Higher PEEP for Acute Respiratory Distress Syndrome: A Bayesian meta–analysis of randomized clinical trials

ONLINE SUPPLEMENT

eMETHODS

Search term

The following search term was used: ((((positive end-expiratory pressure* OR PEEP) OR (open lung strategy* OR open lung approach) OR (recruitment AND (maneuver* OR manoeuvre*))) AND (ARDS OR acute respiratory distress syndrome OR ALI OR acute lung injury).

Inclusion Criteria

Randomized trials that compared strategies to determine PEEP levels in adult patients with ARDS were included. The following inclusion criteria was used: 1) adult patients; 2) use of low tidal volume ventilation in both arms; 3) demonstrated a difference in achieved PEEP levels between the groups; and 4) low-risk of bias RCT, according to the Cochrane Risk of Bias Tool. The definition for adult and ARDS criteria was according to each trial.

Study Selection

Two investigators (ASN and LB) independently reviewed the search results to identify pertinent articles and resolved disagreements on eligibility by consensus. Also, abstracted data and assessed risk of bias assessments was done by the same authors.

Data quality

Each trial was assessed for evidence of bias using the *Cochrane Collaboration Risk of Bias Tool*. Despite the description of the blinding of personnel, patients, or outcome assessors in the assessment of bias, these were not considered for final classification of the studies for the following two reasons: 1) because of the nature of the intervention, blinding investigators and healthcare personnel to the group allocation is not feasible; and 2) blinding of the outcome assessors would

not introduce a differential detection bias because the primary outcome assessed was mortality. An RCT was considered of low-risk of bias when all of the six main components of the assessment were graded as 'low risk of bias'.

Down–Weighting

The following rule was applied to down–weight the maximum recruitment strategy trials altogether:

1. The estimated variance of the log relative risk in trial *i* is:

$$V_i = \frac{S_i}{n_i}, \text{ where } S_i = \left(\frac{1}{p_{ti}} + \frac{1}{p_{ci}} - 2\right) \text{ and } n_i \text{ is the per-arm sample size } (Eq.1)$$

2. We want to discount so that the variance is what we would get in a smaller study of sample size:

$$\text{Sample size} = F \times n_i \ (0 < F < 1) \ (Eq.2)$$

3. The V_i after discount is:

$$V_i = \frac{S_i}{(n_i \times F)} = \left(\frac{1}{F}\right) \times V_i \ (Eq.3)$$

4. F is a factor as:

$$F = 1 - D = 1 - \text{discount factor } (Eq.4)$$

5. The final V_i after down–weighting by D is:

$$V_i = V_i \times \frac{1}{(1-D)}, \ (0 < D < 1)$$

eTable 1 – Probability distributions representing prior beliefs about mortality benefit from higher levels of PEEP in patients with ARDS

Prior Belief	Median RR	SD of log(RR)	Probability of Treatment Effect for a Specific Threshold, %			Rationale
			RR < 1.00	RR < 0.97	RR < 0.90	
Minimally informative	1.00	0.42	50	47	40	Probability of 0.50 < RR < 2.00 is 90%
Enthusiastic	0.75	0.17	95	93	85	Probability of treatment effect ≥ that assumed in ART trial design (RR = 0.75) is 50%; probability of harm (RR > 1) is 5%
Skeptical	1.00	0.17	50	43	27	Probability of treatment effect ≥ that assumed in ART trial design (RR = 0.75) is 5%; probability of harm (RR > 1) is 50%
Pessimistic	1.20	0.11	05	03	01	Probability of treatment effect equal that found in ART trial (RR = 1.20) is 50%; probability of benefit (RR < 1) is 5%
Heterogeneity (*tau*)	0.25	24.35	47	47	47	---

