEEP) may be "best PEEP". Chest. 1988;93:1020–1025.
- Choo-Kang YFJ, Parker SS, Grant IWB. Response of asthmatics to isoprenaline and salbutamol aerosols administered by intermittent positive-pressure ventilation. BMJ. 1970;4(5733):465-468.

Studies with less than 2 levels of peep and/or change in other ventilatory settings and/or crossover studies

- Auler Jr. JOC, Carmona MJC, Barbas CV, Saldiva PHN, Malbouisson LMS. The effects of positive endexpiratory pressure on respiratory system mechanics and hemodynamics in postoperative cardiac surgery patients. Braz J Med Biol Res. 2000;33(1):31-42.
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- Saner FH, Pavlakovic G, Gu Y, et al. Effects of positive end-expiratory pressure on systemic haemodynamics, with special interest to central venous and common iliac venous pressure in liver transplanted patients. Eur J Anaesthesiol. 2006;23(9):766-771.
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- Celebi S, Köner O, Menda F, Korkut K, Suzer K, Cakar N. The pulmonary and hemodynamic effects of two different recruitment maneuvers after cardiac surgery. Anesth Analg. 2007;104:384–90.
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- Kong W, Wang C, Yang Y, Huang K, Jiang C. Effects of extrinsic positive end-expiratory pressure on work of breathing in patients with chronic obstructive pulmonary disease. Chin Med J (Engl). 2001;114(8):791-794.
- Kumar A, Pontoppidan H, Baratz RA, Laver MB. Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. Anesthesiology. 1974;40(3):215-221.
- 12. Mascia L, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med. 2005;31(3):373-379.
- Mauri T, Eronia N, Turrini C, et al. Bedside assessment of the effects of positive end-expiratory pressure on lung inflation and recruitment by the helium dilution technique and electrical impedance tomography. Intensive Care Med. 2016;42(10):1576-1587.
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- Reissmann HK, Ranieri VM, Goldberg P, Gottfried SB. Continuous positive airway pressure facilitates spontaneous breathing in weaning chronic obstructive pulmonary disease patients by improving breathing pattern and gas exchange. Intensive Care Med. 2000;26(12):1764-1772.
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- Tsai Y-H, Lin M-C, Hsieh M-J, et al. Spontaneous variability of arterial oxygenation in critically ill mechanically ventilated patients. Intensive Care Med. 1999;25(1):37-43.
- Vitacca M, Bianchi L, Zanotti E, et al. Assessment of physiologic variables and subjective comfort under different levels of pressure support ventilation. Chest. 2004;126(3):851-859.

Non-RCT study

 Dongelmans DA, Hemmes SN, Kudoga AC, Veelo DP, Binnekade JM, Schultz MJ. Positive end-expiratory pressure following coronary artery bypass grafting. Minerva Anestesiol. 2012;78:790–800.

Studies not on ICU patients

- Calzia E, Lindner KH, Stahl W, Martin A, Radermacher P, Georgieff M. Work of breathing, inspiratory flow response, and expiratory resistance during continuous positive airway pressure with the ventilators EVITA-2, EVITA-4 and SV 300. Intensive Care Med. 1998;24(9):931-938.
- Claxton BA, Morgan P, Mckeague H, Mulpur A, Berridge J. Alveolar recruitment strategy improves arterial oxygenation after cardiopulmonary bypass: Arterial oxygenation after cardiopulmonary bypass. Anaesthesia. 2003;58(2):111-116.
- 3. Oliveira CC, Carrascosa CR, Borghi-Silva A, et al. Influence of respiratory pressure support on hemodynamics and exercise tolerance in patients with COPD. Eur J Appl Physiol. 2010;109(4):681-689.

Study on ARDS patients

 Borelli M, Fumagalli R, Bernasconi F, Cereda M, Gattinoni L, Pesenti A. Relief of hypoxemia contributes to a reduction in cardiac index related to the use of positive end-expiratory pressure. Intensive Care Med. 1996;22(5):382-386.

Conference proceeding

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Online Resource 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Table S1. PRISMA check	list		
Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1, 2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2, 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3, Online Resource 1
Methods	•		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3, Online Resource 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3, Online Resource 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online Resource 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4

Table S1 (continued)			
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3, Online Resource 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4, Online Resource 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	4, 5

Table S2. Genera	al study o	characteristics		
First author	Year	Type of patients	Ν	Main findings
Collier	2002	Post-cardiac surgery	84	Increased postoperative bleeding with higher PEEP
Dyhr	2002	Post-cardiac surgery	15	Increased oxygenation and end-expiratory lung volume and decreased atelectasis with higher PEEP
Feeley	1975	ARF during weaning from MV	25	Improvement in vital capacity and maximum inspiratory force and less increase in intra-pulmonary shunt with higher PEEP
Good	1979	Post-cardiac surgery	24	No differences regarding atelectasis and oxygenation
Holland	2007	Post-cardiac surgery	28	No differences regarding cardiac function, liver function, and gastric mucosal perfusion.
Korovesi	2011- 2016 ^a	Brain injury with MV < 24 hours	27ª	Korovesi 2011: no differences regarding exhaled breath condensate markers, with the exception of interleukin- 10, and lower systemic inflammatory indices with higher PEEP. Korovesi 2016: no differences regarding exhaled nitric oxide trend with significant decrease in exhaled carbon monoxide in the ZEEP group.
Koutsoukou	2006	Severe brain damage	21	No differences regarding exhaled NO trend and significant decrease in exhaled CO in the ZEEP group.
Lago Borges	2013- 2014 ^b	Post-cardiac surgery	136 ^b	Lago Borges 2013: higher compliance and oxygenation with higher PEEP. Lago Borges 2014: shorter duration of ventilation with higher PEEP ^c .
Lesur	2010	ARF	63	No differences regarding incidence of hypotension, duration of ventilation and mortality ^d .
Ма	2014	Brain injury with neurological pulmonary edema	120	Lower blood pressure, higher oxygenation and lower 28-day mortality with higher PEEP
Manzano	2008	Nonhypoxemic patients $(PaO_2/FiO_2 > 250)$	127	Lower incidence of VAP and hypoxemia with higher PEEP; no differences regarding development of ARDS, barotrauma, or atelectasis, and hospital mortality.
Marvel	1986	Post-cardiac surgery	44 ^e	Better oxygenation with higher PEEP; no differences regarding atelectasis and hospital length of stay.
Michalopoulos	1998	Post-cardiac surgery	67 ^f	No differences regarding oxygenation, cardiac index, incidence of pneumothorax and atelectasis, duration of ventilation, and mortality
Murphy	1983	Post-cardiac surgery	139	No differences regarding blood loss and blood products or fluids administration
Nelson	1987	Hypoxemic patients (PaO ₂ /FiO ₂ 144-244)	38	No differences regarding barotrauma, duration of ventilation, length of stay, and mortality
Рере	1984	ARF patients at risk of ARDS	92	No differences regarding incidence of ARDS, barotrauma, atelectasis, hypotension, duration of ventilation, length of stay, and mortality
Relax	2020	ARF patients expected not to be extubated within 24 hours	969	No differences regarding 28-day ventilator free days, duration of ventilation, incidence of ARDS, VAP, pneumothorax, atelectasis, length of stay, and mortality.
Vigil	1996	Nonhypoxic patients after trauma	44	No differences regarding shunt, dead space volume, and oxygenation after correction for baseline values
Weigelt	1979	ARF patients at risk of ARDS	79	Lower incidence of ARDS and pulmonary mortality and higher incidence of pulmonary dysfunction with higher PEEP

Table S2 (continu	able S2 (continued)												
First author	Year	Type of patients	Ν	Main findings									
Zurick	1982	Post-cardiac surgery	83	No differences regarding postoperative blood loss, need for reexploration for bleeding, and blood requirement									
Abbreviations: N, total number of patients; PEEP, positive end-expiratory pressure; ARF, acute respiratory failure; MV, mechanical ventilation; ZEEP, zero end-expiratory pressure; ICU, intensive care unit; PaO ₂ /FiO ₂ , arterial partial pressure of oxygen to fraction of inspired oxygen ratio; VAP, ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome.													
Twenty-two rando	mized co	ntrolled trials (2225 patients), w	hich co	ompared higher PEEP (1007 patients) to lower PEEP (991 patients), were included. The Murphy study did not									
report the number	of patien	ts that were randomized to the two number of patients overall include	vo grou led in t	ups and some study groups of the Lago Borges, Marvel, and Michalopoulos studies were excluded (see below); he studies does not match the sum of the patients in the two groups									
^a The same patient	populatic	on was included in Korovesi 201	1 and 1	Korovesi 2016.									
^b The same patient	populatio	on was included in Lago Borges	2013 a	nd Lago Borges 2014. One group of 47 patients with intermediate level of PEEP (8 cmH2O) was not included in									
this systematic rev	iew and 1	meta-analysis.											
°Only patients extu	bated wi	thin 12 h after ICU admission w	vere con	nsidered by the authors of the original article.									
^d PEEP was mainta	ined for t	he first 90 minutes after intubat	ion onl	у.									
^e One group of 17 p	oatients, v	who exhaled to ambient pressure	e, was r	not included in this systematic review and meta-analysis.									

^fOne group of 24 patients with intermediate level of PEEP (5 cmH2O) was not included in this systematic review and meta-analysis.

Table S3. Patier	nts ar	nd ventilat	ion settings											
				Higher PEE	P						Lower P	EEP		
First author	N	Age (years)	Female gender (N [%])	PEEP titration	PEEP level (cmH ₂ O)	Tidal volume (mL/kg) a	Ventilatory mode	Ν	Age (years)	Female gender (N [%])	PEEP titration	PEEP level (cmH ₂ O)	Tidal volume (mL/kg) ^a	Ventilatory mode
Collier	40	67 ± 11	9 (22)	Arbitrarily	10	10	SIMV	44	65 ± 8	16 (36)	Arbitrarily	5	10	SIMV
Dyhr	7	61 ± 24	0	1 cmH2O above lower inflection point	15	6	VCV ^b	8	63 ± 22	3 (37)	Arbitrarily	0	6	VCV ^b
Feeley	12	59 ± 22	7 (58)	Arbitrarily	5	10	VCV	13	$\begin{array}{c} 64 \pm \\ 10 \end{array}$	7 (54)	Arbitrarily	0	10	VCV
Good	10	51 ± 2	n.a.	Maximum respiratory system compliance	6.3	10-12	VCV	14	57 ± 2	n.a.	Arbitrarily	0	10-12	VCV
Holland	14	63 ± 7	1 (7)	Arbitrarily	10	6-8	PCV	14	68 ± 11	6 (43)	Arbitrarily	5	6-8	PCV
Korovesi ^c	15	33 ± 29	3 (20)	Arbitrarily	8	8	VCV	12	23 ± 5	2 (17)	Arbitrarily	0	8	VCV
Koutsoukou	11	42 ± 19	2 (18)	Arbitrarily	8	8	VCV	10	40 ± 12	3 (30)	Arbitrarily	0	8	VCV
Lago Borges ^d	45	n.a.	10 (22)	Arbitrarily	10	6-8	VCV	44	n.a.	15 (34)	Arbitrarily	5	6-8	VCV
Lesur	30	65 ± 14	13 (43)	Arbitrarily	5	8	VCV/PCV	33	64 ± 18	12 (36)	Arbitrarily	0	7	VCV/PCV
Ма	60	n.a.	n.a.	Arbitrarily	11-30	6-8	n.a.	60	n.a.	n.a.	Arbitrarily	3-10	6-8	n.a.
Manzano	64	44 ± 18	17 (26)	Level of abdomen relative to level of chest	5-8	8	n.a.	63	47 ± 19	20 (32)	Arbitrarily	0	8	n.a.
Marvel ^e	12	56 ± 3	n.a.	Arbitrarily	10	12	VCV	15	61 ± 3	n.a.	Arbitrarily	5	12	VCV
Michalopoulos ^f	21	62 ± 7	5 (24)	Arbitrarily	10	n.a.	ACV	22	61 ± 6	4 (18)	Arbitrarily	0	n.a.	ACV
Murphy	n.a	n.a.	n.a.	Arbitrarily	10	n.a.	n.a.	n.a.	n.a.	n.a.	Arbitrarily	0	n.a.	n.a.
Nelson	20	53 ± 17	n.a.	Incremental until $PaO_2/FiO_2 > 300$ or shunt < 0.2	15	n.a.	IMV	18	55 ± 20	n.a.	Incremental until PaO ₂ > 65 mmHg	8	n.a.	IMV
Рере	44	46 ± 19	14 (32)	Arbitrarily	8	12	VCV	48	$\begin{array}{c} 42 \pm \\ 19 \end{array}$	12 (25)	Arbitrarily	0	12	VCV

Table S3 (conti	nued))																	
				Higher PEE	Р			Lower PEEP											
First author	N	Age (years)	Female gender (N [%])	PEEP titration	PEEP level (cmH ₂ O)	Tidal volume (mL/kg) ^a	Ventilatory mode	Ν	Age (years)	Female gender (N [%])	PEEP titration	PEEP level (cmH ₂ O)	Tidal volume (mL/kg) ^a	Ventilatory mode					
Relax	49 3	66 ± 13	182 (37)	Clinical practice from The Netherlands	8	7	VCV/PCV/ PSV	47 6	65 ± 13	164 (34)	Decremental until SpO ₂ > 92% or PaO ₂ > 60 mmHg	2	7	VCV/PCV/ PSV					
Vigil	23	n.a.	n.a.	Arbitrarily	5	12	n.a.	21	n.a.	n.a.	Arbitrarily	0	12	n.a.					
Weigelt	45	Median 45	15 (33)	Arbitrarily	5	15	n.a.	34	Media n 45	7 (21)	Arbitrarily	0	15	n.a.					
Zurich	41	56 ± 8	4 (10)	Arbitrarily	10	n.a.	VCV	42	57 ± 8	8 (19)	Arbitrarily	0	n.a.	VCV/PVC					

Data are reported as mean (± standard deviation) or number (%), as appropriate, unless otherwise specified.

Abbreviations: N, total number of patients; PEEP, positive end-expiratory pressure; SIMV, synchronized intermittent mandatory ventilation; VCV, volume-controlled ventilation; n.a., not available; PCV, pressure-controlled ventilation; ACV, assist control ventilation; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; PaO₂, arterial partial pressure of oxygen; IMV, intermitted mandatory ventilation; SpO₂, pulse oximetry-measured oxygen saturation.

Twenty-two randomized controlled trials (2225 patients), which compared higher PEEP (1007 patients) to lower PEEP (991 patients), were included. The Murphy study did not report the number of patients that were randomized to the two groups and some study groups of the Lago Borges, Marvel, and Michalopoulos studies were excluded (see below); this explains why the total number of patients overall included in the studies does not match the sum of the patients in the two groups.

^aMany authors did not specify whether the tidal volume was based on ideal body weight or actual body weight.

^bThis study was the only study including recruitment maneuvers in the ventilatory protocol.

^cThe same patient population was included in Korovesi 2011 and Korovesi 2016.

^dThe same patient population was included in Lago Borges 2013 and Lago Borges 2014. One group of 47 patients with intermediate level of PEEP 8 cmH2O was not included in this systematic review and meta-analysis.

"One group of 17 patients, who exhaled to ambient pressure, was not included in this systematic review and meta-analysis.

^fOne group of 24 patients with intermediate level of PEEP (5 cmH2O) was not included in this systematic review and meta-analysis.

Table S4. Or	Cable S4. Outcomes in the higher PEEP group PaO2/Fi A- Crs CI CVP Hypoxe Pneumo Atelecta AR Bleedi PRB Hypotens Barotrau Duratio Hospit ICU 28-day Hospit al																		
First author	PaO ₂ /Fi O ₂ (mmHg)	A- aDO ₂ (mmH g)	Crs (mL/c mH ₂ O)	CI (L/m in/m ²)	CVP (mmH g)	Hypoxe mia (n [%])	Pneumo nia (n [%])	Atelecta sis (n [%])	AR DS (n [%])	Bleedi ng 24 h (mL)	PRB C (unit s)	Hypotens ion (n [%])	Barotrau ma (n [%])	Duratio n of ventilati on	Hospit al stay (days)	ICU stay (days)	ICU morta lity (n [%])	28-day mortali ty (n [%])	Hospit al mortali ty (n [%])
Collier				3.10 ± 0.86						$\begin{array}{c} 395 \pm \\ 392 \end{array}$	$\begin{array}{c} 0.8 \pm \\ 1.4 \end{array}$			409 ± 209 min	5.2 ± 1.7				1 (2%)
Dyhr				2.2 ± 0.6	13 ± 11												0 (0%)		0 (0%)
Feeley		Increa se of 10 ± 22										0 (0%)		258 ± 217 min			2 (17%)		
Good								9 (90%)				0 (0%)	0 (0%)						
Holland	307 ± 82			$\begin{array}{c} 3.0 \pm \\ 0.6 \end{array}$	9 ± 3														
Korovesi ^a	498 ± 75								0 (0%)							17.2 ± 10.1	3 (20%)		
Koutsoukou	409 ± 65	100 ± 41	62 ± 14						0 (0%)										
Lago Borges ^b	328 ± 85	117± 33	56 ± 19			19 (42%)								$\begin{array}{c} 5.1\pm2.9\\ hours \end{array}$					
Lesur	293 ± 135				12 ± 1									$\begin{array}{c} 9.2\pm8.8\\ days \end{array}$				9 (30%)	12 (40%)
Ma	196 ± 45																	15 (25%)	
Manzano ^c	$\begin{array}{c} 359 \pm \\ 104 \end{array}$					12 (19%)	6 (9%)	12 (19%)	3 (5%)				1 (%)	$\begin{array}{c} 5.8\pm6.8\\ days \end{array}$	19.5 ± 18.2	10.5 ± 9.8			19 (30%)
Marvel ^d		$\begin{array}{c} 168 \pm \\ 10 \end{array}$												9.3 ± 0.6 hours	$\begin{array}{c} 8.8 \pm \\ 0.5 \end{array}$				
Michalopou los ^e	315			3				2 (9%)					0 (0%)						0 (0%)
Nelson													1 (5%)	$\begin{array}{c} 5.3\pm5.0\\ days \end{array}$	28 ± 24	6.6 ± 5.0	4 (20%)		5 (25%)
Рере						1 (2%)	4 (9%)	27 (61%)	11 (25 %)			1 (2%)	19 (43%)						13 (30%)

Table S4 (co	ntinued)																		
First author	PaO ₂ /Fi O ₂ (mmHg)	A- aDO ₂ (mmH g)	Crs (mL/c mH ₂ O)	CI (L/m in/m ²)	CVP (mmH g)	Hypoxe mia (n [%])	Pneumo nia (n [%])	Atelecta sis (n [%])	AR DS (n [%])	Bleedi ng 24 h (mL)	PRB C (unit s)	Hypotens ion (n [%])	Barotrau ma (n [%])	Duratio n of ventilati on	Hospit al stay (days)	ICU stay (days)	ICU morta lity (n [%])	28-day mortali ty (n [%])	Hospit al mortali ty (n [%])
Relax ^f	248 ± 112					87 (18%)	7 (1%)	15 (3%)	5 (1%)		1.7 ± 0.7		12 (2%)	$\begin{array}{c} 4.8\pm 6.6\\ days \end{array}$	19 ± 21	7.2 ± 10.3	185 (38%)	207 (50%)	208 (42%)
Vigil														3.2 days					
Weigelt			$\begin{array}{c} 42 \pm \\ 36 \end{array}$						9 (20 %)			1 (2%)	5 (11%)	9.3 ± 13 days		11.7 ± 16.8			16 (35%)
Zurich										542 ± 239	$0.33 \\ \pm \\ 0.87$								

Data are reported as mean (± standard deviation) or number (%), as appropriate, unless otherwise specified. Empty cells are due to not available data; no data were available for the Murphy study.

Abbreviations: PEEP, positive end-expiratory pressure; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; A-aDO₂, alveolar-arterial oxygen pressure difference; Crs, respiratory system compliance; CI, cardiac index; CVP, central venous pressure; ARDS, acute respiratory distress syndrome; bleeding 24 h, bleeding 24 hours after the surgery; PRBC, packed red blood cells; ICU, intensive care unit.

Quantitative variables are expressed as mean ± standard deviations (only mean in Michalopoulos and Vigil), qualitative variables as number (percentage).

^aThe same patient population was included in Korovesi 2011 and Korovesi 2016. Variables included in the table are the variables collected at day 3 in the original study.

^bThe same patient population was included in Lago Borges 2013 and Lago Borges 2014. One group of 47 patients with intermediate level of PEEP 8 cmH2O was not included in this systematic review and meta-analysis.

^cVariables included in the table are the variables collected at day 2 in the original study.

^dOne group of 17 patients, who exhaled to ambient pressure, was not included in this systematic review and meta-analysis.

^eOne group of 24 patients with intermediate level of PEEP (5 cmH2O) was not included in this systematic review and meta-analysis. Variables included in the table are the variables collected before the extubation in the original study.

^fVariables included in the table are the variables collected at day 3 in the original study.

Table S5. O	'able S5. Outcomes in the lower PEEP group First PaO2/Fi Crs CI CVP Hypoxe Pneumo Atelecta AR Bleedi PRB Hypotens Barotrau Duratio ICU ICU 28- Hospit al																		
First author	PaO ₂ /Fi O ₂ (mmHg)	A-aDO ₂ (mmHg)	Crs (mL/ cmH 2O)	CI (L/min/ m ²)	CVP (mmH g)	Hypoxe mia (n [%])	Pneumo nia (n [%])	Atelecta sis (n [%])	AR DS (n [%])	Bleedi ng 24 h (mL)	PRB C (unit s)	Hypotens ion (n [%])	Barotrau ma (n [%])	Duratio n of ventilati on	Hospit al stay (days)	ICU stay (days)	ICU morta lity (n [%])	28- day morta lity (n [%])	Hospit al morta lity (n [%])
Collier				3.10 ± 0.64						587 ± 392	1.1 ± 1.6			440 ± 278 min	5.7 ± 2.5				1 (2%)
Dyhr				2.1 ± 1.1	10 ± 7												0 (0%)		0 (0%)
Feeley		Increase of 102 ± 35										0 (0%)		259 ± 149 min			1 (8%)		
Good								12 (86%)				0 (0%)	0 (0%)						
Holland	337 ± 82			2.9 ± 0.6	9 ± 3														
Korovesi ^a	420 ± 73								0 (0%)							$\begin{array}{c} 14.40 \\ \pm 8.44 \end{array}$	4 (33%)		
Koutsoukou	437 ± 74	87 ± 40	53 ± 11						1 (10 %)										
Lago Borges ^b	270 ± 90	139 ± 34	47 ± 12			30 (68%)								$\begin{array}{c} 6.8\pm3.2\\ hours \end{array}$					
Lesur	228 ± 67				11 ± 3									$\begin{array}{c} 9.2\pm8.5\\ days \end{array}$				14 (42%)	16 (48%)
Ma	134 ± 22																	39 (65%)	
Manzano ^c	301 ± 84					34 (54%)	16 (25%)	17 (27%)	9 (14 %)				5 (8%)	6.5 ± 6.2 days	26.3 ± 22.0	12.3 ± 11.4			16 (25%)
Marvel ^d		224 ± 12												11.1 ± 1.3 hours	$\begin{array}{c} 8.9 \pm \\ 0.4 \end{array}$				
Michalopou los ^e	325			3.2				2 (9%)					0 (0%)						0 (0%)
Nelson													0 (0%)	$\begin{array}{c} 3.4\pm3.0\\ days \end{array}$	26 ± 24	5.3 ± 3.0	4 (22%)		6 (33%)
Рере						4 (8%)	6 (12%)	23 (48%)	13 (27 %)			0 (0%)	24 (50%)						18 (37%)

Table S5 (co	ontinued)																		
First author	PaO ₂ /Fi O ₂ (mmHg)	A-aDO ₂ (mmHg)	Crs (mL/ cmH 2O)	CI (L/min/ m ²)	CVP (mmH g)	Hypoxe mia (n [%])	Pneumo nia (n [%])	Atelecta sis (n [%])	AR DS (n [%])	Bleedi ng 24 h (mL)	PRB C (unit s)	Hypotens ion (n [%])	Barotrau ma (n [%])	Duratio n of ventilati on	Hospit al stay (days)	ICU stay (days)	ICU morta lity (n [%])	28- day morta lity (n [%])	Hospit al morta lity (n [%])
Relax ^f	190 ± 84					98 (21%)	6 (1%)	20 (4%)	13 (3%)		1 ± 0		19 (4%)	$\begin{array}{c} 5.5\pm7.4\\ days \end{array}$	19.9± 22.1	8.1 ± 11.5	163 (34%)	183 (38%)	185 (39%)
Vigil														3.6 days					
Weigelt			39 ± 43						18 (53 %)			0 (0%)	4 (12%)	14.0 ± 21.7 days		21.0± 32.5			17 (50%)
Zurich										562± 261	0.75 ± 1.42								

Data are reported as mean (± standard deviation) or number (%), as appropriate, unless otherwise specified. Empty cells are due to not available data; no data were available for the Murphy study. Abbreviations: PEEP, positive end-expiratory pressure; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; A-aDO₂, alveolar-arterial oxygen pressure difference; Crs, respiratory system compliance; CI, cardiac index; CVP, central venous pressure; ARDS, acute respiratory distress syndrome; bleeding 24 h, bleeding 24 hours after the surgery; PRBC, packed red blood cells; ICU, intensive care unit.

Quantitative variables are expressed as mean ± standard deviations (only mean in Michalopoulos and Vigil), qualitative variables as number (percentage).

^aThe same patient population was included in Korovesi 2011 and Korovesi 2016. Variables included in the table are the variables collected at day 3 in the original study.

^bThe same patient population was included in Lago Borges 2013 and Lago Borges 2014. One group of 47 patients with intermediate level of PEEP 8 cmH2O was not included in this systematic review and meta-analysis.

^cVariables included in the table are the variables collected at day 2 in the original study.

^dOne group of 17 patients, who exhaled to ambient pressure, was not included in this systematic review and meta-analysis.