eTable 2 - PEEP Levels in the Included Studies

	Day 1		Day 3		Day 7	
	PEEP in Intervention	**PEEP in Control**	**PEEP in Intervention**	**PEEP in Control**	**PEEP in Intervention**	**PEEP in Control**
Brower 2004	14.7 ± 3.5	8.9 ± 3.5	12.9 ± 4.5	85. ± 3.7	12.9 ± 4.0	8.4 ± 4.3
Meade 2008	15.6 ± 3.9	10.1 ± 3.0	11.8 ± 4.1	8.8 ± 3.0	10.3 ± 4.3	8.0 ± 3.1
Mercat 2008	14.6 ± 3.2	7.1 ± 1.8	13.4 ± 4.7	6.7 ± 1.8	8.9 ± 5.1	6.2 ± 2.1
Talmor 2008	19	10	17.0 ± 6.0	10.0 ± 4.0	---	---
Hodgson 2011*	15.0 ± 1.0	10.0 ± 0.5	12.1 ± 1.5	9.3 ± 1.4	8.5 ± 1.8	7.8 ± 2.0
Kacmarek 2016	15.8 ± 3.8	11.6 ± 2.5	14.3 ± 3.9	10.7 ± 3.3	11.2 ± 4.4	10.5 ± 3.9
Cavalcanti 2017**	16.2 (15.9 to 16.6)	12.0 (11.7 to 12.3)	14.2 (13.8 to 14.6)	10.5 (10.2 to 10.9)	11.6 (11.2 to 12.1)	9.6 (9.3 to 10.0)
Hodgson 2019	16.1 ± 3.6	11.3 ± 4.0	13.3 ± 4.9	10.8 ± 4.9	9.8 ± 3.6	10.3 ± 4.6

Data are mean ± standard deviation, mean (95% confidence interval)

* Data is mean ± standard error

** Data is mean (95% confidence interval)

eTable 3 – Characteristics of the included studies in the sensitivity analysis of the open lung approach

Study	Centers	Location	ARDS Severity	Intervention			Control			Primary Outcome	Outcome Used in Meta–Analysis
				N	PEEP	Tidal Volume*	N	PEEP	Tidal Volume*		
Brower 2004	23	USA	PF < 300	85	Higher PEEP / FiO_2 chart with RM**	6	273	Lower PEEP / FiO_2 chart	6	Hospital mortality	Hospital mortality
Meade 2008	30	Canada, Australia, and Saudi Arabia	PF ≤ 250	475	Higher PEEP / FiO_2 chart with RM	6	508	Lower PEEP / FiO_2 chart	6	Hospital mortality	28–day mortality
Talmor 2008	01	USA	PF < 300	30	Titrated to PL of 0–10 cmH_2O with RM	6	31	Lower PEEP / FiO_2 chart	6	PF at day 03	28–day mortality
Hodgson 2011	01	Australia	PF < 200	10	Titrated according to SpO_2 with RM	6	10	Lower PEEP / FiO_2 chart	6	Inflammatory biomarkers	Hospital mortality
Kacmarek 2016	20	Brazil, Spain, Chile, USA and South Korea	PF ≤ 200	99	Titrated according C_{RS} with RM	6	101	Lower PEEP / FiO_2 chart	6	60–day mortality	28–day mortality
Cavalcanti 2017	120	Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, and Uruguay	PF ≤ 200	501	Titrated according C_{RS} with RM	6	509	Lower PEEP / FiO_2 chart	6	28–day mortality	28–day mortality
Hodgson 2019	35	Australia, Ireland, Saudi Arabia, New Zealand, and United Kingdom	PF ≤ 200	58	Titrated according to SpO_2 with RM	6	57	Lower PEEP / FiO_2 chart	6	VFD–28	28–day mortality

ARDS: acute respiratory distress syndrome; C_{RS}: respiratory system compliance; N: number of patients; RM: recruitment maneuver; PEEP: positive end–expiratory pressure; PF: PaO_2 / FiO_2; P_L: transpulmonary pressure; P_{plat}: plateau pressure; SpO_2: pulse oximetry; USA: United States of America; VFD–28: ventilator–free days at day 28

* reported in mL/kg predicted body weight

** first 80 patients received recruitment maneuvers

eTable 4 – Characteristics of the included studies in the sensitivity analysis of moderate–to–severe ARDS patients