^eOne group of 24 patients with intermediate level of PEEP (5 cmH2O) was not included in this systematic review and meta-analysis. Variables included in the table are the variables collected before the extubation in the original study.

^fVariables included in the table are the variables collected at day 3 in the original study.

Table S6. Risk of bias summary						
Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Collier 2002	Low	Low	Low	Some concerns	Some concerns	Some concerns
Dyhr 2002	Some concerns	Some concerns	Low	High	Low	High
Feeley 1975	High	Some concerns	Low	High	Some concerns	High
Good 1979	High	Some concerns	Low	High	Some concerns	High
Holland 2007	Some concerns	Some concerns	Low	Low	Low	Some concerns
Korovesi 2011	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Korovesi 2016	High	Some concerns	Low	Some concerns	Low	High
Koutsoukou 2006	High	Some concerns	Low	Some concerns	Some concerns	High
Lago Borges 2013	High	Some concerns	Low	High	High	High
Lago Borges 2014	High	Some concerns	Low	High	High	High
Lesur 2010	Low	Low	Low	Some concerns	Low	Some concerns
Ma 2014	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Manzano 2008	Low	Some concerns	Low	Some concerns	Low	Some concerns
Marvel 1986	Some concerns	Some concerns	Low	High	Low	High
Michalopoulos 1998	High	Some concerns	Low	High	Low	High
Murphy 1983	High	High	High	High	Some concerns	High
Nelson 1987	High	Some concerns	Low	High	Low	High
Pepe 1984	Some concerns	Some concerns	Low	High	Low	High
Relax 2020	Low	Low	Low	Some concerns	Low	Some concerns
Vigil 1996	Some concerns	High	Low	High	Low	High
Weigelt 1979	High	Some concerns	Low	High	Some concerns	High
Zurich 1982	High	Some concerns	Low	High	Low	High

Fig. S1. Risk of bias summary

A summary figure of review authors' judgements for each risk of bias item for each study.

Study	D1	D2	D3	D4	D5	Overall		
Collier 2002	+	+	+	!	!	!	+	Low risk
Dyhr 2002	!	!	+	•	+	-	!	Some concerns
Feeley 1975	•	!	+	•	!	-	•	High risk
Good 1979	•	!	+	•	!	-		
Holland 2007	!	!	+	+	+	!	D1	Randomisation process
Korovesi 2011	!	!	+	!	+	!	D2	Deviations from the intended interventions
Korovesi 2016	•	!	+	!	+	-	D3	Missing outcome data
Koutsoukou 2006	•	!	+	!	!	-	D4	Measurement of the outcome
Lago Borges 2013	•	!	+	•	•	-	D5	Selection of the reported result
Lago Borges 2014	•	!	+	•	•	-		
Lesur 2010	+	+	+	!	+	!		
Ma 2014	!	+	+	!	!	!		
Manzano 2008	+	!	+	!	+	!		
Marvel 1986	!	!	+	•	+	-		
Michalopoulos 1998	•	!	+	•	+	-		
Murphy 1983	•	•	•	•	!	-		
Nelson 1987	•	!	+	•	+	-		
Pepe 1984	!	!	+	•	+	-		
Relax 2020	+	+	+	!	+	!		
Vigil 1996	!	•	+	•	+	-		
Weigelt 1979	•	!	+	•	!	-		
Zurich 1982	•	!	+	•	+	-		

Fig. S2. Risk of bias graph

A plot of the distribution of review authors' judgements across studies for each risk of bias item.



Table S7. Risk of bias for each study with signaling questions				
Study	Collier 2002			
Domain	Signalling question	Response	Comments	
	1.1 Was the allocation sequence random?	Y	"The study design was a prospective, randomized clinical trial Conception patients were	
Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	РҮ	randomized to either a PEEP of 10 cm of H_2O (experimental group) or a PEEP of 5 cm of H_2O (control group). Sealed envelopes arranged in a computer-generated random order were opened sequentially to determine the patients' treatment."	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν		
	Risk of bias judgement	Low		
	2.1.Were participants aware of their assigned intervention during the trial?	PN		
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI		
Bias due to deviations from intended interventions	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Ν		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y		

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Ν	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	

	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Dyhr 2002		
Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	РҮ	"At arrival after surgery in the intensive care unit (ICU) the
Bias arising from the	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	using the sealed envelope technique, into two groups".
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Some concerns	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
Bias due to deviations from intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	РҮ	

	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Feeley 1975		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Patients selected for study were assigned randomly to receive either 5 cm of positive and expiratory
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	s cm of positive end-expiratory pressure or no positive end- expiratory pressure during weaning."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	High	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	РҮ	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	
Overall risk of bias	Risk of bias judgement	High	

Study	Good 1979		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Patients were randomly assigned to a group receiving therapy with
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	PEEP (ten patients) or to a group with no PEEP (14 patients)."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	High	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	

	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	
Overall risk of bias	Risk of bias judgement	High	

Study	Holland 2007		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"On admission to the ICU, patients were randomised by using sealed envelopes into two groups and baseline measurements were taken."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	

	Risk of bias judgement	Some concerns	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	

	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Korovesi 2011		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	РҮ	"All patients [] were randomly assigned to receive either zero end-

	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	expiratory pressure (ZEEP; ZEEP group) or 8 cm H ₂ O of PEEP (PEEP group) following a predesigned chart of randomization."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Some concerns	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
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	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	РҮ	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	РҮ	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Ν	
	Risk of bias judgement	Some concerns	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study

Domain	Signalling question	Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?	NI	"All patients [] were randomly assigned to receive 0 cmH2O of
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	PEEP (ZEEP, n = 12) or 8 (PEEP, n = 15)."
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	High	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	РҮ	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	РҮ	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Koutsoukou		
Domain	Signalling question	Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?	NI	"Patients were randomly assigned to
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	ZEEP."
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	High	
	2.1.Were participants aware of their assigned intervention during the trial?	Ν	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	

	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
Bias in selection of the reported result	Risk of bias judgement	Some concerns	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Ν	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	

Study	Lago Borges 2013		
Domain	Signalling question	Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?	NI	Randomized clinical trial in a
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	universitary hospital."
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	High	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	"After draw, information about which group the patient would be
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	allocated, was given to ICU members."
Bias due to deviations from	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
intended interventions	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y	"We also excluded patients who died in the perioperative period before weaning from mechanical ventilation."

	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	High	
Overall risk of bias	Risk of bias judgement	High	

Study	Lago Borges 2014		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Randomized clinical trial conducted in a federal university hospital in northeastern Brazil."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	"Patients were assigned to one of three groups using a simple draw"
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	High	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	"Patients were assigned to one of
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	three groups using a simple draw"
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data Bias in measurement of the outcome	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	

	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y	"We also excluded patients who died in the perioperative period before weaning from mechanical ventilation." "Comparing only patients extubated within 12 hours after ICU admission, i.e., uncomplicated in the immediate postoperative period, we found a statistically significant difference in mechanical ventilation duration between the groups (p = 0.029)."
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	High	
Overall risk of bias	Risk of bias judgement	High	

Study	Lesur		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"A computer-generated block randomization list was prepared by the principal investigator (Olivier Lesur). Randomization was concealed using numbered, sealed, opaque envelopes. On assessment of
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	

			the patient's eligibility, the randomization process was initiated by the opening of the first numbered envelope by the 'on ward' respiratory therapist. The ICU physician on duty was blinded to this procedure; the respiratory therapist adjusted the MV parameters (according to the physician's recommendations) with ZEEP or PEEP (according to the study's allocation), masking visual identification of allocation for the following 90 min. The ICU physician could halt the blinding at any moment, whenever he or she was not comfortable with the protocol."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Low	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
Bias due to deviations from intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Ν	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	N	"The lowest MAP values for each individual and period were selected to be representative for delta calculation and mean measurements."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	РҮ	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	РҮ	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	"The general characteristics of both intention-to-treat study groups were very similar and representative of a

			typical medical ICU admission profile."
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Ma			
Domain	Signalling question	Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"120 patients with NEP admitted to Department of Critical Care Medicine of the First Affiliated	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	Hospital of Guangxi Traditional Chinese Medical University from January 2010 to August 2013 were enrolled and divided into two grou according to random number table (n=60 in each group)."	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν		
	Risk of bias judgement	Some concerns		
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN		

	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Ν	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	РҮ	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Manzano		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"This prospective, randomized, nonblinded, controlled clinical trial was performed in two general intensive care units (ICUs) and one trauma ICU in two reference centers in Spain."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	РҮ	

			"Patients were assigned to the PEEP group or control group using a computer-generated randomization list in blocks of 12. Allocation to control group or PEEP group was concealed in a closed envelope by an assistant not involved in the study."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Low	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"All analyses were conducted on an intention-to-treat basis."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	N	"Radiographs were interpreted by consensus between two physicians (intensivists with >5 yrs experience) and, if agree- ment could not be reached, by decision of a third physician."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	РҮ	The precise definitions of the outcomes reduce the likelihood of subjective outcome assessment.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Marvel			
Domain	Signalling question	Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The remaining 44 patients were randomly	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	assigned by computer to one of three groups. The computer program maintained an equal distribution of any individual surgeon's patients among the three treatment groups."	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN		
	Risk of bias judgement	Some concerns		
	2.1.Were participants aware of their assigned intervention during the trial?	PN		
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ		
Bias due to deviations from intended interventions	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	РҮ		

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	"These roentgenograms were graded for atelectasis by a chest radiologist who did not know the treatment assignments."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?		РҮ	

	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Michalopoulos					
Domain	Signalling question	Response	Comments			
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Patients were randomly assigned to receive zero PEEP (Group A, n=22) 5 cmH2Q PEEP (Group B			
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	n=24), or 10 cmH2O PEEP (Group C, n=21) during mechanical ventilatory support."			
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν				
	Risk of bias judgement	High				
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN				
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ				

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	РҮ	
Bias in selection of the	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
reported result	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	of bias Risk of bias judgement		

Study	Murphy					
Domain	Signalling question	Response	Comments			
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"After admission to the intensive care unit and after hematologic evaluations, patients in both groups			
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	were randomized to receive either 10 cm H20 of PEEP beginning 1 hour after the completion of the operation or no PEEP, and were studied for 8 hours."			
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI				

	Risk of bias judgement	High	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NI	
	Risk of bias judgement	High	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Ν	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	High	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	NI	

	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
Bias in selection of the	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
reported result	5.3 multiple eligible analyses of the data?	NI	
	Risk of bias judgement	Some concerns	
Overall risk of bias	all risk of bias Risk of bias judgement		

Study	Nelson		
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	

	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	"Patients were assigned randomly to one of two treatment groups."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	High	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from intended interventions	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
reported result	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Рере							
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Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	РҮ	"We randomly assigned patients to receive either no PEEP (control) or
Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	PEEP at a level of 8 cmH2O (early PEEP). [] Random permuted blocks of size 4 were used."
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Some concerns	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	

	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Relax			
Domain	Signalling question	Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"This was a randomized clinical trial conducted at the ICUs of 8 hospitals in the Netherlands."	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	РҮ	"Patients were randomized in a 1:1 ratio to a lower or higher PEEP strategy group. The local investigators performed randomization using a central, dedicated, password-protected, encrypted, web-based automated randomization system (SSL- encrypted website with ALEA software, TenALEA Consortium). Randomization was conducted using random block sizes with a maximum of 8 patients."	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν		
	Risk of bias judgement	Low		
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN		
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN		

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"In all analyses, patients were analyzed according to their randomization group, with the exception of those who withdrew informed consent or were lost to follow-up in the first 28 days."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"An independent committee oversaw conduct of the trial and adverse events while remaining blind to the primary end point at 3 predefined time points, and recommended the trial be continued."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	

	4.3 Were outcome assessors aware of the intervention received by study participants?	РҮ	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	РҮ	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	Some concerns	
Bias in selection of the	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	"The protocol has been published,15 and the final protocol is available in Online Resource 1. An updated statistical analysis plan was written be- fore closing the database; the final plan and a table describing the changes to the original study design are available in Online Resource 2."
reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	Some concerns	

Study	Vigil		
Domain	Signalling question	Response	Comments

Bias arising from the	1.1 Was the allocation sequence random?	РҮ	"Forty-four trauma patients were randomized
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	PEEP (PEEP) or 0-cm H2O PEEP (ZEEP)."
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	
	Risk of bias judgement	Some concerns	
	2.1.Were participants aware of their assigned intervention during the trial?	PN	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ	
Bias due to deviations from intended interventions	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NI	
	Risk of bias judgement	High	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Study	Weigelt			
Domain	Signalling question	Response	Comments	
Bias arising from the	1.1 Was the allocation sequence random?	NI	"This prospective randomized study was	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	effect of early therapeutic PEEP on the incidence and severity of ARDS."	
randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν		
	Risk of bias judgement	High		
	2.1.Were participants aware of their assigned intervention during the trial?	PN		
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI		
Bias due to deviations from	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA		
intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	РҮ		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA		
	Risk of bias judgement	Some concerns		

	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Υ	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	Ν	
Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Some concerns	

Overall	risk	of	bias	
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Study	Zurich			
Domain	Signalling question	Response	Comments	
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Ν	"The patients were randomized preoperatively on the basis of the last digit of their clinical history	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	number; odd-numbered patients were assigned to the group receiving PEEP, and even-numbered patients to the group not receiving PEEP (control group)."	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν		
	Risk of bias judgement	High		
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN		
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	РҮ		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y		
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	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA		
	Risk of bias judgement	Some concerns		
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y		
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA		
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA		
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA		
	Risk of bias judgement	Low		
	4.1 Was the method of measuring the outcome inappropriate?	PN		
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	РҮ		
Bias in measurement of the	4.3 Were outcome assessors aware of the intervention received by study participants?	NA		
outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA		
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA		
	Risk of bias judgement	High		
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre- specified analysis plan that was finalized before unblinded outcome data were available for analysis?	РҮ		

	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall risk of bias	Risk of bias judgement	High	

Online Resource 6. Primary and Secondary Outcomes

Table S8. Sum	Table S8. Summary of main meta-analysis												
Variable	Studies	N	Higher PEEP (N/total or N)	Lower PEEP	Relative effect of higher PEEP (95% CI)	Prediction Interval (95% CI)	I ² (%)	p (I ²)					
Primary outcon	ne												
Hospital mortality	9	1502	274/ 760	259/ 742	1.02 (0.89, 1.16)	1.02ª	0	0.62					
Secondary outc	omes												
PaO ₂ /FiO ₂	8	1444	732	712	50.46 mmHg (33.93, 66.99)	50.46 mmHg (11.87, 89.04)	59	0.02					
Hypoxemia	5	1320	121/ 667	168/ 653	0.60 (0.40, 0.92)	0.60 (-1.55, 2.75)	59	0.05					
ARDS	6	1315	28/ 672	54/ 643	0.50 (0.32, 0.78)	0.50 (-0.26,1.26)	13	0.33					
A-aDO ₂	4	164	80	84	-1.62 (-3.12, - 0.11)	-1.62 (-9.03, 5.80)	92	< 0.01					
Compliance	3	189	101	88	8.46 mL/cmH ₂ O (3.11, 13.82)	8.46 mL/cmH ₂ O ^a	0	0.82					
Atelectasis	5	1255	65/ 632	74/ 623	1.02 (0.81, 1.28)	1.02 (0.38, 1.66)	11	0.34					
Barotrauma	7	1372	38/ 697	52/ 675	0.78 (0.55, 1.11)	0.78ª	0	0.54					
VAP	3	1188	17/ 601	28/ 587	0.62 (0.32, 1.23)	0.62 (-4.01, 5.25)	23	0.27					
Hypotension	5	283	18/ 141	16/ 142	1.15 (0.71, 1.84)	1.15ª	0	0.72					
CI	3	127	61	66	0.04 L/min/m ² (-0.21, 0.29)	0.04ª	0	0.93					
CVP	3	106	51	55	1.37 mmHg (0.38, 2.37)	1.37ª	0	0.38					
24-hour postoperative bleeding	2	601	81	520	26.47 mL (- 99.95, 152.89)	26.47 (-251.37, 304.31)	52	0.15					
PRBC transfusion	3	1138	574	564	-0.38 units (- 0.77, 0.02)	-0.38ª	0	0.77					
Duration of ventilation	10	1510	771	739	-0.03 (-0.27, 0.21)	-0.03 (-1.68, 1.62)	65	< 0.01					
ICU stay	4	1202	617	585	-1.00 days (- 2.51, 0.51)	-1.00 (-3.20, 1.20)	6	0.37					
Hospital stay	5	1245	629	616	-0.02 days (- 0.69, 0.66)	-0.02 (-1.53, 1.48)	26	0.25					
ICU mortality	5	1073	194/ 546	172/ 527	1.09 (0.92, 1.28)	1.09ª	0	0.74					
28-day mortality	3	1152	231/ 583	236/ 569	0.68 (0.33, 1.40)	0.68 (-12.89, 14.25)	89	< 0.01					

Table S8 (c	ontinued)										
Variable	Studies	N	Higher PEEP (N/total or N)	Lower PEEP	Relative effect of higher PEEP (95% CI)	Prediction Interval (95% CI)	I ² (%)	p (I ²)			
Abbreviations: N, number of patients; PEEP, positive end-expiratory pressure; CI, confidence interval; I ² , I ² test;											
PaO ₂ /FiO ₂ ,	PaO ₂ /FiO ₂ , arterial partial pressure of oxygen to fraction of inspired oxygen ratio; A-aDO ₂ , alveolar-arterial oxygen										
pressure dif	ference; VAI	P, ventilator-a	associated pne	eumonia; AR	DS, acute res	piratory distress s	yndrome; C	I, cardiac			
index; CVP	, central vend	ous pressure;	PRBC, packe	d red blood c	ells; ICU, int	ensive care unit.					
Total effect	is expressed	as risk ratio (Mantel-Haen	szel method,	random-effe	cts) for hospital m	ortality, hyp	poxemia,			
atelectasis,	barotrauma, V	VAP, ARDS,	hypotension,	ICU mortali	ty, 28-day mo	ortality; mean diff	erence (inve	erse			
variance method, random-effects) for PaO ₂ /FiO ₂ , compliance, cardiac index, CVP, postoperative bleeding, PRBC											
transfusion, ICU stay, hospital stay; and standardized mean difference (inverse variance, random-effects) for A-aDO ₂											
and duration of ventilation.											
^a I ² and tau a	re zero.										

Forest plots of other secondary outcomes

Abbreviations: A-aDO₂, alveolar-arterial oxygen pressure difference; SD, standard deviation; IV, inverse variance; CI, confidence interval; PEEP, positive end-expiratory pressure; M-H, Mantel-Haenszel; VAP, ventilator-associated pneumonia; CI, cardiac index; CVP, central venous pressure; PRBC, packed red blood cell transfusion; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

A-aDO2

	High	er PE	EEP	Low	er PE	EP		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feeley 1975	10	22	12	102	35	13	23.6%	-3.02 [-4.22, -1.81]	— — —
Koutsoukou 2006	100	41	11	87	40	10	25.5%	0.31 [-0.55, 1.17]	
Lago Borges 2013	117	33	45	139	34	44	27.2%	-0.65 [-1.08, -0.22]	
Marvel 1986	168	10	12	203	10	17	23.7%	-3.40 [-4.60, -2.20]	_ _
Total (95% CI)			80			84	100.0%	-1.62 [-3.12, -0.11]	
Heterogeneity: Tau ² = Test for overall effect	= 2.13; C :: Z = 2.1	hi² = 0 (P =	37.49 = 0.04)	df = 3	(P < 1	0.0000	1); I ² = 92	%	-4 -2 0 2 4 Favours higher PEEP Favours lower PEEP

Compliance

	High	er PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Koutsoukou 2006	62	14	11	53	11	10	24.9%	9.00 [-1.72, 19.72]	
Lago Borges 2013	56	19	45	47	12	44	66.1%	9.00 [2.41, 15.59]	
Weigelt 1979	42	36	45	39	43	34	9.0%	3.00 [-14.88, 20.88]	
Total (95% CI)			101			88	100.0%	8.46 [3.11, 13.82]	-
Heterogeneity: Tau ² =	= 0.00; C	hi² =	0.39, 0	df = 2 (P = 0	.82); I ²	= 0%		
Test for overall effect	:: Z = 3.1	0 (P =	= 0.002	?)					Lower in higher PEEP Higher in higher PEEP

Atelectasis

	Higher PEEP Lower PEEP					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Good 1979	9	10	12	14	44.3%	1.05 [0.78, 1.41]	- -
Manzano 2008	12	64	17	63	11.8%	0.69 [0.36, 1.33]	
Michalopoulos 1998	2	21	2	22	1.5%	1.05 [0.16, 6.77]	
Pepe 1984	27	44	23	48	30.8%	1.28 [0.88, 1.87]	+
Relax 2020	15	493	20	476	11.6%	0.72 [0.38, 1.40]	
Total (95% CI)		632		623	100.0%	1.02 [0.81, 1.28]	•
Total events	65		74				
Heterogeneity: Tau ² =	0.01; Ch	$i^2 = 4.5$	1, df = 4	(P = 0.1)	34); I ² = 1	11%	
Test for overall effect:	Z = 0.15	(P = 0.3)	88)				Favours higher PEEP Favours lower PEEP

Barotrauma

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Good 1979	0	10	0	14		Not estimable	
Manzano 2008	1	64	5	63	2.8%	0.20 [0.02, 1.64]	
Michalopoulos 1998	0	21	0	22		Not estimable	
Nelson 1987	1	20	0	18	1.3%	2.71 [0.12, 62.70]	
Pepe 1984	19	44	24	48	63.5%	0.86 [0.56, 1.34]	
Relax 2020	12	493	19	476	24.4%	0.61 [0.30, 1.24]	
Weigelt 1979	5	45	4	34	8.1%	0.94 [0.27, 3.25]	
Total (95% CI)		697		675	100.0%	0.78 [0.55, 1.11]	•
Total events	38		52				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 3.1$	0, $df = 4$	(P = 0.	54); $I^2 = 0$	D%	
Test for overall effect:	: Z = 1.40	(P=0.	16)				Lower in higher PEEP Higher in higher PEEP

Ventilator-associated pneumonia

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Manzano 2008	6	64	16	63	42.8%	0.37 [0.15, 0.88]	B
Pepe 1984	4	44	6	48	26.3%	0.73 [0.22, 2.41]	
Relax 2020	7	493	6	476	30.9%	1.13 [0.38, 3.33]	_
Total (95% CI)		601		587	100.0%	0.62 [0.32, 1.23]	-
Total events	17		28				
Heterogeneity: Tau ² = Test for overall effect	= 0.08; Ch t: Z = 1.36	$i^2 = 2.5$ i(P = 0.5)	59, df = 2 .17)	2 (P = 0	.27); I ² =	23%	0.02 0.1 1 10 50 Favours higher PEEP Favours lower PEEP

Hypotension

	Higher	PEEP	Lower	PEEP		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M–H, Random, 95% Cl
Feeley 1975	0	12	0	13		Not estimable		
Good 1979	0	10	0	14		Not estimable		
Lesur 2010	16	30	16	33	95.5%	1.10 [0.68, 1.79]		
Pepe 1984	1	44	0	48	2.2%	3.27 [0.14, 78.15]		
Weigelt 1979	1	45	0	34	2.2%	2.28 [0.10, 54.36]		
Total (95% CI)		141		142	100.0%	1.15 [0.71, 1.84]		•
Total events	18		16					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.6$	57, df = 2	P = 0.	72); I ² = (0%		
Test for overall effect	: Z = 0.56	5 (P = 0)	57)				0.01	Favours higher PEEP Favours lower PEEP

Cardiac index

	Higl	her PE	EP	Lov	ver PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	CI IV, Random, 95% CI
Collier 2002	3.1	0.86	40	3.1	0.64	44	59.6%	0.00 [-0.33, 0.33]	3]
Dyhr 2002	2.2	0.6	7	2.1	1.1	8	8.2%	0.10 [-0.78, 0.98]	3]
Holland 2007	3	0.6	14	2.9	0.6	14	32.2%	0.10 [-0.34, 0.54]	4]
Total (95% CI)			61			66	100.0%	0.04 [-0.21, 0.29]	
Heterogeneity: Tau ² =	= 0.00; 0	Chi² =	0.15, c	df = 2 (P = 0.9	93); I ² =	= 0%		+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall effect	: Z = 0.3	81 (P =	= 0.75)						Favours lower PEEP Favours higher PEEP

Central venous pressure

	High	ier PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Dyhr 2002	13	11	7	9.7	7.1	8	1.1%	3.30 [-6.22, 12.82]	
Holland 2007	9	3	14	9	3	14	20.2%	0.00 [-2.22, 2.22]	_
Lesur 2010	12.5	1.5	30	10.8	2.9	33	78.7%	1.70 [0.57, 2.83]	
Total (95% CI)			51			55	100.0%	1.37 [0.38, 2.37]	◆
Heterogeneity: Tau ² = Test for overall effect	= 0.00; C : Z = 2.7	Chi ² = 70 (P =	1.95, 0 = 0.007	-10 -5 0 5 10 Favours lower PEEP Favours higher PEEP					

Postoperative bleeding

	Higher PEEP Lower PEEP					EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Collier 2002	703	395	40	587	392	44	34.2%	116.00 [-52.52, 284.52]	
Zurich 1982	542	239	41	562	261	476	65.8%	-20.00 [-96.82, 56.82]	
Total (95% CI)			81			520	100.0%	26.47 [-99.95, 152.89]	
Heterogeneity: Tau ² =	4783.3	35; Ch	$i^2 = 2.0$						
Test for overall effect	Z = 0.4	41 (P =	= 0.68)						Favours higher PEEP Favours lower PEEP

PRBC transfusion

Higher PEEP				Low	ver PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Collier 2002	0.8	1.4	40	1.1	1.6	44	37.5%	-0.30 [-0.94, 0.34]			
Relax 2020	1.7	0.7	493	1	0	476		Not estimable			
Zurich 1982	0.33	0.87	41	0.75	1.42	44	62.5%	-0.42 [-0.92, 0.08]			
Total (95% CI)			574			564	100.0%	-0.38 [-0.77, 0.02]	•		
Heterogeneity: Tau ² =	= 0.00; 0	Chi² =	0.08, 0								
Test for overall effect	: Z = 1.	87 (P =	= 0.06)		Favours higher PEEP Favours lower PEEP						

Duration of ventilation

	Higher PEEP			Lov	ver PEE	Р	9	Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Collier 2002	409.1	208.6	40	439.3	277.7	44	12.3%	-0.12 [-0.55, 0.31]			
Feeley 1975	258	217	12	259	149	13	6.4%	-0.01 [-0.79, 0.78]			
Good 1979	15.7	0.4	10	14.8	0.5	14	4.5%	1.88 [0.88, 2.88]			
Lago Borges 2014	5.1	2.9	45	6.8	3.2	44	12.4%	-0.55 [-0.98, -0.13]			
Lesur 2010	9.2	8.8	30	9.2	8.5	33	10.9%	0.00 [-0.49, 0.49]			
Manzano 2008	5.8	6.8	64	6.5	6.2	63	14.2%	-0.11 [-0.45, 0.24]			
Marvel 1986	9.3	0.6	12	0	0	0		Not estimable			
Nelson 1987	5.3	5	20	3.4	3	18	8.2%	0.45 [-0.20, 1.09]			
Relax 2020	4.8	6.6	493	5.5	7.4	476	19.2%	-0.10 [-0.23, 0.03]			
Weigelt 1979	9.3	13	45	14	21.7	34	11.9%	-0.27 [-0.72, 0.18]			
Total (95% CI)			771			739	100.0%	-0.03 [-0.27, 0.21]	•		
Heterogeneity: Tau ² =	= 0.07; 0	$Chi^2 = 2$	3.01, d	f = 8 (P	= 0.00	3); I ² =	65%	-			
Test for overall effect	:: Z = 0.2	24 (P =	0.81)						Lower in higher PEEP Higher in higher PEEP		

ICU stay

	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
Korovesi 2011	17.2	10.1	15	14.4	8.44	12	4.6%	2.80 [-4.19, 9.79]]
Manzano 2008	10.5	9.8	64	12.3	11.4	63	15.5%	-1.80 [-5.50, 1.90]]
Relax 2020	7.2	10.3	493	8.1	11.5	476	78.4%	-0.90 [-2.28, 0.48]] -
Weigelt 1979	11.7	16.8	45	21	32.5	34	1.6%	-9.30 [-21.28, 2.68]]
Total (95% CI)			617			585	100.0%	-1.00 [-2.51, 0.51]	1 🔶
Heterogeneity: Tau ² = Test for overall effect	= 0.26; 0 :: Z = 1.3	Chi² = 30 (P =	3.18, c = 0.19)	df = 3 (I	-20 -10 0 10 20 Favours higher PEEP Favours lower PEEP				

Hospital stay

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Collier 2002	5.7	2.5	40	5.2	1.7	44	31.1%	0.50 [-0.42, 1.42]	
Manzano 2008	19.5	18.2	64	26.3	22	63	0.9%	-6.80 [-13.83, 0.23]	
Marvel 1986	8.8	0.5	12	8.9	0.4	15	62.2%	-0.10 [-0.45, 0.25]	•
Nelson 1987	28	24	20	26	24	18	0.2%	2.00 [-13.28, 17.28]	
Relax 2020	19	21.4	493	19.9	22.1	476	5.6%	-0.90 [-3.64, 1.84]	
Total (95% CI)	= 0 16 [.] (⁻ hi ² =	629	lf = 4 (I	P = 0 1	616	100.0%	-0.02 [-0.69, 0.66]	· · · · · · · · · · · · · · · · · · ·
Test for overall effect	z = 0.10, c)4 (P =	= 0.96)		- 0	L J /, T -	- 20/0		–10 –5 0 5 10 Lower in higher PEEP Higher in higher PEEP

ICU mortality

	Higher PEEP Lower PEEP					Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
Dyhr 2002	0	7	0	8		Not estimable			
Feeley 1975	2	12	1	13	0.5%	2.17 [0.22, 20.94]			—
Korovesi 2011	3	15	4	12	1.6%	0.60 [0.17, 2.18]			
Nelson 1987	4	20	4	18	1.8%	0.90 [0.26, 3.08]			
Relax 2020	185	492	163	476	96.0%	1.10 [0.93, 1.30]		—	
Total (95% CI)		546		527	100.0%	1.09 [0.92, 1.28]		•	
Total events	194		172						
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 1.2$	27, df = 3	B (P = 0.	74); I ² =	0%			+
Test for overall effect	: Z = 0.99	P = 0.	32)				0.05	Favours higher PEEP Favours lower PEEP	.0

28-day mortality

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
Lesur 2010	9	30	14	33	28.8%	0.71 [0.36, 1.39]	
Ma 2014	15	60	39	60	33.1%	0.38 [0.24, 0.62]	
Relax 2020	207	493	183	476	38.1%	1.09 [0.94, 1.27]	–
Total (95% CI)		583		569	100.0%	0.68 [0.33, 1.40]	
Total events	231		236				
Heterogeneity: Tau ² =	= 0.35; Ch	$i^2 = 17$.71, df =				
Test for overall effect	Z = 1.05	(P = 0)	.30)				Favours higher PEEP Favours lower PEEP

Online Resource 7. Funnel Plots

Abbreviations: SE, standard error; RR, risk ratio; MD, mean difference; SMD, standardized mean difference; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; A-aDO₂, alveolar-arterial oxygen pressure difference; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

























Barotrauma



Ventilator-associated pneumonia







Hypotension







Central venous pressure



Postoperative bleeding



Packed red blood cell transfusion



Duration of ventilation


















Online Resource 8. Sensitivity Analyses

Sensitivity analyses: timing of measurement

Sensitivity analyses according to the different timing of measurement of the variables in the following studies: Korovesi (day 1 and day 5), Manzano (basal, 6 hours, and day 1), and RELAx (after randomization, day 1, and day 2). Packed red blood cell transfusion became significantly lower in the higher PEEP group when considering this variable after randomization in the RELAx study.

Abbreviations: PRBC, packed red blood cell; afterrand, after randomization; IV, inverse variance; CI, confidence interval; d1, day 1; d2, day 2; 6 h, 6 hours; d5, day 5.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 PRBC transfusion (relax_afterrand)	3	1138	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.64, -0.14]
1.2 PRBC transfusion (relax_d1)	3	1138	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.58, 0.36]
1.3 PRBC transfusion (relax_d2)	3	1138	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.14]
Outcome ou Submer	Stording	Dautiain anta	Statistical Mathed	Effect Estimate

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate		
1.4 PaO ₂ /FiO ₂ (korovesi_d1-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	28.60 [3.69, 53.50]		
relax_afterrand)						
1.5 PaO ₂ /FiO ₂ (korovesi_d1-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	37.18 [17.84, 56.53]		
relax d1)						

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1.6 PaO ₂ /FiO ₂ (korovesi_d1-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	36.37 [17.09, 55.66]
relax_d2)				
1.7 PaO ₂ /FiO ₂ (korovesi_d1-manzano_6h-	8	1444	Mean Difference (IV, Random, 95% CI)	29.70 [4.84, 54.56]
relax_afterrand)				
1.8 PaO ₂ /FiO ₂ (korovesi_d1-manzano_6h-relax_d1)	8	1444	Mean Difference (IV, Random, 95% CI)	38.95 [20.20, 57.70]
1.9 PaO ₂ /FiO ₂ (korovesi_d1-manzano_6h-relax_d2)	8	1444	Mean Difference (IV, Random, 95% CI)	38.01 [19.22, 56.81]
1.10 PaO ₂ /FiO ₂ (korovesi_d1-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	33.94 [9.58, 58.29]
relax_afterrand)				
1.11 PaO ₂ /FiO ₂ (korovesi_d1-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	43.71 [26.22, 61.20]
relax_d1)				
1.12 PaO ₂ /FiO ₂ (korovesi_d1-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	42.56 [24.81, 60.31]
relax_d2)				
1.13 PaO ₂ /FiO ₂ (korovesi_d5-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	28.18 [3.27, 53.08]
relax_afterrand)				
1.14 PaO ₂ /FiO ₂ (korovesi_d5-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	36.82 [17.43, 56.20]
relax_d1)				
1.15 PaO ₂ /FiO ₂ (korovesi_d5-manzano_basal-	8	1444	Mean Difference (IV, Random, 95% CI)	36.01 [16.70, 55.33]
relax_d2)				

1.16 PaO ₂ /FiO ₂ (korovesi_d5-manzano_6h-	8	1444	Mean Difference (IV, Random, 95% CI)	29.28 [4.41, 54.14]
relax_afterrand)				
1.17 PaO ₂ /FiO ₂ (korovesi_d5-manzano_6h-	8	1444	Mean Difference (IV, Random, 95% CI)	38.58 [19.78, 57.38]
relax_d1)				
1.18 PaO ₂ /FiO ₂ (korovesi_d5-manzano_6h-	8	1444	Mean Difference (IV, Random, 95% CI)	37.65 [18.82, 56.49]
relax_d2)				
1.19 PaO ₂ /FiO ₂ (korovesi_d5-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	33.51 [9.15, 57.88]
relax_afterrand)				
1.20 PaO ₂ /FiO ₂ (korovesi_d5-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	43.35 [25.80, 60.91]
relax_d1)				
1.21 PaO ₂ /FiO ₂ (korovesi_d5-manzano_d1-	8	1444	Mean Difference (IV, Random, 95% CI)	42.22 [24.41, 60.02]
relax_d2)				
1.22 PaO ₂ /FiO ₂ (korovesi_d1)	8	1444	Mean Difference (IV, Random, 95% CI)	48.05 [31.50, 64.60]
1.21 PaO ₂ /FiO ₂ (korovesi_d5)	8	1444	Mean Difference (IV, Random, 95% CI)	47.68 [31.04, 64.32]
1.22 PaO ₂ /FiO ₂ (manzano_basal)	8	1444	Mean Difference (IV, Random, 95% CI)	43.04 [24.13, 61.95]
1.23 PaO ₂ /FiO ₂ (manzano_6h)	8	1444	Mean Difference (IV, Random, 95% CI)	44.98 [26.84, 63.12]
1.24 PaO ₂ /FiO ₂ (manzano_d1)	8	1444	Mean Difference (IV, Random, 95% CI)	49.78 [33.24, 66.32]
1.25 PaO ₂ /FiO ₂ (relax_afterrand)	8	1444	Mean Difference (IV, Random, 95% CI)	38.26 [13.53, 62.99]

1.26 PaO ₂ /FiO ₂ (relax_d1)	8	1444	Mean Difference (IV, Random, 95% CI)	46.91 [29.19, 64.62]
1.27 PaO ₂ /FiO ₂ (relax_d2)	8	1444	Mean Difference (IV, Random, 95% CI)	45.79 [27.74, 63.85]

Sensitivity analyses: odds ratio

Sensitivity analyses according to the use of odds ratio instead of risk ratio as effect estimate in dichotomous variables. No difference with respect to the main meta-analyses was observed.

Abbreviations: M-H, Mantel-Haenszel; CI, confidence interval; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Hospital mortality	9	1502	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.83, 1.29]
2.2 Hypoxemia	5	1320	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.20, 0.94]
2.3 Atelectasis	5	1255	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.59, 1.40]
2.4 Barotrauma	7	1372	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.10]
2.5 Ventilator-associated pneumonia	3	1188	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.27, 1.35]
2.6 ARDS	6	1315	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.23, 0.70]
2.7 Hypotension	5	283	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.56, 3.44]
2.8 ICU mortality	5	1073	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.88, 1.47]

2.9 28-day mortality	
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0.51 [0.15, 1.77]

Sensitivity analyses: without studies at high risk of bias

Sensitivity analyses after removing the studies at high risk of bias. Central venous pressure and the incidence of hypoxemia became not significantly different between the 2 groups. We observed a trend (p = 0.09) towards a significantly decreased duration of ventilation with higher PEEP.

Abbreviations: M-H, Mantel–Haenszel; CI, confidence interval; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; IV, inverse variance; ARDS, acute respiratory distress syndrome; CVP, central venous pressure; ICU, intensive care unit.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Hospital mortality	4	1235	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.93, 1.24]
3.2 PaO ₂ /FiO ₂	6	1334	Mean Difference (IV, Random, 95% CI)	56.55 [42.12, 70.98]
3.3 Hypoxemia	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.23, 1.37]
3.4 Atelectasis	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.13]
3.5 Barotrauma	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.07]
3.6 Ventilator-associated pneumonia	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.83]
3.7 ARDS	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.16, 0.78]
3.8 Cardiac index	2	112	Mean Difference (IV, Random, 95% CI)	0.04 [-0.23, 0.30]
3.9 CVP	2	91	Mean Difference (IV, Random, 95% CI)	1.13 [-0.44, 2.70]

3.10 Duration of ventilation	4	1243	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.21, 0.01]
3.11 ICU stay	3	1123	Mean Difference (IV, Random, 95% CI)	-0.88 [-2.15, 0.38]
3.12 Hospital stay	3	1180	Mean Difference (IV, Random, 95% CI)	-0.73 [-3.21, 1.74]
3.13 ICU mortality	2	995	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
3.14 28-day mortality	3	1152	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.33, 1.40]

Forest plots of sensitivity analyses

Sensitivity analysis (timing of measurement)

Packed red blood cell transfusion (relax_afterrand)

	Hig	her PE	EP	Low	ver PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Collier 2002	0.8	1.4	40	1.1	1.6	44	14.8%	-0.30 [-0.94, 0.34]	
Relax 2020	2.3	2.2	493	2.7	2.8	476	60.5%	-0.40 [-0.72, -0.08]	
Zurich 1982	0.33	0.87	41	0.75	1.42	44	24.7%	-0.42 [-0.92, 0.08]	
Total (95% CI)			574			564	100.0%	-0.39 [-0.64, -0.14]	◆
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.09$, $df = 2$ (P = 0.95); $I^2 = 0\%$									+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
lest for overall effect	z = 3.0	J9 (P =	= 0.002)					Favours higher PEEP Favours lower PEEP

Packed red blood cell transfusion (relax_d1)

	Hig	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Collier 2002	0.8	1.4	40	1.1	1.6	44	24.6%	-0.30 [-0.94, 0.34]	
Relax 2020	1.5	0.7	493	1.3	0.7	476	45.2%	0.20 [0.11, 0.29]	
Zurich 1982	0.33	0.87	41	0.75	1.42	44	30.2%	-0.42 [-0.92, 0.08]	
Total (95% CI)			574			564	100.0%	-0.11 [-0.58, 0.36]	-
Heterogeneity: Tau ² = Test for overall effect	= 0.12; 0 :: Z = 0.4	Chi² = 46 (P =	7.92, c = 0.64)						

Packed red blood cell transfusion (relax_d2)

	Higher PEEP Lower PEEP						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Collier 2002	0.8	1.4	40	1.1	1.6	44	14.7%	-0.30 [-0.94, 0.34]	
Relax 2020	1.3	0.7	493	1.3	0.7	476	63.8%	0.00 [-0.09, 0.09]	
Zurich 1982	0.33	0.87	41	0.75	1.42	44	21.5%	-0.42 [-0.92, 0.08]	
Total (95% CI)			574			564	100.0%	-0.13 [-0.41, 0.14]	•
Heterogeneity: Tau ² =	= 0.03; (Chi ² =	3.42, c						
Test for overall effect	Z = 0.9	95 (P =	= 0.34)						Favours higher PEEP Favours lower PEEP

PaO2/FiO2 (korovesi_d1-manzano_basal-relax_afterrand)

	Higl	ner PE	PEEP Lower PEEP					Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	8.9%	-30.00 [-90.75, 30.75]	
Korovesi 2011	481	90	15	442	79	12	8.4%	39.00 [-24.81, 102.81]	
Koutsoukou 2006	409	65	11	437	74	10	9.1%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	13.5%	58.00 [21.61, 94.39]	_
Lesur 2010	293	135	30	228	67	33	10.1%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Ma 2014	196	45	60	134	22	60	18.1%	62.00 [49.33, 74.67]	
Manzano 2008	392	104	64	375	79	63	14.4%	17.00 [-15.09, 49.09]	
Relax 2020	230	140	493	216	124	476	17.5%	14.00 [-2.64, 30.64]	
Total (95% CI)			732			712	100.0%	28.60 [3.69, 53.50]	◆
Heterogeneity: Tau ² =	= 851.49	9; Chi	$^{2} = 34.$	77, df =	= 7 (P	< 0.00	01); $I^2 = 8$	30% -	
Test for overall effect	: Z = 2.2	25 (P	= 0.02)						Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d1-manzano_basal-relax_d1)

	Higl	her PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	7.1%	-30.00 [-90.75, 30.75]	
Korovesi 2011	481	90	15	442	79	12	6.6%	39.00 [-24.81, 102.81]	
Koutsoukou 2006	409	65	11	437	74	10	7.3%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]	_
Lesur 2010	293	135	30	228	67	33	8.5%	65.00 [11.56, 118.44]	
Ma 2014	196	45	60	134	22	60	21.8%	62.00 [49.33, 74.67]	
Manzano 2008	392	104	64	375	79	63	14.5%	17.00 [-15.09, 49.09]	
Relax 2020	272	126	493	226	101	476	21.2%	46.00 [31.65, 60.35]	
Total (95% CI)			732			712	100.0%	37.18 [17.84, 56.53]	◆
Heterogeneity: Tau ² =	= 405.32	2; Chi ²	$^{2} = 21.5$	56, df =	: 7 (P	= 0.00	3); I ² = 68	3%	
Test for overall effect	:: Z = 3.7	77 (P :	= 0.000)2)					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d1-manzano_basal-relax_d2)

	Higl	Higher PEEP Lower PEEP						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	7.1%	-30.00 [-90.75, 30.75]			
Korovesi 2011	481	90	15	442	79	12	6.6%	39.00 [-24.81, 102.81]			
Koutsoukou 2006	409	65	11	437	74	10	7.2%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	12.9%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.4%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·		
Ma 2014	196	45	60	134	22	60	21.7%	62.00 [49.33, 74.67]			
Manzano 2008	392	104	64	375	79	63	14.4%	17.00 [-15.09, 49.09]	- +-		
Relax 2020	250	113	493	208	96	476	21.6%	42.00 [28.81, 55.19]			
Total (95% CI)			732			712	100.0%	36.37 [17.09, 55.66]			
Heterogeneity: Tau ² =	= 403.83	L; Chi ⁱ	$^{2} = 22.$	34, df =	7 (P	= 0.002	2); $I^2 = 69$	9% -			
Test for overall effect	:: Z = 3.2	70 (P =	= 0.000)2)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d1-manzano_6h-relax_afterrand)

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	9.0%	-30.00 [-90.75, 30.75]			
Korovesi 2011	481	90	15	442	79	12	8.5%	39.00 [-24.81, 102.81]			
Koutsoukou 2006	409	65	11	437	74	10	9.1%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	13.6%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	10.2%	65.00 [11.56, 118.44]			
Ma 2014	196	45	60	134	22	60	18.3%	62.00 [49.33, 74.67]			
Manzano 2008	356	100	64	332	108	63	13.7%	24.00 [-12.21, 60.21]			
Relax 2020	230	140	493	216	124	476	17.7%	14.00 [-2.64, 30.64]			
Total (95% CI)			732			712	100.0%	29.70 [4.84, 54.56]	-		
Heterogeneity: Tau ² =	= 836.73	3; Chi ^ź	$^{2} = 33.4$	48, df =	= 7 (P	< 0.00	01); $I^2 = 2$	79% -			
Test for overall effect	:: Z = 2.3	34 (P =	= 0.02)						Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d1-manzano_6h-relax_d1)

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	6.9%	-30.00 [-90.75, 30.75]				
Korovesi 2011	481	90	15	442	79	12	6.5%	39.00 [-24.81, 102.81]				
Koutsoukou 2006	409	65	11	437	74	10	7.1%	-28.00 [-87.83, 31.83]				
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]				
Lesur 2010	293	135	30	228	67	33	8.3%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·			
Ma 2014	196	45	60	134	22	60	22.9%	62.00 [49.33, 74.67]				
Manzano 2008	356	100	64	332	108	63	13.1%	24.00 [-12.21, 60.21]				
Relax 2020	272	126	493	226	101	476	22.2%	46.00 [31.65, 60.35]				
Total (95% CI)			732			712	100.0%	38.95 [20.20, 57.70]				
Heterogeneity: Tau ² =	= 358.05	5; Chi ²	= 19.5	52, df =	= 7 (P	= 0.00	7); $I^2 = 64$	4% -				
Test for overall effect	:: Z = 4.0)7 (P ·	< 0.000)1)					Favours lower PEEP Favours higher PEEP			

PaO2/FiO2 (korovesi_d1-manzano_6h-relax_d2)

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	6.9%	-30.00 [-90.75, 30.75]			
Korovesi 2011	481	90	15	442	79	12	6.5%	39.00 [-24.81, 102.81]			
Koutsoukou 2006	409	65	11	437	74	10	7.1%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.3%	65.00 [11.56, 118.44]			
Ma 2014	196	45	60	134	22	60	22.7%	62.00 [49.33, 74.67]			
Manzano 2008	356	100	64	332	108	63	13.0%	24.00 [-12.21, 60.21]			
Relax 2020	250	113	493	208	96	476	22.5%	42.00 [28.81, 55.19]			
Total (95% CI)			732			712	100.0%	38.01 [19.22, 56.81]			
Heterogeneity: Tau ² =	= 363.63	3; Chi ^ż	² = 20.4	46, df =	- 7 (P	= 0.00	5); $I^2 = 66$	5% -			
Test for overall effect	: Z = 3.9	96 (P ·	< 0.000)1)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d1-manzano_d1-relax_afterrand)

	Higl	Higher PEEP Lower PEEP						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	8.8%	-30.00 [-90.75, 30.75]				
Korovesi 2011	481	90	15	442	79	12	8.3%	39.00 [-24.81, 102.81]				
Koutsoukou 2006	409	65	11	437	74	10	8.9%	-28.00 [-87.83, 31.83]				
Lago Borges 2013	328	85	45	270	90	44	13.5%	58.00 [21.61, 94.39]				
Lesur 2010	293	135	30	228	67	33	10.0%	65.00 [11.56, 118.44]				
Ma 2014	196	45	60	134	22	60	18.4%	62.00 [49.33, 74.67]				
Manzano 2008	362	101	64	309	86	63	14.4%	53.00 [20.39, 85.61]				
Relax 2020	230	140	493	216	124	476	17.7%	14.00 [-2.64, 30.64]	+-			
Total (95% CI)			732			712	100.0%	33.94 [9.58, 58.29]	-			
Heterogeneity: Tau ² =	= 798.91	1; Chi ^ż	² = 32.9	94, df =	- 7 (P	< 0.00	01); $I^2 = 7$	79% -				
Test for overall effect	: Z = 2.7	73 (P =	= 0.006	5)					Favours lower PEEP Favours higher PEEP			

PaO2/FiO2 (korovesi_d1-manzano_d1-relax_d1)

	Higł	Higher PEEP Lower PEEP						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	6.4%	-30.00 [-90.75, 30.75]				
Korovesi 2011	481	90	15	442	79	12	5.9%	39.00 [-24.81, 102.81]				
Koutsoukou 2006	409	65	11	437	74	10	6.5%	-28.00 [-87.83, 31.83]				
Lago Borges 2013	328	85	45	270	90	44	12.5%	58.00 [21.61, 94.39]				
Lesur 2010	293	135	30	228	67	33	7.7%	65.00 [11.56, 118.44]				
Ma 2014	196	45	60	134	22	60	23.9%	62.00 [49.33, 74.67]				
Manzano 2008	362	101	64	309	86	63	14.0%	53.00 [20.39, 85.61]				
Relax 2020	272	126	493	226	101	476	23.1%	46.00 [31.65, 60.35]				
Total (95% CI)			732			712	100.0%	43.71 [26.22, 61.20]	•			
Heterogeneity: Tau ² =	= 291.19); Chi ²	$^{2} = 17.4$	42, df =	= 7 (P	= 0.01)); $I^2 = 60\%$					
Test for overall effect	Z = 4.9	90 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP			

PaO2/FiO2 (korovesi_d1-manzano_d1-relax_d2)

	High	Higher PEEP Lower PEEP						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	6.5%	-30.00 [-90.75, 30.75]				
Korovesi 2011	481	90	15	442	79	12	6.0%	39.00 [-24.81, 102.81]				
Koutsoukou 2006	409	65	11	437	74	10	6.6%	-28.00 [-87.83, 31.83]				
Lago Borges 2013	328	85	45	270	90	44	12.6%	58.00 [21.61, 94.39]	_			
Lesur 2010	293	135	30	228	67	33	7.8%	65.00 [11.56, 118.44]				
Ma 2014	196	45	60	134	22	60	23.4%	62.00 [49.33, 74.67]				
Manzano 2008	362	101	64	309	86	63	14.0%	53.00 [20.39, 85.61]				
Relax 2020	250	113	493	208	96	476	23.2%	42.00 [28.81, 55.19]				
Total (95% CI)			732			712	100.0%	42.56 [24.81, 60.31]	•			
Heterogeneity: Tau ² =	= 308.74	l; Chi ⁱ	$^{2} = 18.0$	58, df =	7 (P	= 0.00	9); $I^2 = 63$	3%				
Test for overall effect	: Z = 4.7	70 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP			

PaO2/FiO2 (korovesi_d5-manzano_basal-relax_afterrand)

	Higl	Higher PEEP Lower PEEP						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	8.9%	-30.00 [-90.75, 30.75]	
Korovesi 2011	441	97	15	407	71	12	8.5%	34.00 [-29.43, 97.43]	
Koutsoukou 2006	409	65	11	437	74	10	9.1%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	13.5%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	10.1%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Ma 2014	196	45	60	134	22	60	18.1%	62.00 [49.33, 74.67]	
Manzano 2008	392	104	64	375	79	63	14.4%	17.00 [-15.09, 49.09]	
Relax 2020	230	140	493	216	124	476	17.5%	14.00 [-2.64, 30.64]	+ - -
Total (95% CI)			732			712	100.0%	28.18 [3.27, 53.08]	
Heterogeneity: Tau ² = Test for overall effect	= 852.22 :: Z = 2.2	2; Chi ² 22 (P =	² = 34.8 = 0.03)	30, df =	- 7 (P	< 0.00	01); $I^2 = 8$		-100 -50 0 50 100 Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d5-manzano_basal-relax_d1)