Study	Centers	Location	ARDS Severity	Intervention			Control			Primary Outcome	Outcome Used in Meta–Analysis
				N	PEEP	Tidal Volume*	N	PEEP	Tidal Volume*		
Brower 2004	23	USA	PF ≤ 200	215	Higher PEEP / FiO^2 chart without RM**	6	196	Lower PEEP / FiO^2 chart	6	Hospital mortality	Hospital mortality
Meade 2008	30	Canada, Australia, and Saudi Arabia	PF ≤ 200	406	Higher PEEP / FiO^2 chart with RM	6	419	Lower PEEP / FiO^2 chart	6	Hospital mortality	28–day mortality
Mercat 2008	37	France	PF ≤ 200	323	Titrated to P_{plat} of 28–30 cmH_2O without RM	6	318	5 – 9 cmH_2O	6	28–day mortality	28–day mortality
Hodgson 2011	01	Australia	PF ≤ 200	10	Titrated according to SpO_2 with RM	6	10	Lower PEEP / FiO^2 chart	6	Inflammatory biomarkers	Hospital mortality
Kacmarek 2016	20	Brazil, Spain, Chile, USA and South Korea	PF ≤ 200	99	Titrated according C_{RS} with RM	6	101	Lower PEEP / FiO^2 chart	6	60–day mortality	28–day mortality
Cavalcanti 2017	120	Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, and Uruguay	PF ≤ 200	501	Titrated according C_{RS} with RM	6	509	Lower PEEP / FiO^2 chart	6	28–day mortality	28–day mortality
Hodgson 2019	35	Australia, Ireland, Saudi Arabia, New Zealand, and United Kingdom	PF ≤ 200	58	Titrated according to SpO_2 with RM	6	57	Lower PEEP / FiO^2 chart	6	VFD–28	28–day mortality

ARDS: acute respiratory distress syndrome; C_{RS}: respiratory system compliance; N: number of patients; RM: recruitment maneuver; PEEP: positive end–expiratory pressure; PF: PaO_2 / FiO_2; P_L: transpulmonary pressure; P_{plat}: plateau pressure; SpO_2: pulse oximetry; USA: United States of America; VFD–28: ventilator–free days at day 28

* reported in mL/kg predicted body weight

** data presented in the individual patient data meta–analysis from three previous trials

eTable 5 - Summary of Findings

Author(s): Serpa Neto et al
Question: Higher versus lower PEEP in ARDS
Setting: Intensive Care
Bibliography: High PEEP versus Low PEEP for ARDS.