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	7.1%	-30.00 [-90.75, 30.75]			
Korovesi 2011	441	97	15	407	71	12	6.7%	34.00 [-29.43, 97.43]			
Koutsoukou 2006	409	65	11	437	74	10	7.3%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.5%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·		
Ma 2014	196	45	60	134	22	60	21.7%	62.00 [49.33, 74.67]			
Manzano 2008	392	104	64	375	79	63	14.5%	17.00 [-15.09, 49.09]	- +		
Relax 2020	272	126	493	226	101	476	21.2%	46.00 [31.65, 60.35]			
Total (95% CI)			732			712	100.0%	36.82 [17.43, 56.20]			
Heterogeneity: Tau ² =	= 408.54	1; Chi ⁱ	$^{2} = 21.0$	58, df =	= 7 (P	= 0.00	3); $I^2 = 68$	3% -			
Test for overall effect	:: Z = 3.2	72 (P :	= 0.000)2)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d5-manzano_basal-relax_d2)

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	7.1%	-30.00 [-90.75, 30.75]			
Korovesi 2011	441	97	15	407	71	12	6.7%	34.00 [-29.43, 97.43]			
Koutsoukou 2006	409	65	11	437	74	10	7.3%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	12.9%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.4%	65.00 [11.56, 118.44]			
Ma 2014	196	45	60	134	22	60	21.7%	62.00 [49.33, 74.67]			
Manzano 2008	392	104	64	375	79	63	14.4%	17.00 [-15.09, 49.09]			
Relax 2020	250	113	493	208	96	476	21.5%	42.00 [28.81, 55.19]			
Total (95% CI)			732			712	100.0%	36.01 [16.70, 55.33]	-		
Heterogeneity: Tau ² =	= 406.40); Chi ²	² = 22.4	44, df =	7 (P	= 0.00	2); $I^2 = 69$	9%			
Test for overall effect	:: Z = 3.0	55 (P =	= 0.000)3)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d5-manzano_6h-relax_afterrand)

	Hig	Higher PEEP			Higher PEEP Lower PEEP						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI					
Holland 2007	307	82	14	337	82	14	8.9%	-30.00 [-90.75, 30.75]						
Korovesi 2011	441	97	15	407	71	12	8.5%	34.00 [-29.43, 97.43]						
Koutsoukou 2006	409	65	11	437	74	10	9.1%	-28.00 [-87.83, 31.83]						
Lago Borges 2013	328	85	45	270	90	44	13.6%	58.00 [21.61, 94.39]						
Lesur 2010	293	135	30	228	67	33	10.2%	65.00 [11.56, 118.44]						
Ma 2014	196	45	60	134	22	60	18.3%	62.00 [49.33, 74.67]						
Manzano 2008	356	100	64	332	108	63	13.6%	24.00 [-12.21, 60.21]						
Relax 2020	230	140	493	216	124	476	17.7%	14.00 [-2.64, 30.64]	+					
Total (95% CI)			732			712	100.0%	29.28 [4.41, 54.14]						
Heterogeneity: Tau ² =	= 837.74	1; Chi ⁱ	$^{2} = 33.1$	53, df =	= 7 (P	< 0.00	01); $I^2 = 7$	- 79%						
Test for overall effect	z = 2.2	31 (P	= 0.02)						Favours lower PEEP Favours higher PEEP					

PaO2/FiO2 (korovesi_d5-manzano_6h-relax_d1)

	Higl	Higher PEEP			/er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	7.0%	-30.00 [-90.75, 30.75]			
Korovesi 2011	441	97	15	407	71	12	6.5%	34.00 [-29.43, 97.43]			
Koutsoukou 2006	409	65	11	437	74	10	7.1%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.3%	65.00 [11.56, 118.44]			
Ma 2014	196	45	60	134	22	60	22.8%	62.00 [49.33, 74.67]			
Manzano 2008	356	100	64	332	108	63	13.1%	24.00 [-12.21, 60.21]			
Relax 2020	272	126	493	226	101	476	22.2%	46.00 [31.65, 60.35]			
Total (95% CI)			732			712	100.0%	38.58 [19.78, 57.38]			
Heterogeneity: Tau ² =	= 361.62	2; Chi ⁱ	$^{2} = 19.0$	55, df =	= 7 (P	= 0.00	6); $I^2 = 6^2$	1% -			
Test for overall effect	:: Z = 4.0	02 (P	< 0.000)1)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d5-manzano_6h-relax_d2)

	Higl	Higher PEEP Low				EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	7.0%	-30.00 [-90.75, 30.75]	
Korovesi 2011	441	97	15	407	71	12	6.5%	34.00 [-29.43, 97.43]	
Koutsoukou 2006	409	65	11	437	74	10	7.1%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	13.0%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	8.3%	65.00 [11.56, 118.44]	
Ma 2014	196	45	60	134	22	60	22.6%	62.00 [49.33, 74.67]	
Manzano 2008	356	100	64	332	108	63	13.0%	24.00 [-12.21, 60.21]	
Relax 2020	250	113	493	208	96	476	22.4%	42.00 [28.81, 55.19]	
Total (95% CI)			732			712	100.0%	37.65 [18.82, 56.49]	
Heterogeneity: Tau ² =	= 366.52	2; Chi ⁱ	$^{2} = 20.1$	57, df =	= 7 (P	= 0.00	4); $I^2 = 66$	5% -	
Test for overall effect	:: Z = 3.9	92 (P ·	< 0.000)1)					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d5-manzano_d1-relax_afterrand)

	Higher PEEP			Low	/er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	8.8%	-30.00 [-90.75, 30.75]			
Korovesi 2011	441	97	15	407	71	12	8.4%	34.00 [-29.43, 97.43]			
Koutsoukou 2006	409	65	11	437	74	10	8.9%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	13.5%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	10.0%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·		
Ma 2014	196	45	60	134	22	60	18.4%	62.00 [49.33, 74.67]			
Manzano 2008	362	101	64	309	86	63	14.3%	53.00 [20.39, 85.61]			
Relax 2020	230	140	493	216	124	476	17.7%	14.00 [-2.64, 30.64]	+ ■		
Total (95% CI)			732			712	100.0%	33.51 [9.15, 57.88]	-		
Heterogeneity: Tau ² =	= 800.47	7; Chi ²	$^{2} = 33.0$	00, df =	= 7 (P	< 0.00	01); $I^2 = 7$	79% -			
Test for overall effect	z = 2.3	70 (P =	= 0.007	7)					-100 -50 0 50 100 Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (korovesi_d5-manzano_d1-relax_d1)

	Higl	ner PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	6.4%	-30.00 [-90.75, 30.75]	
Korovesi 2011	441	97	15	407	71	12	6.0%	34.00 [-29.43, 97.43]	
Koutsoukou 2006	409	65	11	437	74	10	6.5%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	12.5%	58.00 [21.61, 94.39]	_
Lesur 2010	293	135	30	228	67	33	7.7%	65.00 [11.56, 118.44]	
Ma 2014	196	45	60	134	22	60	23.8%	62.00 [49.33, 74.67]	
Manzano 2008	362	101	64	309	86	63	14.0%	53.00 [20.39, 85.61]	_
Relax 2020	272	126	493	226	101	476	23.0%	46.00 [31.65, 60.35]	
Total (95% CI)			732			712	100.0%	43.35 [25.80, 60.91]	
Heterogeneity: Tau ² =	= 295.15	5; Chi ²	$^{2} = 17.5$	57, df =	7 (P	= 0.01); $I^2 = 60\%$	۰ ۲	
Test for overall effect	:: Z = 4.8	84 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d5-manzano_d1-relax_d2)

	Higl	her PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	6.5%	-30.00 [-90.75, 30.75]	
Korovesi 2011	441	97	15	407	71	12	6.1%	34.00 [-29.43, 97.43]	
Koutsoukou 2006	409	65	11	437	74	10	6.6%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	12.6%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	7.8%	65.00 [11.56, 118.44]	
Ma 2014	196	45	60	134	22	60	23.3%	62.00 [49.33, 74.67]	
Manzano 2008	362	101	64	309	86	63	14.0%	53.00 [20.39, 85.61]	
Relax 2020	250	113	493	208	96	476	23.1%	42.00 [28.81, 55.19]	
Total (95% CI)			732			712	100.0%	42.22 [24.41, 60.02]	•
Heterogeneity: Tau ² =	= 311.99	9; Chi ⁱ	$^{2} = 18.3$	81, df =	7 (P	= 0.00	9); $I^2 = 63$	3%	
Test for overall effect	:: Z = 4.0	65 (P	< 0.000	001)					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d1)

	Higl	ner PE	EP	Low	er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Holland 2007	307	82	14	337	82	14	5.9%	-30.00 [-90.75, 30.75]	
Korovesi 2011	481	90	15	442	79	12	5.5%	39.00 [-24.81, 102.81]	
Koutsoukou 2006	409	65	11	437	74	10	6.1%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	12.1%	58.00 [21.61, 94.39]	· · · · · · · · · · · · · · · · · · ·
Lesur 2010	293	135	30	228	67	33	7.2%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Ma 2014	196	45	60	134	22	60	24.8%	62.00 [49.33, 74.67]	
Manzano 2008	359	104	64	301	84	63	13.5%	58.00 [25.15, 90.85]	
Relax 2020	248	112	493	190	84	476	24.9%	58.00 [45.56, 70.44]	
Total (95% CI)			732			712	100.0%	48.05 [31.50, 64.60]	•
Heterogeneity: Tau ² =	= 245.50); Chi ²	² = 16.6	53, df =	7 (P	= 0.02); $I^2 = 58\%$	· ·	
Test for overall effect	:: Z = 5.0	59 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (korovesi_d5)

	Higher PEEP			Low	er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	6.0%	-30.00 [-90.75, 30.75]			
Korovesi 2011	441	97	15	407	71	12	5.6%	34.00 [-29.43, 97.43]			
Koutsoukou 2006	409	65	11	437	74	10	6.1%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	12.1%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	7.3%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·		
Ma 2014	196	45	60	134	22	60	24.7%	62.00 [49.33, 74.67]			
Manzano 2008	359	104	64	301	84	63	13.6%	58.00 [25.15, 90.85]			
Relax 2020	248	112	493	190	84	476	24.8%	58.00 [45.56, 70.44]			
Total (95% CI)			732			712	100.0%	47.68 [31.04, 64.32]	•		
Heterogeneity: Tau ² =	= 250.32	2; Chi ²	² = 16.8	32, df =	7 (P	= 0.02); $I^2 = 5.89$	6 -			
Test for overall effect	:: Z = 5.0	52 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (manzano_basal)

	Higher PEEP			Low	er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	6.9%	-30.00 [-90.75, 30.75]			
Korovesi 2011	498	75	15	420	73	12	7.7%	78.00 [21.91, 134.09]			
Koutsoukou 2006	409	65	11	437	74	10	7.0%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	12.7%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.2%	65.00 [11.56, 118.44]			
Ma 2014	196	45	60	134	22	60	21.6%	62.00 [49.33, 74.67]			
Manzano 2008	392	104	64	375	79	63	14.2%	17.00 [-15.09, 49.09]			
Relax 2020	248	112	493	190	84	476	21.7%	58.00 [45.56, 70.44]			
Total (95% CI)			732			712	100.0%	43.04 [24.13, 61.95]	•		
Heterogeneity: Tau ² =	= 389.19); Chi ²	= 22.4	49, df =	7 (P	= 0.00	2); $I^2 = 69$	9% -			
Test for overall effect	:: Z = 4.4	46 (P	< 0.000)01)					-100 -50 0 50 100 Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (manzano_6h)

	Higher PEEP			Low	/er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Holland 2007	307	82	14	337	82	14	6.6%	-30.00 [-90.75, 30.75]	· · · · · · · · · · · · · · · · · · ·		
Korovesi 2011	498	75	15	420	73	12	7.4%	78.00 [21.91, 134.09]	· · · · · · · · · · · · · · · · · · ·		
Koutsoukou 2006	409	65	11	437	74	10	6.8%	-28.00 [-87.83, 31.83]			
Lago Borges 2013	328	85	45	270	90	44	12.6%	58.00 [21.61, 94.39]			
Lesur 2010	293	135	30	228	67	33	8.0%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·		
Ma 2014	196	45	60	134	22	60	22.9%	62.00 [49.33, 74.67]			
Manzano 2008	356	100	64	332	108	63	12.7%	24.00 [-12.21, 60.21]			
Relax 2020	248	112	493	190	84	476	23.0%	58.00 [45.56, 70.44]			
Total (95% CI)			732			712	100.0%	44.98 [26.84, 63.12]	•		
Heterogeneity: Tau ² =	= 332.89	9; Chi ²	$^{2} = 19.9$	92, df =	= 7 (P	= 0.00	6); $I^2 = 65$	5% -			
Test for overall effect	:: Z = 4.8	86 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP		

PaO2/FiO2 (manzano_d1)

	Higl	Low	er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	5.9%	-30.00 [-90.75, 30.75]	
Korovesi 2011	498	75	15	420	73	12	6.7%	78.00 [21.91, 134.09]	
Koutsoukou 2006	409	65	11	437	74	10	6.0%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	12.0%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	7.2%	65.00 [11.56, 118.44]	
Ma 2014	196	45	60	134	22	60	24.3%	62.00 [49.33, 74.67]	
Manzano 2008	362	101	64	309	86	63	13.5%	53.00 [20.39, 85.61]	
Relax 2020	248	112	493	190	84	476	24.5%	58.00 [45.56, 70.44]	
Total (95% CI)			732			712	100.0%	49.78 [33.24, 66.32]	•
Heterogeneity: Tau ² =	= 250.60); Chi ²	$^{2} = 16.9$	94, df =	7 (P	= 0.02); $I^2 = 59\%$	6 -	
Test for overall effect	: Z = 5.9	Э́О (Р -	< 0.000	(0,1)					
		(.		/					Favours lower PEEP Favours higher PEEP

PaO2/FiO2 (relax_afterrand)

	Higher PEEP			Lower PEEP Mean Difference					Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	8.8%	-30.00 [-90.75, 30.75]	
Korovesi 2011	498	75	15	420	73	12	9.6%	78.00 [21.91, 134.09]	· · · · · · · · · · · · · · · · · · ·
Koutsoukou 2006	409	65	11	437	74	10	8.9%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	13.4%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	10.0%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Ma 2014	196	45	60	134	22	60	17.9%	62.00 [49.33, 74.67]	
Manzano 2008	359	104	64	301	84	63	14.1%	58.00 [25.15, 90.85]	· · · · · · · · · · · · · · · · · · ·
Relax 2020	230	140	493	216	124	476	17.3%	14.00 [-2.64, 30.64]	⊢
Total (95% CI)			732			712	100.0%	38.26 [13.53, 62.99]	-
Heterogeneity: Tau ² =	= 847.41	L; Chi²	= 34.7	77, df =	7 (P	< 0.00	01); $I^2 = 8$		
Test for overall effect	: Z = 3.0)3 (P =	= 0.002	2)					Favours lower PEEP Favours higher PEEP
Sensitivity analysis (timing of measurement)

PaO2/FiO2 (relax_d1)

	Hig	Higher PEEP Lower PEEP						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2007	307	82	14	337	82	14	6.4%	-30.00 [-90.75, 30.75]	
Korovesi 2011	498	75	15	420	73	12	7.2%	78.00 [21.91, 134.09]	
Koutsoukou 2006	409	65	11	437	74	10	6.6%	-28.00 [-87.83, 31.83]	
Lago Borges 2013	328	85	45	270	90	44	12.5%	58.00 [21.61, 94.39]	
Lesur 2010	293	135	30	228	67	33	7.8%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Ma 2014	196	45	60	134	22	60	23.2%	62.00 [49.33, 74.67]	
Manzano 2008	359	104	64	301	84	63	13.8%	58.00 [25.15, 90.85]	
Relax 2020	272	126	493	226	101	476	22.5%	46.00 [31.65, 60.35]	
Total (95% CI)			732			712	100.0%	46.91 [29.19, 64.62]	•
Heterogeneity: Tau ² =	= 309.89	9; Chi ⁱ	$^{2} = 18.1$	18, df =	= 7 (P	= 0.01); $I^2 = 61\%$	6 -	
Test for overall effect	: Z = 5.	19 (P -	< 0.000	-100 -50 0 50 100					
		•							ravours lower PEEP Favours nigher PEEP

Sensitivity analysis (timing of measurement)

PaO2/FiO2 (relax_d2)

	Higl	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	6.6%	-30.00 [-90.75, 30.75]				
Korovesi 2011	498	75	15	420	73	12	7.4%	78.00 [21.91, 134.09]	· · · · · · · · · · · · · · · · · · ·			
Koutsoukou 2006	409	65	11	437	74	10	6.7%	-28.00 [-87.83, 31.83]				
Lago Borges 2013	328	85	45	270	90	44	12.5%	58.00 [21.61, 94.39]				
Lesur 2010	293	135	30	228	67	33	7.9%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·			
Ma 2014	196	45	60	134	22	60	22.7%	62.00 [49.33, 74.67]				
Manzano 2008	359	104	64	301	84	63	13.8%	58.00 [25.15, 90.85]				
Relax 2020	250	113	493	208	96	476	22.5%	42.00 [28.81, 55.19]				
Total (95% CI)			732			712	100.0%	45.79 [27.74, 63.85]	•			
Heterogeneity: Tau ² =	= 332.54	4; Chi ²	² = 19.0	58, df =	7 (P	= 0.00	6); $I^2 = 64$					
Test for overall effect	:: Z = 4.9	97 (P ·	< 0.000	001)					Favours lower PEEP Favours higher PEEP			

Hospital mortality

	Higher	PEEP	Lower	PEEP		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Collier 2002	1	40	1	44	0.6%	1.10 [0.07, 18.23]	· · · · · · · · · · · · · · · · · · ·
Dyhr 2002	0	7	0	8		Not estimable	
Lesur 2010	12	30	16	33	4.8%	0.71 [0.26, 1.93]	
Manzano 2008	19	64	16	63	7.9%	1.24 [0.57, 2.71]	•
Michalopoulos 1998	0	21	0	22		Not estimable	
Nelson 1987	5	20	6	18	2.4%	0.67 [0.16, 2.73]	
Pepe 1984	13	44	18	48	6.3%	0.70 [0.29, 1.67]	
Relax 2020	208	489	185	472	72.2%	1.15 [0.89, 1.49]	
Weigelt 1979	16	45	17	34	5.8%	0.55 [0.22, 1.37]	
Total (95% CI)		760		742	100.0%	1.03 [0.83, 1.29]	•
Total events	274		259				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 4.3$	8, df = 6	(P = 0.	62); $I^2 = 0$		
Test for overall effect:	Z = 0.30	(P=0.	76)		.,		0.1 0.2 0.5 1 2 5 10 Favours higher PEEP Favours lower PEEP

Hypoxemia

	Higher PEEP Low			PEEP		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl		
Lago Borges 2013	19	45	30	44	23.9%	0.34 [0.14, 0.81]				
Manzano 2008	12	64	34	63	25.0%	0.20 [0.09, 0.44]		_		
Michalopoulos 1998	2	21	2	22	10.0%	1.05 [0.13, 8.24]				
Pepe 1984	1	44	4	48	8.9%	0.26 [0.03, 2.38]				
Relax 2020	87	493	98	476	32.2%	0.83 [0.60, 1.14]				
Total (95% CI)		667		653	100.0%	0.43 [0.20, 0.94]				
Total events	121		168							
Heterogeneity: Tau ² =	0.46; Chi	$i^2 = 13.$	68, df = -	4 (P = 0)).008); I ²	= 71%			100	
Test for overall effect:	Z = 2.13	(P=0)	03)				0.01	Favours higher PEEP Favours lower PEEP	100	

Atelectasis

	Higher	PEEP	Lower	PEEP		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Good 1979	9	10	12	14	2.8%	1.50 [0.12, 19.24]	
Manzano 2008	12	64	17	63	26.3%	0.62 [0.27, 1.44]	
Michalopoulos 1998	2	21	2	22	4.4%	1.05 [0.13, 8.24]	
Pepe 1984	27	44	23	48	26.8%	1.73 [0.75, 3.96]	
Relax 2020	15	493	20	476	39.7%	0.72 [0.36, 1.41]	
Total (95% CI)		632		623	100.0%	0.91 [0.59, 1.40]	-
Total events	65		74				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 3.7$	1, $df = 4$	(P = 0.4)	45); $I^2 = 0$	0%	
Test for overall effect:	Z = 0.44	(P=0)	66)				Favours higher PEEP Favours lower PEEP

Barotrauma

	Higher PEEP Lower PEEP					Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Good 1979	0	10	0	14		Not estimable	
Manzano 2008	1	64	5	63	5.1%	0.18 [0.02, 1.62]	
Michalopoulos 1998	0	21	0	22		Not estimable	
Nelson 1987	1	20	0	18	2.3%	2.85 [0.11, 74.38]	
Pepe 1984	19	44	24	48	35.6%	0.76 [0.33, 1.73]	
Relax 2020	12	493	19	476	44.7%	0.60 [0.29, 1.25]	
Weigelt 1979	5	45	4	34	12.3%	0.94 [0.23, 3.79]	
Total (95% CI)		697		675	100.0%	0.67 [0.41, 1.10]	•
Total events	38		52				
Heterogeneity: Tau ² =	0.00; Chi	$^{2} = 2.5$	1, df = 4	(P = 0.6)	54); I ² = (0%	
Test for overall effect:	Z = 1.58	(P = 0.1)	11)				Favours higher PEEP Favours lower PEEP

Ventilator-associated pneumonia

	Higher	PEEP	Lower	PEEP		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
Manzano 2008	6	64	16	63	38.5%	0.30 [0.11, 0.84]	
Pepe 1984	4	44	6	48	26.6%	0.70 [0.18, 2.67]	
Relax 2020	7	493	6	476	34.9%	1.13 [0.38, 3.38]	
Total (95% CI)		601		587	100.0%	0.60 [0.27, 1.35]	-
Total events Heterogeneity: Tau ² = Test for overall effect	17 = 0.18; Ch :: Z = 1.23	$i^2 = 3.0$ (P = 0.1)	28)5, df = 2 .22)	: (P = 0.	.22); I ² =	34%	0.005 0.1 1 10 200 Favours higher PEEP Favours lower PEEP

ARDS

	Higher PEEP		Lower PEEP			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
Korovesi 2016	0	15	0	12		Not estimable			
Koutsoukou 2006	0	11	1	10	2.8%	0.28 [0.01, 7.57]			
Manzano 2008	3	64	9	63	15.5%	0.30 [0.08, 1.15]			
Pepe 1984	11	44	13	48	29.9%	0.90 [0.35, 2.28]			
Relax 2020	5	493	13	476	24.9%	0.36 [0.13, 1.03]			
Weigelt 1979	9	45	18	34	26.9%	0.22 [0.08, 0.60]		_	
Total (95% CI)		672		643	100.0%	0.40 [0.23, 0.70]		•	
Total events	28		54						
Heterogeneity: Tau ² =	= 0.05; Ch	$i^2 = 4.4$	9, df = 4	P = 0.	34); I ² =	11%			
Test for overall effect	: Z = 3.20	(P = 0.	001)				0.01	Favours higher PEEP Favours lower PEEP	00

Hypotension

	Higher PEEP Lower PEEP			PEEP		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Feeley 1975	0	12	0	13		Not estimable	
Good 1979	0	10	0	14		Not estimable	
Lesur 2010	16	30	16	33	84.2%	1.21 [0.45, 3.27]	— —
Pepe 1984	1	44	0	48	7.9%	3.34 [0.13, 84.28]	
Weigelt 1979	1	45	0	34	7.9%	2.33 [0.09, 58.88]	
Total (95% CI)		141		142	100.0%	1.39 [0.56, 3.44]	
Total events	18		16				
Heterogeneity: Tau ² =	= 0.00; Cł	$ni^2 = 0.4$	46, df = 2	P = 0.	80); I ² =	0%	
Test for overall effect	: Z = 0.70	(P = 0)	.48)				Favours higher PEEP Favours lower PEEP

ICU mortality

	Higher PEEP Lower PE			PEEP		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Dyhr 2002	0	7	0	8		Not estimable	
Feeley 1975	2	12	1	13	1.0%	2.40 [0.19, 30.52]	
Korovesi 2011	3	15	4	12	2.1%	0.50 [0.09, 2.86]	
Nelson 1987	4	20	4	18	2.7%	0.88 [0.18, 4.17]	
Relax 2020	185	492	163	476	94.2%	1.16 [0.89, 1.51]	
Total (95% CI)		546		527	100.0%	1.14 [0.88, 1.47]	•
Total events	194		172				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 1.3$	31, df = 3	B (P = 0.	73); I ² =	0%	
Test for overall effect	: Z = 0.98	P = 0	.33)	Favours higher PEEP Favours lower PEEP			

28-day mortality

	Higher	Higher PEEP Lower PEEP				Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Lesur 2010	9	30	14	33	29.9%	0.58 [0.21, 1.65]			
Ma 2014	15	60	39	60	32.8%	0.18 [0.08, 0.40]			
Relax 2020	207	493	183	476	37.3%	1.16 [0.90, 1.50]	• • • • • • • • • • • • • • • • • • •		
Total (95% CI)		583		569	100.0%	0.51 [0.15, 1.77]	-		
Total events	231		236						
Heterogeneity: Tau ² =	= 1.06; Ch	$i^2 = 20$.29, df =	2 (P < 0	0.0001); I	$^{2} = 90\%$			
Test for overall effect	Z = 1.06	(P = 0)	29)				Favours higher PEEP Favours lower PEEP		

Hospital mortality

	Higher PEEP Lower PEEP					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Collier 2002	1	40	1	44	0.3%	1.10 [0.07, 17.01]	· · · · · · · · · · · · · · · · · · ·
Lesur 2010	12	30	16	33	6.4%	0.82 [0.47, 1.45]	
Manzano 2008	19	64	16	63	6.3%	1.17 [0.66, 2.06]	<u> </u>
Relax 2020	208	489	185	472	87.0%	1.09 [0.93, 1.26]	•
Total (95% CI)		623		612	100.0%	1.07 [0.93, 1.24]	•
Total events	240		218				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.9$	95, df = 3	0%			
Test for overall effect	: Z = 0.95	(P=0)	34)		Favours higher PEEP Favours lower PEEP		

PaO2/FiO2

	Higl	ier PE	EP	Low	er PE	EP		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	307	82	14	337	82	14	5.0%	-30.00 [-90.75, 30.75]				
Korovesi 2011	498	75	15	420	73	12	5.8%	78.00 [21.91, 134.09]				
Lesur 2010	293	135	30	228	67	33	6.3%	65.00 [11.56, 118.44]				
Ma 2014	196	45	60	134	22	60	34.4%	62.00 [49.33, 74.67]				
Manzano 2008	359	104	64	301	84	63	13.7%	58.00 [25.15, 90.85]				
Relax 2020	248	112	493	190	84	476	34.8%	58.00 [45.56, 70.44]				
Total (95% CI)			676			658	100.0%	56.55 [42.12, 70.98]	•			
Heterogeneity: Tau ² = Test for overall effect	= 115.66 :: Z = 7.6	5; Chi ² 58 (P -	² = 8.9 < 0.000	– <u>I I I I I</u> – 100 – 50 0 50 100 Favours lower PEEP Favours higher PEEP								

Hypoxemia

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Manzano 2008	12	64	34	63	46.1%	0.35 [0.20, 0.61]	_ _	
Relax 2020	87	493	98	476	53.9%	0.86 [0.66, 1.11]		
Total (95% CI)		557		539	100.0%	0.57 [0.23, 1.37]		
Total events	99		132					
Heterogeneity: Tau ² =	= 0.36; Ch	$i^2 = 8.2$	25, df = 1	(P = 0.	.004); I ² =	- 88%		
Test for overall effect	: Z = 1.27	(P = 0.	21)				Favours higher PEEP Favours lower PEEP	20

Atelectasis

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Manzano 2008	12	64	17	63	50.4%	0.69 [0.36, 1.33]	
Relax 2020	15	493	20	476	49.6%	0.72 [0.38, 1.40]	
Total (95% CI)		557		539	100.0%	0.71 [0.45, 1.13]	
Total events	27		37				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$)1, df = 1	(P = 0.	93); I ² =	0%	
Test for overall effect	: Z = 1.45	(P=0.	15)				Favours higher PEEP Favours lower PEEP

Barotrauma

	Higher	PEEP	Lower	PEEP		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl		
Manzano 2008	1	64	5	63	10.1%	0.20 [0.02, 1.64]	•		 		
Relax 2020	12	493	19	476	89.9%	0.61 [0.30, 1.24]			 _		
Total (95% CI)		557		539	100.0%	0.54 [0.28, 1.07]			•		
Total events	13		24								
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.9$	9, df = 1	I (P = 0.	32); I ² =	0%	$\frac{1}{01}$	0.2 0.5	+	<u>-</u> [10
Test for overall effect	: Z = 1.77	(P=0.	08)				0.1	Favours higher PEEP	Favours lower	PEEP	10

Ventilator-associated pneumonia

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% CI		
Manzano 2008	6	64	16	63	54.3%	0.37 [0.15, 0.88]				
Relax 2020	7	493	6	476	45.7%	1.13 [0.38, 3.33]				
Total (95% CI)		557		539	100.0%	0.61 [0.21, 1.83]				
Total events	13		22							
Heterogeneity: Tau ² =	= 0.37; Ch	$i^2 = 2.4$	17, df = 1	(P = 0)	12); $I^2 = 0$	60%	0.01	0.1 1 10	100	
Test for overall effect:	Z = 0.88	P = 0.	.38)					Favours higher PEEP Favours lower PEEP		

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	Higher	PEEP	Lower	PEEP		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl			
Manzano 2008	3	64	9	63	39.8%	0.33 [0.09, 1.16]			_		
Relax 2020	5	493	13	476	60.2%	0.37 [0.13, 1.03]					
Total (95% CI)		557		539	100.0%	0.35 [0.16, 0.78]					
Total events	8		22								
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$)2, df = 1	(P = 0.	.88); I ² =	0%					
Test for overall effect	: Z = 2.57	'(P = 0)	01)				0.02	Favours higher PEEP Favours lower PEEP			

Cardiac index

	Hig	her PE	EP	Low	ver PE	EP	Mean Difference			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI
Collier 2002	3.1	0.86	40	3.1	0.64	44	64.9%	0.00 [-0.33, 0.33]		#
Holland 2007	3	0.6	14	2.9	0.6	14	35.1%	0.10 [-0.34, 0.54]		
Total (95% CI)			54			58	100.0%	0.04 [-0.23, 0.30]		
Heterogeneity: Tau ² = Test for overall effect	= 0.00; 0 : Z = 0.2	Chi² = 26 (P =	0.13, d = 0.79)	df = 1 (F	P = 0.7	72); I ² =	= 0%		+ -1	-0.5 0 0.5 1 Favours lower PEEP Favours higher PEEP

Central venous pressure

	High	er PE	EΡ	Low	er PE	EP		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Holland 2007	9	3	14	9	3	14	33.5%	0.00 [-2.22, 2.22]	_			
Lesur 2010	12.5	1.5	30	10.8	2.9	33	66.5%	1.70 [0.57, 2.83]				
						. –						
Total (95% CI)			44			47	100.0%	1.13 [-0.44, 2.70]				
Heterogeneity: Tau ² =	= 0.64; C	:hi² =	1.79, 0	df = 1 (F	P = 0.	.18); I ²	= 44%	-				
Test for overall effect	: Z = 1.4	1 (P =	= 0.16)						Favours lower PEEP Favours higher PEEP			

Duration of ventilation

	Higher PEEP Lower PEEP						9	Std. Mean Difference	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Collier 2002	409.1	208.6	40	439.3	277.7	44	6.7%	-0.12 [-0.55, 0.31]				
Lesur 2010	9.2	8.8	30	9.2	8.5	33	5.1%	0.00 [-0.49, 0.49]				
Manzano 2008	5.8	6.8	64	6.5	6.2	63	10.2%	-0.11 [-0.45, 0.24]	- <u>+</u>			
Relax 2020	4.8	6.6	493	5.5	7.4	476	78.0%	-0.10 [-0.23, 0.03]	•			
Total (95% CI) Heterogeneity: Tau ² =	= 0.00; 0	Chi² = 0	627 .17. df	= 3 (P =	= 0.98);	616 $I^2 = 0\%$	100.0%	-0.10 [-0.21, 0.01]	+			
Test for overall effect	: Z = 1.7	71 (P =	0.09)		,,				-4 -2 0 2 4 Favours higher PEEP Favours lower PEEP			

ICU stay

	Higl	her PE	EP	Low	ver PE	EP		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Korovesi 2011	17.2	10.1	15	14.4	8.44	12	3.3%	2.80 [-4.19, 9.79]				
Manzano 2008	10.5	9.8	64	12.3	11.4	63	11.8%	-1.80 [-5.50, 1.90]				
Relax 2020	7.2	10.3	493	8.1	11.5	476	85.0%	-0.90 [-2.28, 0.48]				
Total (95% CI)			572			551	100.0%	-0.88 [-2.15, 0.38]	•			
Heterogeneity: Tau ² = Test for overall effect	= 0.00; 0 : Z = 1.3	Chi ² = 37 (P =	1.30, c = 0.17)	df = 2 (F	P = 0.!	52); I ² =	= 0%		-20 -10 0 10 20 Favours higher PEEP Favours lower PEEP			

Hospital stay

	Hig	her PE	EP	Low	/er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Collier 2002	5.7	2.5	40	5.2	1.7	44	55.2%	0.50 [-0.42, 1.42]	+
Manzano 2008	19.5	18.2	64	26.3	22	63	10.3%	-6.80 [-13.83, 0.23]	
Relax 2020	19	21.4	493	19.9	22.1	476	34.5%	-0.90 [-3.64, 1.84]	
Total (95% CI)			597			583	100.0%	-0.73 [-3.21, 1.74]	-
Heterogeneity: Tau ² =	= 2.67; 0	Chi ² =	4.82, c	f = 2 (F	P = 0.0); I ² =	= 59%		
Test for overall effect	Z = 0.5	58 (P =	= 0.56)						Favours higher PEEP Favours lower PEEP

ICU mortality

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Korovesi 2011	3	15	4	12	1.7%	0.60 [0.17, 2.18]	
Relax 2020	185	492	163	476	98.3%	1.10 [0.93, 1.30]	
Total (95% CI)		507		488	100.0%	1.09 [0.92, 1.28]	◆
Total events	188		167				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.8$	3, df = 1	I (P = 0.	36); $I^2 =$	0%	
Test for overall effect	Z = 0.98	(P=0)	33)				Favours higher PEEP Favours lower PEEP

28-day mortality

	Higher PEEP		EEP Lower PEEP			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Lesur 2010	9	30	14	33	28.8%	0.71 [0.36, 1.39]	
Ma 2014	15	60	39	60	33.1%	0.38 [0.24, 0.62]	
Relax 2020	207	493	183	476	38.1%	1.09 [0.94, 1.27]	
Total (95% CI)		583		569	100.0%	0.68 [0.33, 1.40]	
Total events	231		236				
Heterogeneity: Tau ² = 0.35; Chi ² = 17.71, df = 2 (P = 0.0001); I^2 = 89% Test for overall effect: Z = 1.05 (P = 0.30)					0.05 0.2 1 5 20		
		,					Favours nigher PEEP Favours lower PEEP

Online Resource 9. Subgroup Analyses

Subgroup analyses: medical vs. surgical patients

Subgroup analyses according to the inclusion of medical or surgical patients in the studies. No subgroup difference was observed.

Abbreviations: M-H, Mantel–Haenszel; CI, confidence interval; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; IV, inverse variance; A-aDO₂, alveolar-arterial oxygen pressure difference; CVP, central venous pressure; PRBC, packed red blood cell; ICU, intensive care unit.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Hospital mortality	9	1502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
1.1.1 Medical	6	1360	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
1.1.2 Surgical	3	142	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.07, 17.01]
1.2 PaO ₂ /FiO ₂	8	1444	Mean Difference (IV, Random, 95% CI)	50.46 [33.93, 66.99]
1.2.1 Medical	6	1327	Mean Difference (IV, Random, 95% CI)	56.58 [42.29, 70.87]
1.2.2 Surgical	2	117	Mean Difference (IV, Random, 95% CI)	17.50 [-68.47, 103.46]
1.3 A-aDO ₂	4	164	Std. Mean Difference (IV, Random, 95% CI)	-1.62 [-3.12, -0.11]
1.3.1 Medical	2	46	Std. Mean Difference (IV, Random, 95% CI)	-1.33 [-4.58, 1.93]
1.3.2 Surgical	2	118	Std. Mean Difference (IV, Random, 95% CI)	-1.97 [-4.66, 0.73]
1.4 Compliance	3	189	Mean Difference (IV, Random, 95% CI)	8.46 [3.11, 13.82]

1.4.1 Medical	2	100	Mean Difference (IV, Random, 95% CI)	7.41 [-1.78, 16.61]
1.4.2 Surgical	1	89	Mean Difference (IV, Random, 95% CI)	9.00 [2.41, 15.59]
1.5 Hypoxemia	5	1320	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.40, 0.92]
1.5.1 Medical	3	1188	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.16]
1.5.2 Surgical	2	132	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.93]
1.6 Atelectasis	5	1255	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.28]
1.6.1 Medical	3	1188	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.58, 1.46]
1.6.2 Surgical	2	67	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.41]
1.7 Barotrauma	7	1372	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
1.7.1 Medical	5	1305	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
1.7.2 Surgical	2	67	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.8 Hypotension	5	283	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.71, 1.84]
1.8.1 Medical	4	259	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.71, 1.84]
1.8.2 Surgical	1	24	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9 CVP	3	106	Mean Difference (IV, Random, 95% CI)	1.37 [0.38, 2.37]
1.9.1 Medical	1	63	Mean Difference (IV, Random, 95% CI)	1.70 [0.57, 2.83]
1.9.2 Surgical	2	43	Mean Difference (IV, Random, 95% CI)	0.17 [-1.99, 2.33]
1.10 PRBC transfusion	3	1138	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.77, 0.02]

1.10.1 Medical	1	969	Mean Difference (IV, Random, 95% CI)	Not estimable
1.10.2 Surgical	2	169	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.77, 0.02]
1.11 Duration of ventilation	10	1510	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.21]
1.11.1 Medical	6	1301	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.20, 0.02]
1.11.2 Surgical	4	209	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.71, 1.27]
1.12 Hospital stay	5	1245	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.69, 0.66]
1.12.1 Medical	3	1134	Mean Difference (IV, Random, 95% CI)	-2.11 [-5.95, 1.72]
1.12.2 Surgical	2	111	Mean Difference (IV, Random, 95% CI)	0.04 [-0.46, 0.54]
1.13 ICU mortality	5	1073	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
1.13.1 Medical	4	1058	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
1.13.2 Surgical	1	15	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Subgroup analyses: zero end-expiratory pressure (ZEEP) vs. positive end-expiratory pressure (PEEP) different from ZEEP as lower PEEP

Subgroup analyses according to the use of zero end-expiratory pressure (ZEEP) or positive end-expiratory pressure (PEEP) different from ZEEP as lower PEEP in the studies. A significantly lower incidence of hypoxemia with higher PEEP in studies comparing higher PEEP with ZEEP vs. studies comparing higher PEEP different from ZEEP (p = 0.02) was observed.

Abbreviations: M-H, Mantel–Haenszel; CI, confidence interval; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; IV, inverse variance; A-aDO₂, alveolar-arterial oxygen pressure difference; ARDS, acute respiratory distress syndrome; CVP, central venous pressure; PRBC, packed red blood cell; ICU, intensive care unit.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Hospital mortality	9	1502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
2.1.1 ZEEP	6	419	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.12]
2.1.2 Lower PEEP	3	1083	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.25]
2.2 PaO ₂ /FiO ₂	8	1444	Mean Difference (IV, Random, 95% CI)	50.46 [33.93, 66.99]
2.2.1 ZEEP	4	238	Mean Difference (IV, Random, 95% CI)	45.75 [5.42, 86.09]
2.2.2 Lower PEEP	4	1206	Mean Difference (IV, Random, 95% CI)	52.97 [34.89, 71.05]
2.3 A-aDO ₂	4	164	Std. Mean Difference (IV, Random, 95% CI)	-1.62 [-3.12, -0.11]
2.3.1 ZEEP	2	46	Std. Mean Difference (IV, Random, 95% CI)	-1.33 [-4.58, 1.93]
2.3.2 Lower PEEP	2	118	Std. Mean Difference (IV, Random, 95% CI)	-1.97 [-4.66, 0.73]
2.4 Compliance	3	189	Mean Difference (IV, Random, 95% CI)	8.46 [3.11, 13.82]
2.4.1 ZEEP	2	100	Mean Difference (IV, Random, 95% CI)	7.41 [-1.78, 16.61]
2.4.2 Lower PEEP	1	89	Mean Difference (IV, Random, 95% CI)	9.00 [2.41, 15.59]
2.5 Hypoxemia	5	1320	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.40, 0.92]
2.5.1 ZEEP	3	262	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.22, 0.63]
2.5.2 Lower PEEP	2	1058	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.04]
2.6 Atelectasis	5	1255	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.28]

2.6.1 ZEEP	4	286	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.33]
2.6.2 Lower PEEP	1	969	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.38, 1.40]
2.7 Barotrauma	7	1372	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
2.7.1 ZEEP	5	365	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.55, 1.24]
2.7.2 Lower PEEP	2	1007	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.31]
2.8 Ventilator-associated pneumonia	3	1188	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.23]
2.8.1 ZEEP	2	219	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.94]
2.8.2 Lower PEEP	1	969	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.38, 3.33]
2.9 ARDS	6	1315	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.32, 0.78]
2.9.1 ZEEP	5	346	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.92]
2.9.2 Lower PEEP	1	969	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.13, 1.03]
2.10 Cardiac index	3	127	Mean Difference (IV, Random, 95% CI)	0.04 [-0.21, 0.29]
2.10.1 ZEEP	1	15	Mean Difference (IV, Random, 95% CI)	0.10 [-0.78, 0.98]
2.10.2 Lower PEEP	2	112	Mean Difference (IV, Random, 95% CI)	0.04 [-0.23, 0.30]
2.11 CVP	3	106	Mean Difference (IV, Random, 95% CI)	1.37 [0.38, 2.37]
2.11.1 ZEEP	2	78	Mean Difference (IV, Random, 95% CI)	1.72 [0.60, 2.84]
2.11.2 Lower PEEP	1	28	Mean Difference (IV, Random, 95% CI)	0.00 [-2.22, 2.22]
2.12 Postoperative bleeding	2	601	Mean Difference (IV, Random, 95% CI)	26.47 [-99.95, 152.89]

2.12.1 ZEEP	1	517	Mean Difference (IV, Random, 95% CI)	-20.00 [-96.82, 56.82]
2.12.2 Lower PEEP	1	84	Mean Difference (IV, Random, 95% CI)	116.00 [-52.52, 284.52]
2.13 PRBC transfusion	3	1138	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.77, 0.02]
2.13.1 ZEEP	1	85	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.92, 0.08]
2.13.2 Lower PEEP	2	1053	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.94, 0.34]
2.14 Duration of ventilation	10	1510	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.21]
2.14.1 ZEEP	5	318	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.33, 0.63]
2.14.2 Lower PEEP	5	1192	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
2.15 ICU stay	4	1202	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.51, 0.51]
2.15.1 ZEEP	3	233	Mean Difference (IV, Random, 95% CI)	-1.41 [-6.15, 3.32]
2.15.2 Lower PEEP	1	969	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.28, 0.48]
2.16 Hospital stay	5	1245	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.69, 0.66]
2.16.1 ZEEP	1	127	Mean Difference (IV, Random, 95% CI)	-6.80 [-13.83, 0.23]
2.16.2 Lower PEEP	4	1118	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.36, 0.29]
2.17 ICU mortality	5	1073	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
2.17.1 ZEEP	3	67	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.27, 2.52]
2.17.2 Lower PEEP	2	1006	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.93, 1.29]
2.18 28-day mortality	3	1152	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.33, 1.40]

2.18.1 ZEEP	1	63	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.36, 1.39]
2.18.2 Lower PEEP	2	1089	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.24, 1.85]

Subgroup analyses: tidal volume > 8 mL/kg vs. tidal volume < 8 mL/kg

Subgroup analyses according to the use of tidal volumes (TV) greater than or lower than 8 mL/kg in the studies. We observed a significantly lower alveolar-arterial oxygen pressure difference (A-aDO₂) with higher PEEP in studies using tidal volumes > 8 mL/kg vs. studies using tidal volumes < 8 mL/kg (p < 0.01) and a trend towards a reduction of hospital mortality (p = 0.09) and atelectasis (p = 0.08) with higher PEEP in studies using tidal volumes > 8 mL/kg and < 8 mL/kg, respectively. Abbreviations: M-H, Mantel–Haenszel; CI, confidence interval; IV, inverse variance; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Hospital mortality	7	1421	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.90, 1.17]
3.1.1 VT>8	3	255	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.51, 1.10]
3.1.2 VT<8	4	1166	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.93, 1.24]
3.2 A-aDO ₂	4	164	Std. Mean Difference (IV, Random, 95% CI)	-1.62 [-3.12, -0.11]
3.2.1 VT>8	2	54	Std. Mean Difference (IV, Random, 95% CI)	-3.21 [-4.06, -2.36]
3.2.2 VT<8	2	110	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.18, 0.68]
3.3 Compliance	3	189	Mean Difference (IV, Random, 95% CI)	8.46 [3.11, 13.82]
3.3.1 VT>8	1	79	Mean Difference (IV, Random, 95% CI)	3.00 [-14.88, 20.88]

3.3.2 VT<8	2	110	Mean Difference (IV, Random, 95% CI)	9.00 [3.39, 14.61]
3.4 Hypoxemia	4	1277	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.37, 0.92]
3.4.1 VT>8	1	92	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.35]
3.4.2 VT<8	3	1185	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.37, 0.96]
3.5 Atelectasis	4	1212	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.76, 1.32]
3.5.1 VT>8	2	116	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.90, 1.43]
3.5.2 VT<8	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.13]
3.6 Barotrauma	5	1291	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.09]
3.6.1 VT>8	3	195	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.58, 1.32]
3.6.2 VT<8	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.07]
3.7 Ventilator-associated pneumonia	3	1188	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.23]
3.7.1 VT>8	1	92	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.22, 2.41]
3.7.2 VT<8	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.83]
3.8 ARDS	6	1315	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.32, 0.78]
3.8.1 VT>8	2	171	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.24, 1.41]
3.8.2 VT<8	4	1144	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.16, 0.76]
3.9 Hypotension	5	283	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.71, 1.84]
3.9.1 VT>8	4	220	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.29, 25.73]

3.9.2 VT<8	1	63	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.68, 1.79]
3.10 Cardiac index	3	127	Mean Difference (IV, Random, 95% CI)	0.04 [-0.21, 0.29]
3.10.1 VT>8	1	84	Mean Difference (IV, Random, 95% CI)	0.00 [-0.33, 0.33]
3.10.2 VT<8	2	43	Mean Difference (IV, Random, 95% CI)	0.10 [-0.30, 0.50]
3.11 Duration of ventilation	9	1472	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.32, 0.17]
3.11.1 VT>8	5	224	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.44, 0.93]
3.11.2 VT<8	4	1248	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.34, 0.02]
3.12 ICU stay	4	1202	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.51, 0.51]
3.12.1 VT>8	1	79	Mean Difference (IV, Random, 95% CI)	-9.30 [-21.28, 2.68]
3.12.2 VT<8	3	1123	Mean Difference (IV, Random, 95% CI)	-0.88 [-2.15, 0.38]
3.13 Hospital stay	4	1207	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.84, 0.76]
3.13.1 VT>8	2	111	Mean Difference (IV, Random, 95% CI)	0.04 [-0.46, 0.54]
3.13.2 VT<8	2	1096	Mean Difference (IV, Random, 95% CI)	-2.93 [-8.42, 2.56]
3.14 ICU mortality	4	1035	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.29]
3.14.1 VT>8	1	25	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.22, 20.94]
3.14.2 VT<8	3	1010	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]

Subgroup analyses: studies published before 2000 vs. studies published after 2000

Subgroup analyses according to year of publication (before 2000 vs. after 2000). A significantly lower alveolar-arterial oxygen pressure difference (A-aDO₂) with higher PEEP in studies published before 2000 (p < 0.01) was detected. Further, a trend towards lower atelectasis occurrence with higher PEEP in studies published after 2000 (p = 0.08) and towards lower hospital mortality with higher PEEP in studies published before 2000 (p = 0.08) and before 2000 (p = 0.07) was observed.

Abbreviations: IV, inverse variance; CI, confidence interval; M-H, Mantel-Haenszel; ARDS, acute respiratory distress syndrome; PRBC, packed red blood cell; ICU, intensive care unit.