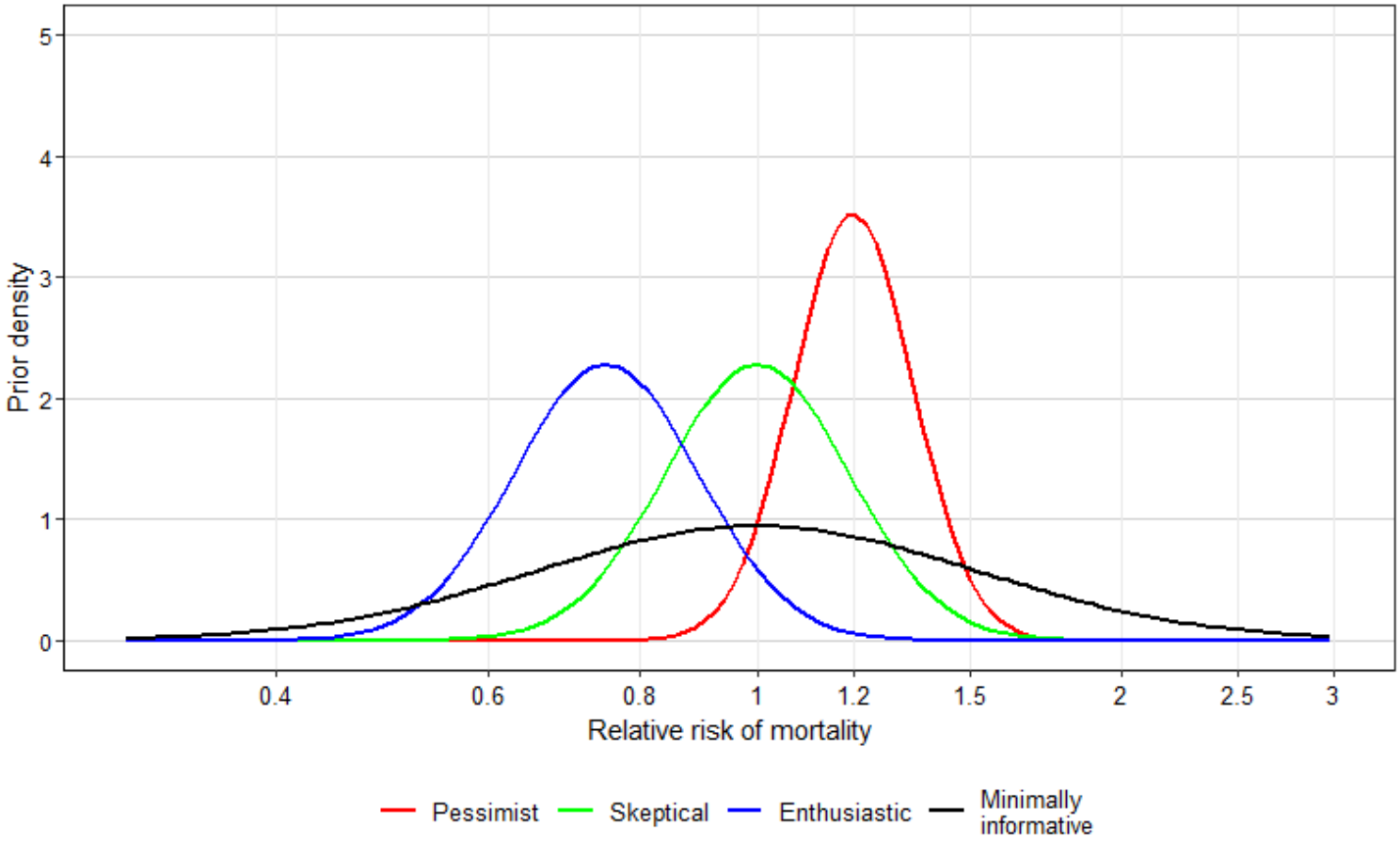
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher PEEP	Lower PEEP	Relative (95% CI)	Absolute (95% CI)		
28-Day mortality												
8	randomized trials	not serious	serious	not serious	serious	none	639/1833 (34.9%)	658/1814 (36.3%)	**RR 0.99** (0.91 to 1.08)	**4 fewer per 1,000** (from 33 fewer to 29 more)	⨁⨁◯◯ LOW	CRITICAL
28-Day mortality - Not maximum recruitment strategy												
4	randomized trials	not serious	not serious	not serious	serious	none	323/1166 (27.7%)	363/1194 (30.4%)	**RR 0.91** (0.80 to 1.04)	**27 fewer per 1,000** (from 61 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
28-Day mortality - Maximum recruitment strategy												
4	randomized trials	not serious	serious [a]	not serious	serious	none	316/667 (47.4%)	295/620 (47.6%)	**RR 1.10** (0.98 to 1.23)	**48 more per 1,000** (from 10 fewer to 109 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The ART trial increased mortality in the higher PEEP group compared to the other trials.

Figure S1 – Priors over the plausible range of values for relative risks for mortality with higher levels of PEEP in patients with ARDS



ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure. Prior distributions trying to match the range of beliefs about the benefit of higher levels of PEEP.

Figure S2 – Heterogeneity prior over the plausible range of *tau* values

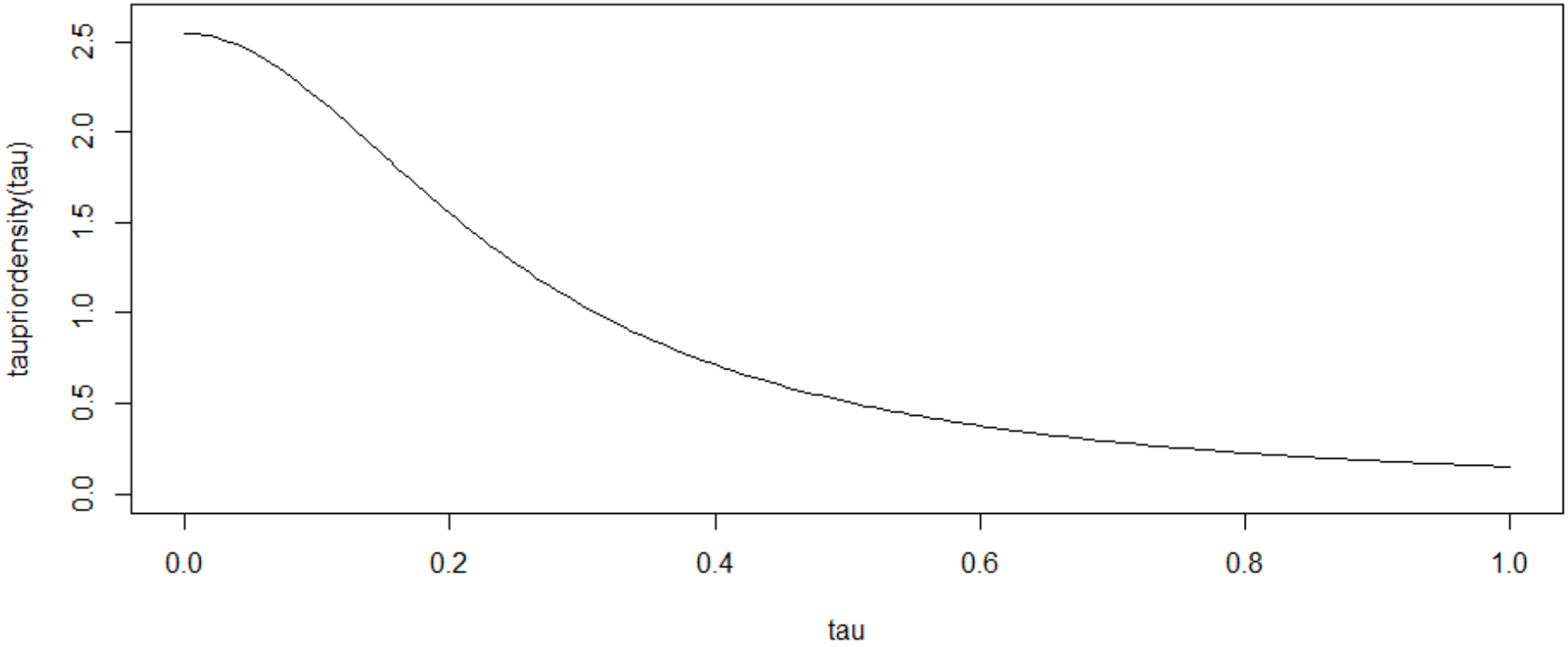