Outcome or Subgroup	Studies	s Participants	Statistical Method	Effect Estimate
4.1 Hospital mortality	9	1502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
4.1.1 >2000	5	1250	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.93, 1.24]
4.1.2 <2000	4	252	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.52, 1.07]
4.2 A-aDO2	4	164	Std. Mean Difference (IV, Random, 95% CI)	-1.62 [-3.12, -0.11]
4.2.1 >2000	2	110	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.18, 0.68]
4.2.2 <2000	2	54	Std. Mean Difference (IV, Random, 95% CI)	-3.21 [-4.06, -2.36]
4.3 Compliance	3	189	Mean Difference (IV, Random, 95% CI)	8.46 [3.11, 13.82]
4.3.1 >2000	2	110	Mean Difference (IV, Random, 95% CI)	9.00 [3.39, 14.61]
4.3.2 <2000	1	79	Mean Difference (IV, Random, 95% CI)	3.00 [-14.88, 20.88]
4.4 Hypoxemia	5	1320	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.40, 0.92]

4.4.1 >2000	3	1185	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.37, 0.96]
4.4.2 <2000	2	135	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.14, 2.41]
4.5 Atelectasis	5	1255	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.28]
4.5.1 >2000	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.13]
4.5.2 <2000	3	159	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.90, 1.43]
4.6 Barotrauma	7	1372	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
4.6.1 >2000	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.07]
4.6.2 <2000	5	276	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.34]
4.7 Ventilator-associated pneumonia	3	1188	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.23]
4.7.1 >2000	2	1096	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.83]
4.7.2 <2000	1	92	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.22, 2.41]
4.8 ARDS	6	1315	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.32, 0.78]
4.8.1 >2000	4	1144	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.16, 0.76]
4.8.2 <2000	2	171	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.24, 1.41]
4.9 Hypotension	5	283	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.71, 1.84]
4.9.1 >2000	1	63	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.68, 1.79]
4.9.2 <2000	4	220	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.29, 25.73]
4.10 Postoperative bleeding	2	601	Mean Difference (IV, Random, 95% CI)	26.47 [-99.95, 152.89]
4.10.1 >2000	1	84	Mean Difference (IV, Random, 95% CI)	116.00 [-52.52, 284.52]
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4.10.2 <2000	1	517	Mean Difference (IV, Random, 95% CI)	-20.00 [-96.82, 56.82]
4.11 PRBC transfusion	3	1138	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.77, 0.02]
4.11.1 >2000	2	1053	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.94, 0.34]
4.11.2 <2000	1	85	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.92, 0.08]
4.12 Duration of ventilation	10	1510	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.27, 0.21]
4.12.1 >2000	5	1332	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.26, -0.01]
4.12.2 <2000	5	178	Std. Mean Difference (IV, Random, 95% CI)	0.43 [-0.35, 1.22]
4.13 ICU stay	4	1202	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.51, 0.51]
4.13.1 >2000	3	1123	Mean Difference (IV, Random, 95% CI)	-0.88 [-2.15, 0.38]
4.13.2 <2000	1	79	Mean Difference (IV, Random, 95% CI)	-9.30 [-21.28, 2.68]
4.14 Hospital stay	5	1245	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.69, 0.66]
4.14.1 >2000	3	1180	Mean Difference (IV, Random, 95% CI)	-0.73 [-3.21, 1.74]
4.14.2 <2000	2	65	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.45, 0.25]
4.15 ICU mortality	5	1073	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
4.15.1 >2000	3	1010	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
4.15.2 <2000	2	63	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.37, 3.24]

Hospital mortality

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl					
7.13.1 Medical												
Lesur 2010	12	30	16	33	5.5%	0.82 [0.47, 1.45]						
Manzano 2008	19	64	16	63	5.5%	1.17 [0.66, 2.06]						
Nelson 1987	5	20	6	18	1.7%	0.75 [0.28, 2.04]						
Pepe 1984	13	44	18	48	5.1%	0.79 [0.44, 1.41]						
Relax 2020	208	489	185	472	75.4%	1.09 [0.93, 1.26]	· · · · · · · · · · · · · · · · · · ·					
Weigelt 1979	16	45	17	34	6.5%	0.71 [0.42, 1.19]						
Subtotal (95% CI)		692		668	99.8%	1.02 [0.89, 1.16]	•					
Total events	273		258									
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.38$, $df = 5$ (P = 0.50); $I^2 = 0\%$												
Test for overall effect:	Z = 0.30	(P=O.	77)									
7 13 2 Surgical												
Collier 2002	1	10	1	4.4	0.20/							
Dubr 2002	1	40	1	44	0.2%	1.10 [0.07, 17.01] Not octimable						
Michalanaulas 1008	0	21	0	0 22		Not estimable						
Subtotal (95% CI)	0	68	0	22 74	0.2%							
Total events	1	00	1	1 -	0.270	1.10 [0.07, 17.01]						
Hotorogonoity: Not an	nlicablo		T									
Test for overall effect:	7 - 0.07	$(\mathbf{P} = 0)$	95)									
rest for overall effect.	2 - 0.07	(r = 0.	33)									
Total (95% CI)		760		742	100.0%	1.02 [0.89, 1.16]	•					
Total events	274		259									
Heterogeneity: Tau ² =	0.00; Chi	$i^2 = 4.3$	9, df = 6									
Test for overall effect:	Z = 0.30	(P = 0.	77)				Eavours higher PEEP Favours lower PEEP					
Test for subgroup diff	erences: 0	Chi ² = 0	ravours inglier reer ravours lower reer									

PaO2/FiO2

	Higł	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
7.1.1 Medical										
Korovesi 2011	498	75	15	420	73	12	6.7%	78.00 [21.91, 134.09]	————	
Koutsoukou 2006	409	65	11	437	74	10	6.0%	-28.00 [-87.83, 31.83]		
Lesur 2010	293	135	30	228	67	33	7.2%	65.00 [11.56, 118.44]		
Ma 2014	196	45	60	134	22	60	24.4%	62.00 [49.33, 74.67]		
Manzano 2008	359	104	64	301	84	63	13.4%	58.00 [25.15, 90.85]		
Relax 2020 Subtotal (95% CI)	248	112	493 673	190	84	476 654	24.5% 82.2%	58.00 [45.56, 70.44] 56.58 [42.29, 70.87]		
Test for overall effect 7.1.2 Surgical	:: Z = 7.7	76 (P	< 0.00	001)						
Holland 2007	307	82	14	337	82	14	5 9%	-30 00 [-90 75 30 75]		
Lago Borges 2013 Subtotal (95% CI)	328	85	45 59	270	90	44 58	12.0% 17.8%	58.00 [21.61, 94.39] 17.50 [-68.47, 103.46]		
Heterogeneity: Tau ² = Test for overall effect	= 3219.3 :: Z = 0.4	39; Ch 40 (P :	ni ² = 5. = 0.69)	93, df =	1 (P	= 0.01)); $I^2 = 832$	%		
Total (95% CI)			732			712	100.0%	50.46 [33.93, 66.99]	•	
Heterogeneity: Tau ²	= 249.71	L; Chi	$^{2} = 16.$	89, df =	7 (P	= 0.02); $I^2 = 592$	<i>—</i>	-200 -100 0 100 200	
Test for overall effect	:: Z = 5.9	98 (P	< 0.00	001)					Favours lower PEEP Favours higher PEEP	
Test for subgroup dif	ferences	s: Chi'	f = 0.7	7, df = 1	l (P =	0.38),	$I^{2} = 0\%$		5	

A-aDO2

	High	er PE	EP	Low	er PE	EP	:	Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
7.2.1 Medical											
Feeley 1975	10	22	12	102	35	13	23.6%	-3.02 [-4.22, -1.81]	+		
Koutsoukou 2006	100	41	11	87	40	10	25.5%	0.31 [-0.55, 1.17]	.+		
Subtotal (95% CI)			23			23	49.1%	-1.33 [-4.58, 1.93]			
Heterogeneity: $Tau^2 = 5.24$; $Chi^2 = 19.38$, $df = 1$ (P < 0.0001); $I^2 = 95\%$											
Test for overall effect	Z = 0.8	80 (P =	= 0.42)								
7.2.2 Surgical											
Lago Borges 2013	117	33	45	139	34	44	27.2%	-0.65 [-1.08, -0.22]			
Marvel 1986	168	10	12	203	10	17	23.7%	-3.40 [-4.60, -2.20]	-		
Subtotal (95% CI)			57			61	50.9%	-1.97 [-4.66, 0.73]	\bullet		
Heterogeneity: Tau ² :	= 3.57; C	:hi² =	17.99	df = 1	(P <	0.0001)); $I^2 = 94\%$	6			
Test for overall effect	:: Z = 1.4	3 (P =	= 0.15)								
							100.00/	1 () () () () () () () () () (
Total (95% CI)			80			84	100.0%	-1.62 [-3.12, -0.11]	\bullet		
Heterogeneity: Tau ² :	= 2.13; C	:hi² =	37.49	, df = 3	(P <	0.0000	1); $I^2 = 92$	2%			
Test for overall effect: Z = 2.10 (P = 0.04)											
Test for subgroup differences: $Chi^2 = 0.09$, $df = 1$ (P = 0.77), $I^2 = 0\%$											

Compliance

	High	ier PE	EP	Low	er PE	EP		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
7.3.1 Medical											
Koutsoukou 2006	62	14	11	53	11	10	24.9%	9.00 [-1.72, 19.72]	+		
Weigelt 1979	42	36	45	39	43	34	9.0%	3.00 [-14.88, 20.88]			
Subtotal (95% CI)			56			44	33.9%	7.41 [-1.78, 16.61]			
Heterogeneity: Tau ² =	= 0.00; C	:hi² =	0.32,	df = 1 (F	P = 0	.57); I ²	= 0%				
Test for overall effect	: Z = 1.5	8 (P =	= 0.11)								
7.3.2 Surgical											
Lago Borges 2013	56	19	45	47	12	44	66.1%	9.00 [2.41, 15.59]			
Subtotal (95% CI)			45			44	66.1%	9.00 [2.41, 15.59]			
Heterogeneity: Not ap	oplicable										
Test for overall effect	:: Z = 2.6	68 (P =	= 0.00	7)							
Total (95% CI)			101			88	100.0%	8.46 [3.11, 13.82]			
Heterogeneity: Tau ² =	= 0.00; C	Chi² =	0.39,	-							
Test for overall effect	:: Z = 3.1	.0 (P =	= 0.002	Favours lower PEEP Favours higher PEEP							
Test for subgroup dif	ferences	: Chi²	= 0.03								

Нурохетіа

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl		
7.4.1 Medical									
Manzano 2008	12	64	34	63	24.3%	0.35 [0.20, 0.61]	_ _		
Pepe 1984	1	44	4	48	3.4%	0.27 [0.03, 2.35]	· · · · · · · · · · · · · · · · · · ·		
Relax 2020	87	493	98	476	36.9%	0.86 [0.66, 1.11]			
Subtotal (95% CI)		601		587	64.6%	0.52 [0.24, 1.16]			
Total events	100		136						
Heterogeneity: Tau ² =	• 0.33; Ch	$i^2 = 9.0$	5, df = 2	(P = 0.	01); $I^2 = 1$	78%			
Test for overall effect:	Z = 1.59	(P=0.	11)						
7.4.2 Surgical									
Lago Borges 2013	19	45	30	44	30.9%	0.62 [0.42, 0.92]			
Michalopoulos 1998	2	21	2	22	4.5%	1.05 [0.16, 6.77]			
Subtotal (95% CI)		66		66	35.4%	0.63 [0.43, 0.93]	\bullet		
Total events	21		32						
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.3$	0, df = 1	(P = 0.	58); I ² = (0%			
Test for overall effect:	Z = 2.30	(P = 0.)	02)						
Total (95% CI)		667		653	100.0%	0.60 [0.40, 0.92]	\bullet		
Total events	121		168						
Heterogeneity: Tau ² =	• 0.11; Ch	$i^2 = 9.6$	6, df = 4	(P = 0.	05); $I^2 = 1$	59%			
Test for overall effect:	Z = 2.37	(P = 0.)	02)				U.U.S U.2 I S 2U Favours higher PEEP Favours lower PEEP		
Test for subgroup diff	ferences: (Chi ² = 0).18, df =	1 (P =	$0.67), 1^2$	= 0%	ravours inglier reer ravours lower reer		

Atelectasis

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
7.5.1 Medical							
Manzano 2008	12	64	17	63	11.8%	0.69 [0.36, 1.33]	
Pepe 1984	27	44	23	48	30.8%	1.28 [0.88, 1.87]	
Relax 2020	15	493	20	476	11.6%	0.72 [0.38, 1.40]	
Subtotal (95% CI)		601		587	54.2%	0.92 [0.58, 1.46]	\bullet
Total events	54		60				
Heterogeneity: Tau ² =	0.09; Ch	$i^2 = 4.1$	7, df = 2	(P = 0.	12); $I^2 = 1$	52%	
Test for overall effect:	Z = 0.34	(P=0.	73)				
7.5.2 Surgical							
Good 1979	9	10	12	14	44.3%	1.05 [0.78, 1.41]	- -
Michalopoulos 1998	2	21	2	22	1.5%	1.05 [0.16, 6.77]	
Subtotal (95% CI)		31		36	45.8%	1.05 [0.78, 1.41]	\bullet
Total events	11		14				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.0$	0, df = 1	(P = 1.)	$00); I^2 = 0$	0%	
Test for overall effect:	Z = 0.33	(P = 0.	74)				
Total (95% CI)		632		623	100.0%	1.02 [0.81, 1.28]	•
Total events	65		74				
Heterogeneity: Tau ² =	0.01; Ch	$i^2 = 4.5$	1, df = 4	(P = 0.	34); $I^2 = 1$	11%	
Test for overall effect:	Z = 0.15	(P = 0.	88)				U.I U.Z U.S I Z S IU Eavours higher PEEP Eavours lower PEEP
Test for subgroup diff	erences: ($Chi^2 = 0$).22, df =	1 (P =	0.64), l ²	= 0%	Tavours inglier reci Tavours lower recr
Test for subgroup diff	erences: ($Chi^2 = 0$	0.22, df =	1 (P =	0.64), l ²	= 0%	Favours higher PEEP Favours lower PEEP

Barotrauma

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
7.6.1 Medical							
Manzano 2008	1	64	5	63	2.8%	0.20 [0.02, 1.64]	←
Nelson 1987	1	20	0	18	1.3%	2.71 [0.12, 62.70]	
Pepe 1984	19	44	24	48	63.5%	0.86 [0.56, 1.34]	
Relax 2020	12	493	19	476	24.4%	0.61 [0.30, 1.24]	
Weigelt 1979 Subtotal (95% CI)	5	45 666	4	34 639	8.1% 100.0%	0.94 [0.27, 3.25] 0.78 [0.55, 1.11]	
Total events Heterogeneity: Tau ² = Test for overall effect:	38 = 0.00; Chi = Z = 1.40	$e^{2} = 3.1$ (P = 0.	52 0, df = 4 16)	(P= 0 .	54); I ² = (0%	
7.6.2 Surgical							
Good 1979	0	10	0	14		Not estimable	
Michalopoulos 1998 Subtotal (95% CI)	0	21 31	0	22 36		Not estimable Not estimable	
Total events Heterogeneity: Not ap	0 plicable		0				
lest for overall effect:	Not appli	cable					
Total (95% CI)		697		675	100.0%	0.78 [0.55, 1.11]	-
Total events Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	38 = 0.00; Chi = Z = 1.40 ferences: N	$f^2 = 3.1$ (P = 0. Not app	52 0, df = 4 16) licable	(P = 0.	54); I ² = (0%	0.1 0.2 0.5 1 2 5 10 Favours higher PEEP Favours lower PEEP

Hypotension

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl				
7.7.1 Medical											
Feeley 1975	0	12	0	13		Not estimable	\perp				
Lesur 2010	16	30	16	33	95.5%	1.10 [0.68, 1.79]					
Pepe 1984	1	44	0	48	2.2%	3.27 [0.14, 78.15]					
Weigelt 1979	1	45	0	34	2.2%	2.28 [0.10, 54.36]					
Subtotal (95% CI)		131		128	100.0%	1.15 [0.71, 1.84]	•				
Total events	18		16								
Heterogeneity: Tau ² = 0.00; Chi ² = 0.67, df = 2 (P = 0.72); $I^2 = 0\%$											
Test for overall effect:	Z = 0.56	(P=0.	57)								
7.7.2 Surgical											
Good 1979	0	10	0	14		Not estimable					
Subtotal (95% CI)		10		14		Not estimable					
Total events	0		0								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Not appl	icable									
Total (95% CI)		141		142	100.0%	1.15 [0.71, 1.84]	•				
Total events	18		16								
Heterogeneity: Tau ² =	• 0.00; Ch	$i^2 = 0.6$	57, df = 2	(P = 0.	72); I ² =	0%					
Test for overall effect:	Z = 0.56	(P = 0.	57)				U.UUI U.I I IU 1000 Eavours higher PEEP Eavours lower PEEP				
Test for subgroup dif	ferences:	Not app	licable				ravours myner i Eli Favours lower FEF				

Central venous pressure

	Higher PEEP Lower PEEP							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.8.1 Medical									
Lesur 2010 Subtotal (95% CI)	12.5	1.5	30 30	10.8	2.9	33 33	78.7% 78.7%	1.70 [0.57, 2.83] 1.70 [0.57, 2.83]	
Heterogeneity: Not ap	oplicable								
Test for overall effect	: Z = 2.9	96 (P =	= 0.003	3)					
7.8.2 Surgical									
Dyhr 2002	13	11	7	9.7	7.1	8	1.1%	3.30 [-6.22, 12.82]	
Holland 2007	9	3	14	9	3	14	20.2%	0.00 [-2.22, 2.22]	+
Subtotal (95% CI)			21			22	21.3%	0.17 [-1.99, 2.33]	\bullet
Heterogeneity: Tau ² =	= 0.00; 0	Chi ² =	0.44, 0	df = 1 (P = 0.	51); I ²	= 0%		
Test for overall effect	:: Z = 0.1	L5 (P =	= 0.88)						
Total (95% CI)			51			55	100.0%	1.37 [0.38, 2.37]	◆
Heterogeneity: Tau ² =	= 0.00; 0	Chi ² =	1.95, 0	df = 2 (P = 0.	38); I ²	= 0%	-	
Test for overall effect	: Z = 2.7	70 (P =	= 0.007	-10 -5 0 5 10 Eavours Jower PEEP Eavours higher PEEP					
Test for subgroup dif	ferences	: Chi ²	= 1.51	avours lower reer ravours higher reer					

Packed red blood cell transfusion

	Hig	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.9.1 Medical									
Relax 2020 Subtotal (95% CI)	1.7	0.7	493 493	1	0	476 476		Not estimable Not estimable	
Heterogeneity: Not a	pplicable	è							
Test for overall effect	t: Not ap	plicab	le						
7.9.2 Surgical									
Collier 2002	0.8	1.4	40	1.1	1.6	44	37.5%	-0.30 [-0.94, 0.34]	— • +
Zurich 1982	0.33	0.87	41	0.75	1.42	44	62.5%	-0.42 [-0.92, 0.08]	
Subtotal (95% CI)			81			88	100.0%	-0.38 [-0.77, 0.02]	\bullet
Heterogeneity: Tau ²	= 0.00; 0	Chi² =	0.08, 0	f = 1 (I)	P = 0.7	77); I ² =	= 0%		
Test for overall effect	t: Z = 1.8	87 (P =	= 0.06)						
Total (95% CI)			574			564	100.0%	-0.38 [-0.77, 0.02]	•
Heterogeneity: Tau ²	= 0.00; 0	Chi ² =	0.08, 0	df = 1 (F	P = 0.2	77); I ² =	= 0%		+ + +
Test for overall effect	t: $Z = 1.3$	87 (P =	= 0.06)						-4 -2 U 2 4
Test for subgroup di	fferences	s: Not	applica	ble					Favours nighter PEEP Favours lower PEEP

Duration of ventilation

	High	her PEE	P	Lov	ver PEE	P	9	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.10.1 Medical									
Feeley 1975	258	217	12	259	149	13	6.4%	-0.01 [-0.79, 0.78]	
Lesur 2010	9.2	8.8	30	9.2	8.5	33	10.9%	0.00 [-0.49, 0.49]	
Manzano 2008	5.8	6.8	64	6.5	6.2	63	14.2%	-0.11 [-0.45, 0.24]	
Nelson 1987	5.3	5	20	3.4	3	18	8.2%	0.45 [-0.20, 1.09]	+
Relax 2020	4.8	6.6	493	5.5	7.4	476	19.2%	-0.10 [-0.23, 0.03]	-
Weigelt 1979 Subtotal (95% CI)	9.3	13	45 664	14	21.7	34 637	11.9% 70.8%	-0.27 [-0.72, 0.18] -0.09 [-0.20, 0.02]	•
Heterogeneity: Tau ² -	= 0.00: Cl	$hi^{2} = 3$.46. df	= 5 (P =	= 0.63):	$l^2 = 0$ %	6		
Test for overall effect	Z = 1.59	9 (P = 0	D.11)		,				
7.10.2 Surgical									
Collier 2002	409.1	208.6	40	439.3	277.7	44	12.3%	-0.12 [-0.55, 0.31]	_ _
Good 1979	15.7	0.4	10	14.8	0.5	14	4.5%	1.88 [0.88, 2.88]	
Lago Borges 2014	5.1	2.9	45	6.8	3.2	44	12.4%	-0.55 [-0.98, -0.13]	_ _
Marvel 1986 Subtotal (95% CI)	9.3	0.6	12	0	0	0	20.2%	Not estimable	
Hotorogonaity: Tau ²	0 66. 0	h; ² _ 1	۲ ۰۰	f (D	< 0.00	01): 12	- 0.0%	0.20[0.71, 1.27]	
Test for overall effect	= 0.66; Cl	F = 1 5 (P = 0	9.38, d).58)	I = 2 (P	< 0.00	01); 1- :	= 90%		
Total (95% CI)			771			739	100.0%	-0.03 [-0.27, 0.21]	•
Heterogeneity: Tau ² =	= 0.07; Cl	hi² = 2	3.01, d	f = 8 (P	= 0.00	3); I ² =	65%		+
Test for overall effect	: Z = 0.24	4 (P = 0	0.81)			-4 -2 U Z 4 Eavours higher PEEP Eavours lower PEEP			
Test for subgroup dif	ferences:	Chi ² =	0.52,	ravours inglier reer ravours lower reer					

Hospital stay

	Hig	her PE	EP	Lov	/er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.11.1 Medical									
Manzano 2008	19.5	18.2	64	26.3	22	63	0.9%	-6.80 [-13.83, 0.23]	
Nelson 1987	28	24	20	26	24	18	0.2%	2.00 [-13.28, 17.28]	
Relax 2020	19	21.4	493	19.9	22.1	476	5.6%	-0.90 [-3.64, 1.84]	
Subtotal (95% CI)			577			557	6.7%	-2.11 [-5.95, 1.72]	
Heterogeneity: Tau ² =	= 3.47; 0	Chi² =	2.57, c	lf = 2 (I	P = 0.2	28); I ² =	= 22%		
Test for overall effect	Z = 1.0	08 (P =	= 0.28)						
7.11.2 Surgical									
Collier 2002	5.7	2.5	40	5.2	1.7	44	31.1%	0.50 [-0.42, 1.42]	1
Marvel 1986	8.8	0.5	12	8.9	0.4	15	62.2%	-0.10 [-0.45, 0.25]	—
Subtotal (95% CI)			52			59	93.3%	0.04 [-0.46, 0.54]	•
Heterogeneity: Tau ² = Test for overall effect	= 0.05; 0 :: Z = 0.1	Chi² = 16 (P =	1.42, c = 0.87)	df = 1 (I	P = 0.2	23); I ² =	= 30%		
Total (95% CI)			629			616	100.0%	-0.02 [-0.69, 0.66]	•
Heterogeneity: Tau ² =	= 0.16; 0	Chi² =	5.42, c	lf = 4 (I	P = 0.2	25); I ² =	= 26%	-	
Test for overall effect	Z = 0.0	04 (P =	= 0.96)				_		Favours higher PEEP Favours lower PEEP
Test for subgroup dif	ferences	s: Chi ²	= 1.19), df = 1	L (P =	0.28), I	$^{2} = 15.9\%$	2	

ICU mortality

	Higher PEEP Lower PEEP			Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
7.12.1 Medical								
Feeley 1975	2	12	1	13	0.5%	2.17 [0.22, 20.94]		
Korovesi 2011	3	15	4	12	1.6%	0.60 [0.17, 2.18]		
Nelson 1987	4	20	4	18	1.8%	0.90 [0.26, 3.08]		
Relax 2020 Subtotal (95% CI)	185	492 539	163	476 519	96.0% 100.0%	1.10 [0.93, 1.30] 1.09 [0.92, 1.28]		↓
Total events	194		172					
Heterogeneity: Tau ² =	• 0.00; Ch	$i^2 = 1.2$	7, df = 3	(P = 0.	74); $I^2 =$	0%		
Test for overall effect	Z = 0.99	(P=0)	32)					
7.12.2 Surgical								
Dyhr 2002	0	7	0	8		Not estimable		
Subtotal (95% CI)		7		8		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appl	icable						
Total (95% CI)		546		527	100.0%	1.09 [0.92, 1.28]		◆
Total events	194		172					
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 1.2$	7, df = 3	(P = 0.	74); I ² =	0%		
Test for overall effect:	Z = 0.99	(P = 0.	32)				0.05	U.2 I D 20 Favours higher PEEP Favours lower PEEP
Test for subgroup dif	ferences:	Not app	licable					

Hospital mortality

	Higher PEEP		EP Lower PEEP			Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl					
8.17.1 ZEEP												
Dyhr 2002	0	7	0	8		Not estimable						
Lesur 2010	12	30	16	33	5.5%	0.82 [0.47, 1.45]						
Manzano 2008	19	64	16	63	5.5%	1.17 [0.66, 2.06]						
Michalopoulos 1998	0	21	0	22		Not estimable						
Pepe 1984	13	44	18	48	5.1%	0.79 [0.44, 1.41]						
Weigelt 1979	16	45	17	34	6.5%	0.71 [0.42, 1.19]						
Subtotal (95% CI)		211		208	22.7%	0.85 [0.64, 1.12]	\bullet					
Total events	60		67									
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.76$, $df = 3$ (P = 0.62); $I^2 = 0\%$												
Test for overall effect:	Z = 1.14	(P = 0.1)	25)									
8.17.2 Lower PEEP												
Collier 2002	1	40	1	44	0.2%	1.10 [0.07, 17.01]						
Nelson 1987	5	20	6	18	1.7%	0.75 [0.28, 2.04]						
Relax 2020	208	489	185	472	75.4%	1.09 [0.93, 1.26]	r 📕					
Subtotal (95% CI)		549		534	77.3%	1.08 [0.93, 1.25]	•					
Total events	214		192									
Heterogeneity: Tau ² =	0.00; Chi	$^{2} = 0.5$	1, df = 2	(P = 0.7)	77); I ² = (0%						
Test for overall effect:	Z = 0.96	(P= 0)	34)									
Total (95% CI)		760		742	100.0%	1.02 [0.89, 1.16]						
Total events	274		259									
Heterogeneity: Tau ² =	0.00; Chi	$^{2} = 4.3$	9, df = 6	(P = 0.0)	62); $I^2 = 0$	0%						
Test for overall effect:	Z = 0.30	(P = 0.1)	77)				U.1 U.2 U.5 I 2 5 IU					
Test for subgroup diff	erences: C	$Chi^2 = 2$.13, df =	1 (P =	0.14), I ² =	= 53.0%	ravours nighter reer ravours lower PEP					