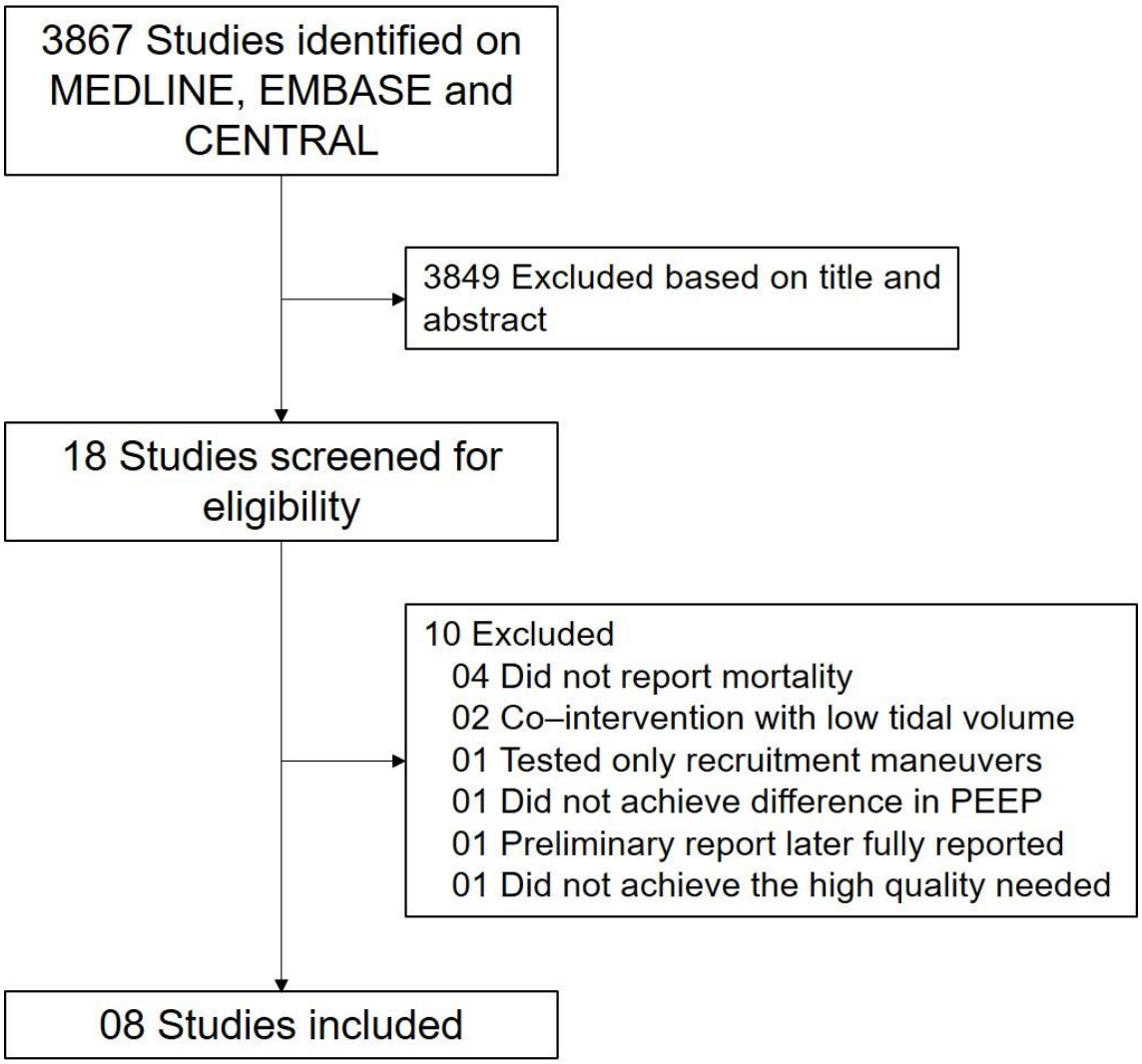
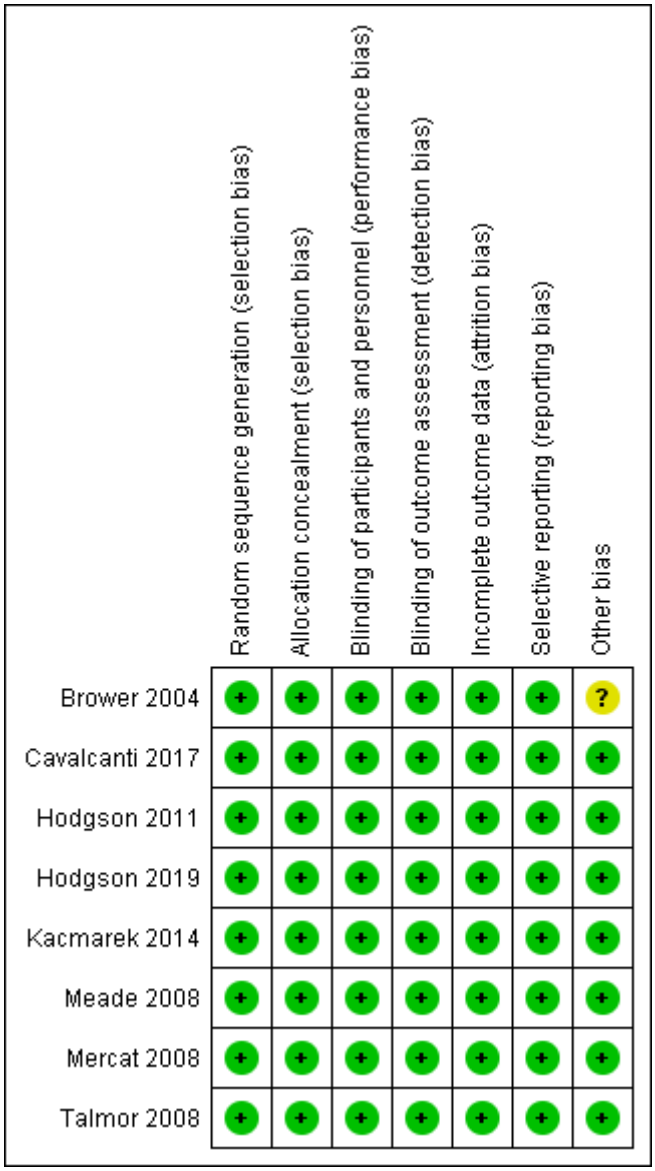