PaO2/FiO2

	Higher PEEP Lower PEEP				EP		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.1.1 ZEEP									
Korovesi 2011	498	75	15	420	73	12	6.7%	78.00 [21.91, 134.09]	
Koutsoukou 2006	409	65	11	437	74	10	6.0%	-28.00 [-87.83, 31.83]	
Lesur 2010	293	135	30	228	67	33	7.2%	65.00 [11.56, 118.44]	· · · · · · · · · · · · · · · · · · ·
Manzano 2008 Subtotal (95% CI)	359	104	64 120	301	84	63 118	13.4% 33.2%	58.00 [25.15, 90.85] 45.75 [5.42, 86.09]	
Heterogeneity: Tau ² =	= 1040.9	99: Ch	$i^2 = 8.0$	02. df =	3 (P	= 0.05	$I^2 = 63\%$	6	
Test for overall effect	t: $Z = 2.2$	22 (P =	= 0.03)	,		,			
8.1.2 Lower PEEP									
Holland 2007	307	82	14	337	82	14	5.9%	-30.00 [-90.75, 30.75]	
Lago Borges 2013	328	85	45	270	90	44	12.0%	58.00 [21.61, 94.39]	_
Ma 2014	196	45	60	134	22	60	24.4%	62.00 [49.33, 74.67]	
Relax 2020 Subtotal (95% CI)	248	112	493 612	190	84	476 594	24.5% 66.8%	58.00 [45.56, 70.44] 52.97 [34.89, 71.05]	
Heterogeneity: Tau ² =	= 181.76	5; Chi ²	= 8.4	4, df = 3	3 (P =	0.04);	$I^2 = 64\%$		
Test for overall effect	t: Z = 5.7	74 (P •	< 0.000)01)					
Total (95% CI)			732			712	100.0%	50 46 [33 93 66 99]	
Hotorogonoity: Tau ²	- 240 71	· Chi ²	- 16	20 df -	7 (D	- 0.02	100.070	/	
Teat for everall offered	= 249.71		= 10.	59, ui =	7 (P	= 0.02,	1, 1 = 59%	0	–1'00 –5'0 Ö 5'0 1Ö0
Test for overall effect	L. ∠ = 5.9	20 (P 4)UI)	. / D	0.75)	12 00/		Favours lower PEEP Favours higher PEEP
lest for subgroup dif	rrences	: Chi	= 0.10), at = 1	L (P =	0.75),	$1^{-} = 0\%$		

A-aDO2

	High	Higher PEEP			er PE	EP	:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.2.1 ZEEP									
Feeley 1975	10	22	12	102	35	13	23.6%	-3.02 [-4.22, -1.81]	
Koutsoukou 2006	100	41	11	87	40	10	25.5%	0.31 [-0.55, 1.17]	-
Subtotal (95% CI)			23			23	49.1%	-1.33 [-4.58, 1.93]	
Heterogeneity: Tau ² =	= 5.24; C	:hi² =	19.38						
Test for overall effect	Z = 0.8	30 (P =	= 0.42)						
8.2.2 Lower PEEP									
Lago Borges 2013	117	33	45	139	34	44	27.2%	-0.65 [-1.08, -0.22]	+
Marvel 1986	168	10	12	203	10	17	23.7%	-3.40 [-4.60, -2.20]	
Subtotal (95% CI)			57			61	50.9%	-1.97 [-4.66, 0.73]	
Heterogeneity: Tau ² =	= 3.57; C	:hi² =	17.99	df = 1	(P <	0.0001)); $I^2 = 94\%$	6	
Test for overall effect	: Z = 1.4	3 (P =	= 0.15)						
Total (95% CI)			80			84	100.0%	-1.62 [-3.12, -0.11]	\bullet
Heterogeneity: Tau ² =	= 2.13; C	:hi² =	37.49	, df = 3	(P <	0.0000	1); $I^2 = 92$	2%	
Test for overall effect	:: Z = 2.1	.0 (P =	= 0.04)						Favours higher PEEP Favours lower PEEP
Test for subgroup dif	ferences	: Chi²	= 0.09	9, df = 1	L (P =	0.77),	$I^2 = 0\%$		

Compliance

	High	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.3.1 ZEEP									
Koutsoukou 2006	62	14	11	53	11	10	24.9%	9.00 [-1.72, 19.72]	
Weigelt 1979	42	36	45	39	43	34	9.0%	3.00 [-14.88, 20.88]	
Subtotal (95% CI)			56			44	33.9%	7.41 [-1.78, 16.61]	
Heterogeneity: Tau ² =	= 0.00; C	:hi² =	0.32,	df = 1 (F	P = 0	.57); I ²	= 0%		
Test for overall effect	: Z = 1.5	8 (P =	= 0.11)						
8.3.2 Lower PEEP									
Lago Borges 2013	56	19	45	47	12	44	66.1%	9.00 [2.41, 15.59]	
Subtotal (95% CI)			45			44	66.1%	9.00 [2.41, 15.59]	
Heterogeneity: Not ap	plicable								
Test for overall effect	: Z = 2.6	68 (P =	= 0.007	7)					
Total (95% CI)			101			88	100.0%	8 46 [3 11 13 82]	
Hotorogonoity: Tau ² -	- 0 00. C	'hi ² –	0.30	df - 2 (6	- n	821.12	- 0%		
Test for overall effect	- 0.00, C	– 	- 0.003	ui — 2 (r 2)	- 0	.02), 1	- 0%		-20 -10 0 10 20
Test for subaroun dif	ferences	· Chi ²	= 0.002	-, 8 df = 1	(P =	0.78)	$l^2 = 0\%$		Favours lower PEEP Favours higher PEEP
reserver subgroup un	i ci ci i ci c	. em	5.00	, a. – 1		5.7 0),	. 0/0		

Нурохетіа

Higher PEEP		P Lower PEEP			Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
12	64	34	63	24.3%	0.35 [0.20, 0.61]	
2	21	2	22	4.5%	1.05 [0.16, 6.77]	
1	44	4	48	3.4%	0.27 [0.03, 2.35]	· · · · · · · · · · · · · · · · · · ·
	129		133	32.2%	0.37 [0.22, 0.63]	\bullet
15		40				
0.00; Chi	$i^2 = 1.3$	2, df = 2	(P = 0.	52); I ² = (0%	
Z = 3.72	(P = 0.)	0002)				
19	45	30	44	30.9%	0.62 [0.42, 0.92]	
87	493	98	476	36.9%	0.86 [0.66, 1.11]	
	538		520	67.8%	0.75 [0.55, 1.04]	\bullet
106		128				
0.03; Chi	$i^2 = 1.8$	8, df = 1	(P = 0.	17); I ² = 4	47%	
Z = 1.74	(P = 0.)	08)				
	667		653	100.0%	0.60 [0.40, 0.92]	•
121		168				
0.11; Chi	$i^2 = 9.6$	6, df = 4	(P = 0.0)	$()5); I^2 = !$	59%	
Z = 2.37	(P = 0.)	02)				U.U.D. U.Z I D.ZU Eavours higher PEEP Eavours lower PEEP
erences: C	$Chi^2 = 5$.13, df =	1 (P =	0.02), I ² :	= 80.5%	ravours inglier reer ravours lower reer
	Higher Events 12 2 1 15 0.00; Chi Z = 3.72 19 87 106 0.03; Chi Z = 1.74 121 0.11; Chi Z = 2.37 rences: C	Higher PEEP Events Total 12 64 2 21 1 44 129 15 0.00; Chi ² = 1.3 2 2 3.72 (P = 0.4 19 45 87 493 538 106 0.03; Chi ² = 1.8 2 2 1.74 (P = 0.4 667 121 0.11; Chi ² = 9.6 2 2 2.37 (P = 0.4) wences: Chi ² = 5 5	HigherPEEPLower IEventsTotalEvents1264342212144412915400.00; Chi ² = 1.32, df = 2Z = 3.72 (P = 0.0002)19453087493985381061280.03; Chi ² = 1.88, df = 1Z = 1.74 (P = 0.08)6671211680.11; Chi ² = 9.66, df = 4Z = 2.37 (P = 0.02)ences: Chi ² = 5.13, df =	Higher EventsPEEP TotalLower EventsPEEP Total12643463221222144412913315400.00; Chi ² = 1.32, df = 2 (P = 0.9)Z = 3.72 (P = 0.0002)194530448787493984765385201061280.03; Chi ² = 1.88, df = 1 (P = 0.3)2 = 1.74 (P = 0.08)6676531211680.11; Chi ² = 9.66, df = 4 (P = 0.02)rences: Chi ² = 5.13, df = 1 (P =	Higher EventsPEEP TotalLower EventsPEEP TotalWeight1264346324.3% 22212224.5% 11444483.4% 12913332.2%15400.00; Chi² = 1.32, df = 2 (P = 0.52); l² = 02 = 3.72 (P = 0.0002)194530448749398476874939847690.03; Chi² = 1.88, df = 1 (P = 0.17); l² = 42 = 1.74 (P = 0.08)667653100.0%121168 1680.11; Chi² = 9.66, df = 4 (P = 0.05); l² = 1Z = 2.37 (P = 0.02) erences: Chi² = 5.13, df = 1 (P = 0.02), l²	Higher EventsPEP TotalLower EventsPEP TotalRisk Ratio M-H, Random, 95% CI1264346324.3%0.35 [0.20, 0.61]2212224.5%1.05 [0.16, 6.77]1444483.4%0.27 [0.03, 2.35]12913332.2%0.37 [0.22, 0.63]1540

Atelectasis

	Higher PEEP		P Lower PEEP			Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl					
8.5.1 ZEEP												
Good 1979	9	10	12	14	44.3%	1.05 [0.78, 1.41]						
Manzano 2008	12	64	17	63	11.8%	0.69 [0.36, 1.33]						
Michalopoulos 1998	2	21	2	22	1.5%	1.05 [0.16, 6.77]						
Pepe 1984	27	44	23	48	30.8%	1.28 [0.88, 1.87]	±					
		139		147	00.4%	1.07 [0.86, 1.55]	—					
lotal events	50	-	54									
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.70$, $df = 3$ (P = 0.44); $I^2 = 0\%$												
Test for overall effect:	Z = 0.62	(P = 0.5)	53)									
8.5.2 Lower PEEP												
Relax 2020	15	493	20	476	11.6%	0.72 [0.38, 1.40]						
Subtotal (95% CI)		493		476	11.6%	0.72 [0.38, 1.40]						
Total events	15		20									
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.96	(P = 0.3)	34)									
Total (95% CI)		632		623	100.0%	1.02 [0.81, 1.28]	•					
Total events	65		74									
Heterogeneity: Tau ² =	0.01; Chi	$^{2} = 4.52$	1, df = 4	(P = 0.1)	34); $I^2 = 1$	11% -						
Test for overall effect:	Z = 0.15	(P = 0.8)	38)				U.1 U.2 U.5 I 2 5 IU					
Test for subgroup diff	erences: C	$hi^2 = 1$.23, df =	1 (P =	0.27), I ²	= 18.7%	ravours myner reer ravours lower PEEP					

Barotrauma

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
8.6.1 ZEEP							
Good 1979	0	10	0	14		Not estimable	2
Manzano 2008	1	64	5	63	2.8%	0.20 [0.02, 1.64]] ←
Michalopoulos 1998	0	21	0	22		Not estimable	
Pepe 1984	19	44	24	48	63.5%	0.86 [0.56, 1.34]	
Weigelt 1979	5	45	4	34	8.1%	0.94 [0.27, 3.25]	
Subtotal (95% CI)		184		181	74.3%	0.83 [0.55, 1.24]	
Total events	25		33				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 1.9$	5, df = 2	(P = 0.1)	38); I ² = (0%	
Test for overall effect:	Z = 0.92	(P=0.	36)				
8.6.2 Lower PEEP							
Nelson 1987	1	20	0	18	1.3%	2.71 [0.12, 62.70]]
Relax 2020	12	493	19	476	24.4%	0.61 [0.30, 1.24]	
Subtotal (95% CI)		513		494	25.7%	0.66 [0.33, 1.31]	
Total events	13		19				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.8$	3, df = 1	(P = 0.1)	36); I ² = (0%	
Test for overall effect:	Z = 1.19	(P=O.	23)				
		~~-					
Total (95% CI)		697		675	100.0%	0.78 [0.55, 1.11]	
Total events	38	2	52		2		
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 3.1$	0, df = 4	(P=0.	54); $I^2 = 0$	0%	0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 1.40	(P = 0.	16)				Favours higher PEEP Favours lower PEEP
Test for subgroup diff	erences: (Chi² = 0).31, df =	1 (P =	0.58), I ² :	= 0%	-

Ventilator-associated pneumonia

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
8.7.1 ZEEP							
Manzano 2008	6	64	16	63	42.8%	0.37 [0.15, 0.88]	
Pepe 1984	4	44	6	48	26.3%	0.73 [0.22, 2.41]	
Subtotal (95% CI)		108		111	69.1%	0.47 [0.23, 0.94]	\bullet
Total events	10		22				
Heterogeneity: Tau ² =	• 0.00; Ch	$i^2 = 0.8$	31, df = 1	(P = 0)	.37); I ² =	0%	
Test for overall effect:	Z = 2.12	P = 0	.03)				
8.7.2 Lower PEEP							
Relax 2020	7	493	6	476	30.9%	1.13 [0.38, 3.33]	_
Subtotal (95% CI)		493		476	30.9%	1.13 [0.38, 3.33]	
Total events	7		6				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.22	P = 0	.83)				
Total (95% CI)		601		587	100.0%	0.62 [0.32, 1.23]	
Total events	17		28				
Heterogeneity: $Tau^2 =$	0.08; Ch	$i^2 = 2.5$	59, df = 2	P = 0	.27); I ² =	23%	
Test for overall effect:	Z = 1.36	6 (P = 0)	17)				U.UI U.I I IU IUU Favours higher PEEP Favours lower PEEP
Test for subgroup diff	ferences:	Chi ² =	1.79, df =	= 1 (P =	0.18), I ²	= 44.0%	ravours inglier reer ravours lower reer

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	Higher PEEP		Lower PEEP			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
8.8.1 ZEEP							
Korovesi 2016	0	15	0	12		Not estimable	
Koutsoukou 2006	0	11	1	10	2.1%	0.31 [0.01, 6.74]	
Manzano 2008	3	64	9	63	11.9%	0.33 [0.09, 1.16]	
Pepe 1984	11	44	13	48	33.3%	0.92 [0.46, 1.84]	_
Weigelt 1979 Subtotal (95% CI)	9	45 179	18	34 167	35.4% 82.7%	0.38 [0.19, 0.73] 0.52 [0.29, 0.92]	
Total events	23		41				
Heterogeneity: Tau ² = Test for overall effect	= 0.10; Ch : Z = 2.23	$i^2 = 4.1$ (P = 0.	.6, df = 3 03)	(P = 0)	.24); I ² =	28%	
Balay 2020	-	402	10	476	17 20/	0.27 [0.12, 1.02]	
Subtotal (95% CI)	C	495 493	12	476 476	17.3% 17.3%	0.37 [0.13, 1.03] 0.37 [0.13, 1.03]	
Total events Heterogeneity: Not ap Test for overall effect	5 oplicable : Z = 1.90	(P = 0.	13 06)				
Total (95% CI)		672		643	100.0%	0.50 [0.32, 0.78]	\bullet
Total events Heterogeneity: Tau ² = Test for overall effect Test for subgroup dif	28 = 0.04; Ch : Z = 3.03 ferences:	$i^{2} = 4.5$ (P = 0. Chi ² = 0	54 9, df = 4 002) 0.31, df =	0.02 0.1 1 10 50 Favours higher PEEP Favours lower PEEP			

Cardiac index



Central venous pressure

	High	Higher PEEP Lower PEEP				EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.10.1 ZEEP									
Dyhr 2002	13	11	7	9.7	7.1	8	1.1%	3.30 [-6.22, 12.82]	
Lesur 2010 Subtotal (95% CI)	12.5	1.5	30 37	10.8	2.9	33 41	78.7% 79.8%	1.70 [0.57, 2.83] 1.72 [0.60, 2.84]	
Heterogeneity: Tau ² =	= 0.00; C	:hi² =	0.11, 0	df = 1 (F	P = 0	74); I ²	= 0%		
Test for overall effect	: Z = 3.0)2 (P =	= 0.003	3)					
8.10.2 Lower PEEP									
Holland 2007 Subtotal (95% CI)	9	3	14 14	9	3	14 14	20.2% 20.2%	0.00 [-2.22, 2.22] 0.00 [-2.22, 2.22]	
Heterogeneity: Not ap	oplicable								
Test for overall effect	: Z = 0.0)0 (P =	= 1.00)						
Total (95% CI)			51			55	100.0%	1.37 [0.38, 2.37]	◆
Heterogeneity: Tau ² = Test for overall effect Test for subgroup dif	= 0.00; C :: Z = 2.7 ferences	Chi ² = '0 (P = : Chi ²	1.95, 0 = 0.007 = 1.84	-10 -5 0 5 10 Favours lower PEEP Favours higher PEEP					

Postoperative bleeding



Packed red blood cell transfusion



Duration of ventilation



ICU stay



Hospital stay



ICU mortality

	Higher PEEP		Lower PEEP			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
8.16.1 ZEEP							
Dyhr 2002	0	7	0	8		Not estimable	
Feeley 1975	2	12	1	13	0.5%	2.17 [0.22, 20.94]	
Korovesi 2011	3	15	4	12	1.6%	0.60 [0.17, 2.18]	
Subtotal (95% CI)		34		33	2.2%	0.82 [0.27, 2.52]	
Total events	5		5				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.9$	94, df = 1	(P = 0.	33); $I^2 =$	0%	
Test for overall effect:	Z = 0.34	(P=0)	.73)				
8.16.2 Lower PEEP Nelson 1987 Relax 2020 Subtotal (95% CI)	4 185	20 492 512	4 163	18 476 494	1.8% 96.0% 97.8%	0.90 [0.26, 3.08] 1.10 [0.93, 1.30] 1.09 [0.93, 1.29]	
Total events	189		167				·
Heterogeneity: Tau ² =	• 0.00; Ch	$i^2 = 0.1$	10, df = 1	(P = 0.	75); I ² =	0%	
Test for overall effect:	Z = 1.05	(P = 0.	.29)				
Total (95% CI)	104	546	170	527	100.0%	1.09 [0.92, 1.28]	•
Heterogeneity: Tau ² =	194 • 0.00; Ch • 7 – 0.99	$i^2 = 1.2$	27, df = 3	(P = 0.	74); I ² =	0%	
Test for subgroup diff	ferences:	$Chi^2 = 0$	0.25, df =	= 1 (P =	0.62), I ²	= 0%	Favours higher PEEP Favours lower PEEP

28-day mortality



Hospital mortality

	Higher PEEP		Lower PEEP			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
9.15.1 VT>8											
Collier 2002	1	40	1	44	0.2%	1.10 [0.07, 17.01]	·				
Pepe 1984	13	44	18	48	5.2%	0.79 [0.44, 1.41]					
Weigelt 1979	16	45	17	34	6.7%	0.71 [0.42, 1.19]					
Subtotal (95% CI)		129		126	12.1%	0.75 [0.51, 1.10]	\bullet				
Total events	30		36								
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, $df = 2$ (P = 0.93); $I^2 = 0\%$											
Test for overall effect	z = 1.47	P = 0.	14)								
9.15.2 VT<8											
Dyhr 2002	0	7	0	8		Not estimable					
Lesur 2010	12	30	16	33	5.6%	0.82 [0.47, 1.45]					
Manzano 2008	19	64	16	63	5.5%	1.17 [0.66, 2.06]	<u> </u>				
Relax 2020	208	489	185	472	76.7%	1.09 [0.93, 1.26]					
Subtotal (95% CI)		590		576	87.9%	1.07 [0.93, 1.24]	•				
Total events	239		217								
Heterogeneity: Tau ² :	= 0.00; Ch	$i^2 = 0.9$	5, df = 2	(P = 0.	62); I ² =	0%					
Test for overall effect	t: Z = 0.95	(P = 0.	34)								
Total (95% CI)		719		702	100.0%	1.03 [0.90, 1.17]	•				
Total events	269		253								
Heterogeneity: Tau ² :	= 0.00; Ch										
Test for overall effect	z = 0.38	(P = 0.	U.I U.Z U.J I Z J IU Favours higher PEEP Favours lower PEEP								
Test for subgroup dif											

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	Higher PEEP			Low	er PE	EP		Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
9.1.1 VT>8										
Feeley 1975	10	22	12	102	35	13	23.6%	-3.02 [-4.22, -1.81]	_	
Marvel 1986	168	10	12	203	10	17	23.7%	-3.40 [-4.60, -2.20]	_	
Subtotal (95% CI)			24			30	47.3%	-3.21 [-4.06, -2.36]	\bullet	
Heterogeneity: Tau ² =	= 0.00; C	Chi² =	0.20,	df = 1 (F	P = 0	.66); I ²	= 0%			
Test for overall effect	: Z = 7.4	I2 (P ∢	< 0.000	001)						
9.1.2 VT<8										
Koutsoukou 2006	100	41	11	87	40	10	25.5%	0.31 [-0.55, 1.17]	- +e	
Lago Borges 2013	117	33	45	139	34	44	27.2%	-0.65 [-1.08, -0.22]		
Subtotal (95% CI)			56			54	52.7%	-0.25 [-1.18, 0.68]		
Heterogeneity: Tau ² =	= 0.34; C	Chi² =	3.81,	df = 1 (F	P = 0	.05); I ²	= 74%			
Test for overall effect	: Z = 0.5	52 (P =	= 0.60)							
Total (95% CI)			80			84	100.0%	-1.62 [-3.12, -0.11]		
Heterogeneity: Tau ² =	= 2.13; C	Chi² =	37.49	df = 3	(P <	0.0000	1); $I^2 = 92$	2% —		
Test for overall effect	: Z = 2.1	.0 (P =	= 0.04)		-4 -2 U 2 4 Eavours higher PEEP Eavours lower PEEP					
Test for subgroup differences: $Chi^2 = 21.32$, $df = 1$ (P < 0.00001), $I^2 = 95.3\%$									ravours myner felf Favours lower feer	

Compliance



Нурохетіа

	Higher PEEP		Lower PEEP		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
9.3.1 VT>8							
Pepe 1984 Subtotal (95% CI)	1	44 44	4	48 48	4.0% 4.0%	0.27 [0.03, 2.35] 0.27 [0.03, 2.35]	
Total events	1		4				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 1.18	(P = 0.	24)				
9.3.2 VT<8							
Lago Borges 2013	19	45	30	44	32.3%	0.62 [0.42, 0.92]	
Manzano 2008	12	64	34	63	26.0%	0.35 [0.20, 0.61]	
Relax 2020 Subtotal (95% CI)	87	493 602	98	476 583	37.7% 96.0%	0.86 [0.66, 1.11]	-
Total events	118	002	162	505	50.070	0.00 [0.57, 0.50]	•
Heterogeneity: Tau ² =	= 0 13 [.] Ch	$i^2 = 8.7$	102	P = 0	$(01) \cdot 1^2 =$	77%	
Test for overall effect	: Z = 2.11	(P = 0.	03)	. (1 0.	01), 1		
			,				
Total (95% CI)		646		631	100.0%	0.58 [0.37, 0.92]	\bullet
Total events	119		166				
Heterogeneity: Tau ² =	= 0.12; Ch	$i^2 = 9.4$	7, df = 3	(P = 0.	02); $I^2 =$	68%	
Test for overall effect	: Z = 2.34	(P = 0.	02)				0.002 0.1 1 10 500 Eavours higher PEEP Eavours lower PEEP
Test for subgroup dif	ferences:	Chi ² = ().49, df =	= 1 (P =	0.48), I ²	= 0%	ravours inglier i Lei Tavours lower FLEF
Atelectasis

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
9.4.1 VT>8					-		
Good 1979	9	10	12	14	39.9%	1.05 [0.78, 1.41]	- -
Pepe 1984 Subtotal (95% CI)	27	44 5 4	23	48 62	31.2% 71.1%	1.28 [0.88, 1.87] 1.13 [0.90, 1.43]	—
Total events	36		35				•
Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch t: Z = 1.05	$ii^2 = 0.9$ 5 (P = 0.	95, df = 1 .29)	L(P = 0)	.33); I ² =	0%	
9.4.2 VT<8							
Manzano 2008	12	64	17	63	14.5%	0.69 [0.36, 1.33]	
Relax 2020 Subtotal (95% CI)	15	493 557	20	476 539	14.3% 28.9%	0.72 [0.38, 1.40] 0.71 [0.45, 1.13]	
Total events	27		37				
Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch t: Z = 1.45	$ii^2 = 0.0$ i (P = 0.0))1, df = 1 .15)	I(P=O)	.93); I ² =	0%	
Total (95% CI)		611		601	100.0%	1.00 [0.76, 1.32]	•
Total events	63		72				
Heterogeneity: Tau ²	= 0.03; Ch	$i^2 = 4.5$	5, df = 3	B (P = 0)	.21); $I^2 =$	34%	
Test for overall effec	t: Z = 0.02	P = 0	.99)				Favours higher PEEP Favours lower PEEP
Test for subgroup di	fferences:	Chi ² = 1	3.14, df =	= 1 (P =	$0.08), 1^2$	= 68.1%	

Barotrauma

	Higher	PEEP	Lower	PEEP		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
9.5.1 VT>8								
Good 1979	0	10	0	14		Not estimable		
Pepe 1984	19	44	24	48	64.3%	0.86 [0.56, 1.34]		
Weigelt 1979 Subtotal (95% CI)	5	45 99	4	34 96	8.2% 72.5%	0.94 [0.27, 3.25] 0.87 [0.58, 1.32]		
Total events	24		28					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$	2, df = 1	(P = 0.	89); I ² =	0%		
Test for overall effect:	: Z = 0.64	(P=0.	52)					
9.5.2 VT<8								
Manzano 2008	1	64	5	63	2.8%	0.20 [0.02, 1.64]	•	
Relax 2020	12	493	19	476	24.7%	0.61 [0.30, 1.24]		
Subtotal (95% CI)		557		539	27.5%	0.54 [0.28, 1.07]		
Total events	13		24					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.9$	9, df = 1	(P = 0.	32); I ² =	0%		
Test for overall effect:	: Z = 1.77	(P=0)	08)					
Total (95% CI)		656		635	100.0%	0.77 [0.54, 1.09]		•
Total events	37		52					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 2.5$	4, df = 3	(P = 0.	47); I ² =	0%	$\frac{1}{1}$	
Test for overall effect:	Z = 1.48	(P = 0.	14)				0.1	U.2 U.3 I 2 5 IU Favours higher PEEP Favours lower PEEP
Test for subgroup diff	ferences:	Chi² = 🛛	1.37, df =	= 1 (P =	0.24), I ²	= 26.9%		

Ventilator-associated pneumonia



ARDS

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
9.7.1 VT>8							
Pepe 1984	11	44	13	48	33.3%	0.92 [0.46, 1.84]	— —
Weigelt 1979	9	45	18	34	35.4%	0.38 [0.19, 0.73]	
Subtotal (95% CI)		89		82	68.7%	0.59 [0.24, 1.41]	
Total events	20		31				
Heterogeneity: Tau ² =	= 0.28; Ch	$i^2 = 3.3$	4, df = 1	(P = 0)	.07); $I^2 =$	70%	
Test for overall effect	: Z = 1.19	(P=0.	23)				
9.7.2 VI <8							
Korovesi 2016	0	15	0	12		Not estimable	
Koutsoukou 2006	0	11	1	10	2.1%	0.31 [0.01, 6.74]	
Manzano 2008	3	64	9	63	11.9%	0.33 [0.09, 1.16]	
Relax 2020	5	493	13	476	17.3%	0.37 [0.13, 1.03]	
Subtotal (95% CI)		583		561	31.3%	0.35 [0.16, 0.76]	
Total events	8		23				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$	3, df = 2	P = 0	.98); $I^2 =$	0%	
Test for overall effect	: Z = 2.67	P = 0.	008)				
Total (95% CI)		672		643	100.0%	0.50 [0.32, 0.78]	◆
Total events	28		54				
Heterogeneity: Tau ² =	= 0.04; Ch	$i^2 = 4.5$	9, $df = 4$	(P = 0)	.33); $I^2 =$	13%	
Test for overall effect	: Z = 3.03	(P = 0.	002)				U.UZ U.I I IO 50
Test for subgroup dif	ferences:	$Chi^2 = 0$).76, df =	= 1 (P =	0.38), I ²	= 0%	Favours myner reer Favours lower PEP

Hypotension

	Higher	PEEP	Lower PEEP			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl
9.8.1 VT>8							
Feeley 1975	0	12	0	13		Not estimable	
Good 1979	0	10	0	14		Not estimable	
Pepe 1984	1	44	0	48	2.2%	3.27 [0.14, 78.15]	· · · · · · · · · · · · · · · · · · ·
Weigelt 1979	1	45	0	34	2.2%	2.28 [0.10, 54.36]	
Subtotal (95% CI)		111		109	4.5%	2.73 [0.29, 25.73]	
Total events	2		0				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$	2, df = 1	(P = 0.	88); $I^2 =$	0%	
Test for overall effect	: Z = 0.88	(P = 0.	38)				
9.8.2 VT<8							
Lesur 2010	16	30	16	33	95.5%	1.10 [0.68, 1.79]	
Subtotal (95% CI)		30		33	95.5%	1.10 [0.68, 1.79]	•
Total events	16		16				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 0.38	P = 0.	70)				
Total (95% CI)		141		142	100.0%	1.15 [0.71, 1.84]	•
Total events	18		16				
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.6$	7, df = 2	(P = 0.	72); I ² =	0%	
Test for overall effect	: Z = 0.56	(P = 0.	57)				Favours higher PEEP Favours lower PEEP
Test for subgroup dif	ferences:	Chi ² = (0.60, df =	= 1 (P =	0.44), I ²	= 0%	

Cardiac index



Duration of ventilation



ICU stay



Hospital stay



ICU mortality

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
9.14.1 VT>8							
Feeley 1975 Subtotal (95% CI)	2	12 12	1	13 13	0.5% 0.5%	2.17 [0.22, 20.94] 2.17 [0.22, 20.94]	
Total events	2		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.67	'(P = 0.)	50)				
9.14.2 VT<8							
Dyhr 2002	0	7	0	8		Not estimable	
Korovesi 2011	3	15	4	12	1.7%	0.60 [0.17, 2.18]	
Relax 2020 Subtotal (95% CI)	185	492 514	163	476 496	97.8% 99.5%	1.10 [0.93, 1.30] 1.09 [0.92, 1.28]	•
Total events	188		167				
Heterogeneity: Tau ² = Test for overall effect	= 0.00; Ch t: Z = 0.98	$ii^2 = 0.8$ 8 (P = 0.	33, df = 1 33)	(P = 0)	36); I ² =	0%	
		520	,	500	100.00/	1 00 [0 02 1 20]	
Total (95% CI)		526		509	100.0%	1.09 [0.92, 1.29]	T
Total events	190	2	168		2		
Heterogeneity: Tau ² :	= 0.00; Cł	$i^2 = 1.1$.8, df = 2	P = 0.	55); I ² =	0%	
Test for overall effect	t: Z = 1.02	P = 0.	31)				Favours higher PEEP Favours lower PEEP
Test for subgroup dif	fferences:	Chi ² = (0.35, df =	= 1 (P =	0.55), I ²	= 0%	

Hospital mortality

	Higher	PEEP	Lower PEEP		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
10.15.1 >2000							
Collier 2002	1	40	1	44	0.2%	1.10 [0.07, 17.01]	
Dyhr 2002	0	7	0	8		Not estimable	
Lesur 2010	12	30	16	33	5.5%	0.82 [0.47, 1.45]	
Manzano 2008	19	64	16	63	5.5%	1.17 [0.66, 2.06]	
Relax 2020	208	489	185	472	75.4%	1.09 [0.93, 1.26]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		630		620	86.6%	1.07 [0.93, 1.24]	◆
Total events	240		218				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.9$	5, df = 3	(P = 0.3)	81); $I^2 = 0$	0%	
Test for overall effect:	Z = 0.95	(P = 0.1)	34)				
10.15.2 <2000							
Michalopoulos 1998	0	21	0	22		Not estimable	
Nelson 1987	5	20	6	18	1.7%	0.75 [0.28, 2.04]	
Pepe 1984	13	44	18	48	5.1%	0.79 [0.44, 1.41]	
Weigelt 1979	16	45	17	34	6.5%	0.71 [0.42, 1.19]	
Subtotal (95% CI)		130		122	13.4%	0.74 [0.52, 1.07]	\bullet
Total events	34		41				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.0$	7, df = 2	(P = 0.9)	97); l ² = (0%	
Test for overall effect:	Z = 1.60	(P = 0.1)	11)				
Total (95% CI)		760		742	100.0%	1.02 [0.89, 1.16]	•
Total events	274	2	259		2		
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 4.3$	9, df = 6	(P = 0.0)	62); $I^2 = 0$	0%	
Test for overall effect:	Z = 0.30	(P = 0.1)	77)				Lower in higher PEEP Higher in higher PEEP
Test for subgroup diff	erences: 0	Chi² = 3	8.37, df =	1 (P =	0.07), l ²	= 70.3%	3

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	High	er PE	EP	Low	er PE	EP	:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
10.1.1 >2000									
Koutsoukou 2006	100	41	11	87	40	10	25.5%	0.31 [-0.55, 1.17]	
Lago Borges 2013	117	33	45	139	34	44	27.2%	-0.65 [-1.08, -0.22]	+
Subtotal (95% CI)			56			54	52.7%	-0.25 [-1.18, 0.68]	•
Heterogeneity: Tau ² :	= 0.34; C	hi² =	3.81, 0	df = 1 (F	? = 0.	05); I ²	= 74%		
Test for overall effect	t: Z = 0.5	2 (P =	= 0.60)						
10.1.2 <2000 Feeley 1975 Marvel 1986 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect	10 168 = 0.00; C t: Z = 7.4	22 10 :hi ² = 2 (P -	12 12 24 0.20, 0 < 0.000	$102 \\ 203 \\ df = 1 (F \\ 001)$	35 10 P = 0.	13 17 30 66); I ²	23.6% 23.7% 47.3% = 0%	-3.02 [-4.22, -1.81] -3.40 [-4.60, -2.20] - 3.21 [-4.06, -2.36]	 ◆
Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Test for subgroup dit	= 2.13; C t: Z = 2.1 fferences	:hi² = .0 (P = : Chi²	80 37.49, = 0.04) = 21.3	- 1.62 [- 3.12, -0.11]	-4 -2 0 2 4 Favours higher PEEP Favours lower PEEP				

Compliance



Hypoxemia

	Higher PEEP			PEEP		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI		
10.3.1 >2000									
Lago Borges 2013	19	45	30	44	30.9%	0.62 [0.42, 0.92]			
Manzano 2008	12	64	34	63	24.3%	0.35 [0.20, 0.61]	_ _		
Relax 2020	87	493	98	476	36.9%	0.86 [0.66, 1.11]			
Subtotal (95% CI)		602		583	92.1%	0.60 [0.37, 0.96]	\bullet		
Total events	118		162						
Heterogeneity: Tau ² =	0.13; Chi	$^{2} = 8.7$	5, df = 2	(P = 0.)	01); $I^2 = 7$	77%			
Test for overall effect:	Z = 2.11	(P = 0.)	03)						
10.3.2 <2000									
Michalopoulos 1998	2	21	2	22	4.5%	1.05 [0.16, 6.77]			
Pepe 1984	1	44	4	48	3.4%	0.27 [0.03, 2.35]			
Subtotal (95% CI)		65		70	7.9%	0.59 [0.14, 2.41]			
Total events	3		6						
Heterogeneity: Tau ² =	0.00; Chi	$^{2} = 0.8$	7, df = 1	(P = 0.1)	35); I ² = C	0%			
Test for overall effect:	Z = 0.74	(P = 0.4)	46)						
Total (95% CI)		667		653	100.0%	0.60 [0.40, 0.92]	\bullet		
Total events	121		168						
Heterogeneity: Tau ² =	0.11; Chi	$^{2} = 9.6$	6, df = 4	(P = 0.0)	05); $I^2 = 5$	59%			
Test for overall effect:	Z = 2.37	(P = 0.)	02)				U.U2 U.I I IU SU		
Test for subgroup diff	erences: C	Chi ² = C	.00, df =	1 (P =	0.98), I ² =	= 0%			

Atelectasis

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
10.4.1 >2000							
Manzano 2008	12	64	17	63	11.8%	0.69 [0.36, 1.33]	
Relax 2020	15	493	20	476	11.6%	0.72 [0.38, 1.40]	
Subtotal (95% CI)		557		539	23.4%	0.71 [0.45, 1.13]	
Total events	27		37				
Heterogeneity: Tau ² =	• 0.00; Chi	$i^2 = 0.0$	1, df = 1	(P = 0.1)	93); I ² = (0%	
Test for overall effect:	: Z = 1.45	(P = 0.	15)				
10.4.2 <2000							
Good 1979	9	10	12	14	44.3%	1.05 [0.78, 1.41]	
Michalopoulos 1998	2	21	2	22	1.5%	1.05 [0.16, 6.77]	
Pepe 1984	27	44	23	48	30.8%	1.28 [0.88, 1.87]	+
Subtotal (95% CI)		75		84	76.6%	1.13 [0.90, 1.43]	★
Total events	38		37				
Heterogeneity: Tau ² =	= 0.00; Chi	$i^2 = 0.9$	0, df = 2	(P = 0.	64); I ² = (0%	
Test for overall effect:	Z = 1.05	(P = 0.1)	29)				
Total (95% CI)		632		623	100.0%	1.02 [0.81, 1.28]	•
Total events	65		74				
Heterogeneity: $Tau^2 =$	= 0.01; Chi	$i^2 = 4.5$	1, df = 4	(P = 0.	34); I ² = 3	11% —	
Test for overall effect:	Z = 0.15	(P = 0.5)	88)				U.2 U.5 I 2 5 Eavours higher PEEP Eavours lower PEEP
Test for subaroup diff	ferences [.] ($hi^2 = 3$	13 df =	= 1 (P =	$0.08)$ 1^2	- 68 1%	ravours myner reef Favours lower feer

Barotrauma

	Higher	PEEP	Lower PEEP		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl
10.5.1 >2000							
Manzano 2008	1	64	5	63	2.8%	0.20 [0.02, 1.64]	
Relax 2020	12	493	19	476	24.4%	0.61 [0.30, 1.24]	
Subtotal (95% CI)		557		539	27.2%	0.54 [0.28, 1.07]	
Total events	13		24				
Heterogeneity: Tau ² =	0.00; Chi	$i^2 = 0.9$	9, df = 1	(P = 0.1)	32); I ² = (0%	
Test for overall effect:	Z = 1.77	(P=O.	08)				
10.5.2 <2000							
Good 1979	0	10	0	14		Not estimable	
Michalopoulos 1998	0	21	0	22		Not estimable	
Nelson 1987	1	20	0	18	1.3%	2.71 [0.12, 62.70]	•
Pepe 1984	19	44	24	48	63.5%	0.86 [0.56, 1.34]	
Weigelt 1979	5	45	4	34	8.1%	0.94 [0.27, 3.25]	
Subtotal (95% CI)		140		136	72.8%	0.89 [0.59, 1.34]	\bullet
Total events	25		28				
Heterogeneity: Tau ² =	0.00; Chi	$i^2 = 0.5$	2, df = 2	(P = 0.)	77); I ² = (0%	
Test for overall effect:	Z = 0.56	(P=0.	58)				
		607		675	100.0%	0 70 [0 55 1 11]	
Total (95% CI)		697		675	100.0%	0.78 [0.55, 1.11]	
Total events	38	2	52				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 3.1$	0, $df = 4$				
Test for overall effect:	Z = 1.40	(P=0.	16)				Lower in higher PEEP Higher in higher PEEP
Test for subgroup diff	erences: (Chi ² = 1	L.49, df =	1 (P =	0.22), l ² =	= 32.9%	

Ventilator-associated pneumonia

	Higher	PEEP	Lower l	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
10.6.1 >2000							
Manzano 2008	6	64	16	63	42.8%	0.37 [0.15, 0.88]	_
Relax 2020 Subtotal (95% CI)	7	493 557	6	476 539	30.9% 73.7%	1.13 [0.38, 3.33] 0.61 [0.21, 1.83]	
Total events	13		22				
Heterogeneity: Tau ² = Test for overall effect:	= 0.37; Ch : Z = 0.88	$i^2 = 2.4$ i(P = 0.1)	7, df = 1 38)	(P = 0.	.12); I ² =	60%	
10.6.2 <2000							
Pepe 1984 Subtotal (95% CI)	4	44 44	6	48 48	26.3% 26.3%	0.73 [0.22, 2.41] 0.73 [0.22, 2.41]	
Total events	4		6				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 0.52	(P=0.	60)				
Total (95% CI)		601		587	100.0%	0.62 [0.32, 1.23]	-
Total events Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	17 = 0.08; Ch : Z = 1.36 ferences:	$i^2 = 2.5$ (P = 0. Chi ² = 0	28 59, df = 2 17) 0.04, df =	(P = 0) = 1 (P =	.27); $I^2 = 0.84$), I^2	23% = 0%	0.02 0.1 1 10 50 Favours higher PEEP Favours lower PEEP

ARDS

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight M-H	H, Random, 95% CI	M–H, Random, 95% Cl	
10.7.1 >2000								
Korovesi 2016	0	15	0	12		Not estimable		
Koutsoukou 2006	0	11	1	10	2.1%	0.31 [0.01, 6.74]	· · · · · · · · · · · · · · · · · · ·	
Manzano 2008	3	64	9	63	11.9%	0.33 [0.09, 1.16]		
Relax 2020	5	493	13	476	17.3%	0.37 [0.13, 1.03]		
Subtotal (95% CI)		583		561	31.3%	0.35 [0.16, 0.76]		
Total events	8		23					
Heterogeneity: Tau ² =	= 0.00; Ch	$i^2 = 0.0$)3, df = 2	(P = 0.	98); $I^2 = 0\%$			
Test for overall effect	: Z = 2.67	(P = 0.)	008)					
10.7.2 <2000								
Pepe 1984	11	44	13	48	33.3%	0.92 [0.46, 1.84]	_	
Weigelt 1979	9	45	18	34	35.4%	0.38 [0.19, 0.73]		
Subtotal (95% CI)		89		82	68.7%	0.59 [0.24, 1.41]		
Total events	20		31					
Heterogeneity: Tau ² =	= 0.28; Ch	$i^2 = 3.3$	14, df = 1	(P = 0.	07); $I^2 = 70\%$			
Test for overall effect	: Z = 1.19	(P=0.	23)					
-								
Total (95% CI)		672		643	100.0%	0.50 [0.32, 0.78]	•	
Total events	28	_	54		_			
Heterogeneity: Tau ² =	= 0.04; Ch	$i^2 = 4.5$	59, df = 4	(P=0.	33); $I^2 = 13\%$			50
Test for overall effect	: Z = 3.03	(P=0.	002)				Lower in higher PEEP Higher in higher PEEP	50
Test for subgroup dif	ferences:	Chi ² = (0.76, df =	= 1 (P =	0.38), $I^2 = 0\%$	2 2		

Hypotension

Study or Subgroup Event: 10.8.1 > 2000 16 Lesur 2010 16 Subtotal (95% Cl) 16 Total events 16 Heterogeneity: Not applicable 16 Tostal events 16 Heterogeneity: Not applicable 10.8.2 < 2000 Feeley 1975 0 Good 1979 0 Pepe 1984 2	s Tota 6 30 30 6	Events 16 16	Total 33 33	95.5%	М-H, Random, 95% Cl 1.10 [0.68, 1.79]	M-H, Random, 95% Cl
10.8.1 > 2000 Lesur 2010 10 Subtotal (95% Cl) Total events 16 Heterogeneity: Not applicable Test for overall effect: Z = 0.3 10.8.2 < 2000 Feeley 1975 0 Good 1979 0 Pepe 1984 2	6 30 30 5) 16 16	33 33	95.5% 95 5%	1.10 [0.68, 1.79]	
Lesur 2010 16 Subtotal (95% Cl) 16 Total events 16 Heterogeneity: Not applicable 10.8.2 < 2000	6 30 30 5 3	16 16	33 33	95.5% 95.5%	1.10 [0.68, 1.79]	
Subtotal (95% Cl) Total events 14 Heterogeneity: Not applicable Test for overall effect: Z = 0.3 10.8.2 <2000	3C 6 غ	16	33	95 5%		
Total events16Heterogeneity: Not applicableTest for overall effect: Z = 0.310.8.2 <2000	6 3 28 (P - 0	16		53.3/0	1.10 [0.68, 1.79]	•
Heterogeneity: Not applicable Test for overall effect: Z = 0.: 10.8.2 <2000 Feeley 1975 (Good 1979 (Pepe 1984 (30 (D 0					
Test for overall effect: Z = 0. 10.8.2 <2000 Feeley 1975 (Good 1979 (Pepe 1984 (20 /D 0					
10.8.2 <2000 Feeley 1975 (Good 1979 (Pepe 1984 (50 (P = 0)).70)				
Feeley 1975 (Good 1979 (Pepe 1984 2						
Good 1979 (Pepe 1984 2	0 12	. 0	13		Not estimable	
Pepe 1984	0 10) 0	14		Not estimable	
	1 44	0	48	2.2%	3.27 [0.14, 78.15]	
Weigelt 1979	1 45	0	34	2.2%	2.28 [0.10, 54.36]	
Subtotal (95% CI)	111		109	4.5%	2.73 [0.29, 25.73]	
Total events 2	2	0				
Heterogeneity: $Tau^2 = 0.00$; ($Chi^2 = 0.$	02, df = 1	(P = 0.	.88); $I^2 = 0$	0%	
Test for overall effect: $Z = 0.8$	88 ($P = 0$).38)				
Total (95% CI)	141		142	100.0%	1.15 [0.71, 1.84]	•
Total events 18	8	16				
Heterogeneity: $Tau^2 = 0.00$; ($Chi^2 = 0.$	67, df = 2	(P = 0.	(72); $I^2 = 0$	0%	
Test for overall effect: $Z = 0.1$	56 (P = C).57)				U.UI U.I I IU IU Equation DEED Equation DEED
Test for subgroup differences						

Postoperative bleeding

Higher PEEP			EP	Low	/er PE	EP		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
10.9.1 >2000									
Collier 2002 Subtotal (95% CI)	703	395	40 40	587	392	44 44	34.2% 34.2%	116.00 [-52.52, 284.52] 116.00 [-52.52, 284.52]	
Heterogeneity: Not ap	plicable								
Test for overall effect	Z = 1.3	35 (P =	= 0.18)	I					
10.9.2 <2000									
Zurich 1982 Subtotal (95% CI)	542	239	41 41	562	261	476 476	65.8% 65.8%	-20.00 [-96.82, 56.82] - 20.00 [-96.82, 56.82]	
Heterogeneity: Not ap	plicable	2							
Test for overall effect	Z = 0.5	51(P=	= 0.61)	1					
Total (95% CI)			81			520	100.0%	26.47 [-99.95, 152.89]	-
Heterogeneity: $Tau^2 = 4783.35$; $Chi^2 = 2.07$, $df = 1$ (P = 0.15); $l^2 = 52\%$ Test for overall effect: Z = 0.41 (P = 0.68) Test for subgroup differences: $Chi^2 = 2.07$, $df = 1$ (P = 0.15), $l^2 = 51.7\%$									– – – – – – – –500 –250 0 250 500 Favours higher PEEP Favours lower PEEP

Packed red blood cell transfusion



Duration of ventilation



ICU stay

Higher PEEP			EP	Lov	ver PE	EP		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
10.12.1 >2000										
Korovesi 2011	17.2	10.1	15	14.4	8.44	12	4.6%	2.80 [-4.19, 9.79]	- -	
Manzano 2008	10.5	9.8	64	12.3	11.4	63	15.5%	-1.80 [-5.50, 1.90]		
Relax 2020	7.2	10.3	493	8.1	11.5	476	78.4%	-0.90 [-2.28, 0.48]		
Subtotal (95% CI)			572			551	98.4%	-0.88 [-2.15, 0.38]	\blacklozenge	
Heterogeneity: Tau ² =	= 0.00; 0	Chi² =	1.30, a	df = 2 (I	P = 0.	52); I ² =	= 0%			
Test for overall effect	: Z = 1.	37 (P =	= 0.17)							
10.12.2 <2000										
Weigelt 1979	11.7	16.8	45	21	32.5	34	1.6%	-9.30 [-21.28, 2.68]		
Subtotal (95% CI)			45			34	1.6%	-9.30 [-21.28, 2.68]		
Heterogeneity: Not a	oplicable	5								
Test for overall effect	Z = 1.1	52 (P =	= 0.13)							
Total (95% CI)			617			585	100.0%	-1.00 [-2.51, 0.51]	•	
Heterogeneity: Tau ² =	= 0.26; 0	Chi ² =	3.18, 0	df = 3 (I	P = 0.	37); I ² =	= 6%	—		
Test for overall effect	:: Z = 1.	30 (P =	= 0.19)						-20 -10 0 10 20	
Test for subgroup differences: $Chi^2 = 1.88$ df = 1 (P = 0.17) $I^2 = 46.7\%$								6	Favours nigher PEEP Favours lower PEEP	
				-,						

Hospital stay



ICU mortality

	Higher	PEEP	Lower	PEEP		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
10.14.1 >2000							
Dyhr 2002	0	7	0	8		Not estimable	
Korovesi 2011	3	15	4	12	1.6%	0.60 [0.17, 2.18]	
Relax 2020	185	492	163	476	96.0%	1.10 [0.93, 1.30]	
Subtotal (95% CI)		514		496	97.7%	1.09 [0.92, 1.28]	•
Total events	188		167				
Heterogeneity: Tau ² =	= 0.00; Ch	$ni^2 = 0.8$	33, df = 1	I (P = 0)	.36); I ² =	0%	
Test for overall effect	: Z = 0.98	B(P=0)	.33)				
10.14.2 <2000							
Feeley 1975	2	12	1	13	0.5%	2.17 [0.22, 20.94]	
Nelson 1987	4	20	4	18	1.8%	0.90 [0.26, 3.08]	
Subtotal (95% CI)		32		31	2.3%	1.10 [0.37, 3.24]	
Total events	6		5				
Heterogeneity: Tau ² =	= 0.00; Ch	$10^2 = 0.4$	15, df = 1	I (P = 0)	.50); $I^2 =$	0%	
Test for overall effect	Z = 0.17	P = 0	.86)				
Total (95% CI)		546		527	100.0%	1.09 [0.92, 1.28]	•
Total events	194		172				
Heterogeneity: Tau ² =	= 0.00; Ch	$11^2 = 1.2$	27, df = 3	B (P = 0)	.74); $I^2 =$	0%	
Test for overall effect	: Z = 0.99	$\Theta(P=0)$.32)				Eavours higher PEEP Eavours lower PEEP
Test for subgroup dif	ferences:	$Chi^2 = 0$	0.00, df =	= 1 (P =	0.98), I ²	= 0%	

Online Resource 10. Meta-regression

Table S9. Meta-regression for the association between PEEP level and primary outcome and
main secondary outcomes using tidal volume as covariate

Outcome	β (95% confidence interval)	P value						
Hospital mortality	-0.056 (-0.116 - 0.003)	0.07						
PaO ₂ /FiO ₂	-8.20 (-32.8 - 16.4)	0.51						
Risk of hypoxemia	-0.41 (-0.770.06)	0.02						
Risk of barotrauma	0.08 (-0.06 - 0.22)	0.28						
Risk of ARDS	0.01 (-0.12 – 0.15)	0.84						
Duration of ventilation	0.01 (-0.05 - 0.06)	0.80						
Hospital stay	-0.03 (-0.39 - 0.34)	0.89						
Abbreviations: PEEP positive and expiratory pressure: PaO_{2}/FiO_{2} arterial partial pressure of								

Abbreviations: PEEP, positive end-expiratory pressure; PaO₂/FiO₂, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; ARDS, acute respiratory distress syndrome.

Online Resource 11. Trial sequential analysis

Trial sequential analysis assessing the relationship between higher vs. lower positive end-expiratory pressure (PEEP) and hospital mortality. The required information sizes to demonstrate or reject an 11% (vertical red line) relative risk reduction (RRR) for higher PEEP with a control group proportion of 33%, an alpha of 5%, and a beta of 10% is 6845 patients. The blue line represents the cumulative Z-curve of the meta-analysis of 1502 patients. The oblique red lines represent the trial sequential monitoring boundaries and the futility boundaries for 11% RRR, respectively. The green horizontal lines are the conventional 5% significance thresholds (Z-value = 1.96). A constant continuity correction of 1 was applied.



References

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