Figure S3 – Flowchart of study inclusion



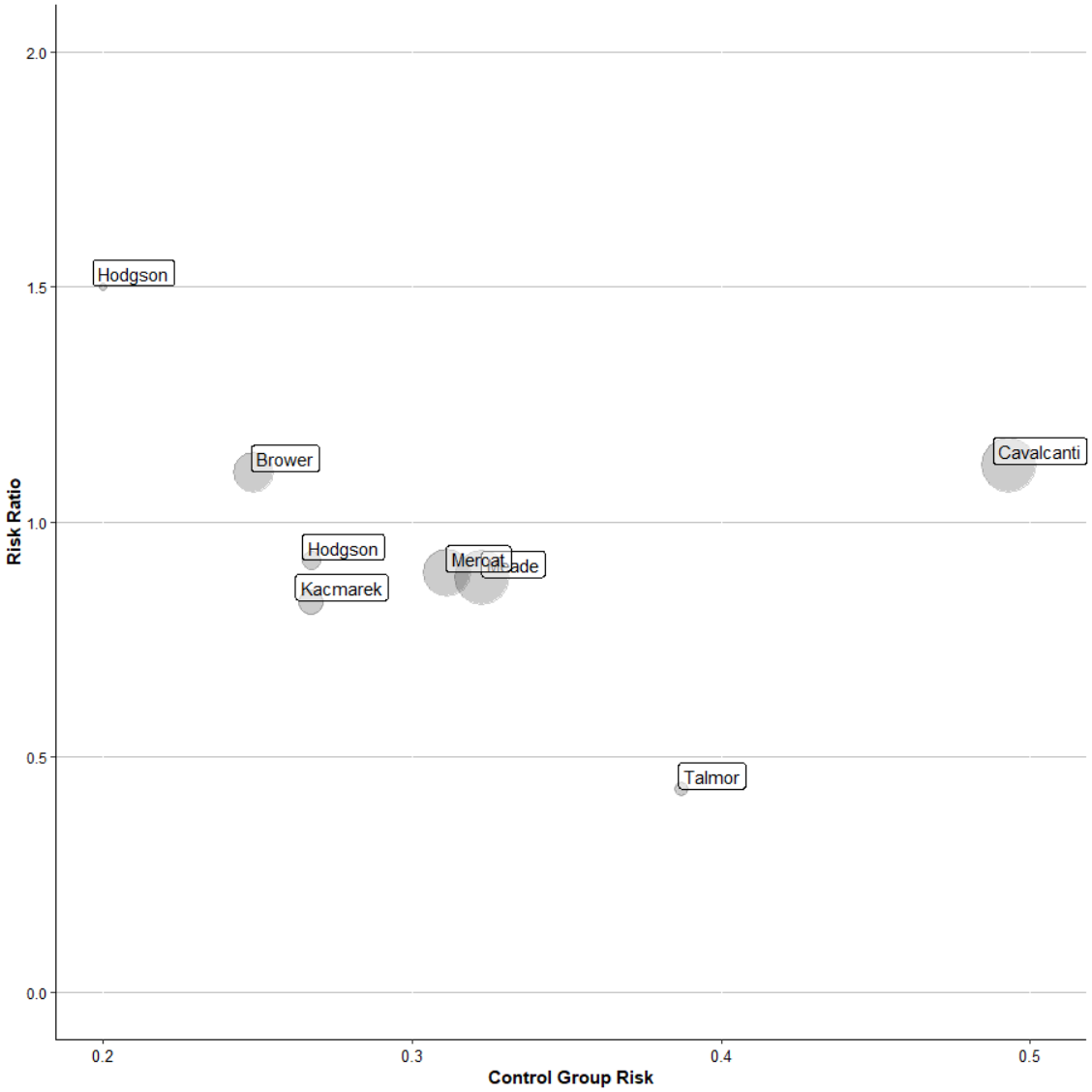
PEEP: positive end–expiratory pressure

Figure S4 – Quality of the studies considered in the data–derived priors



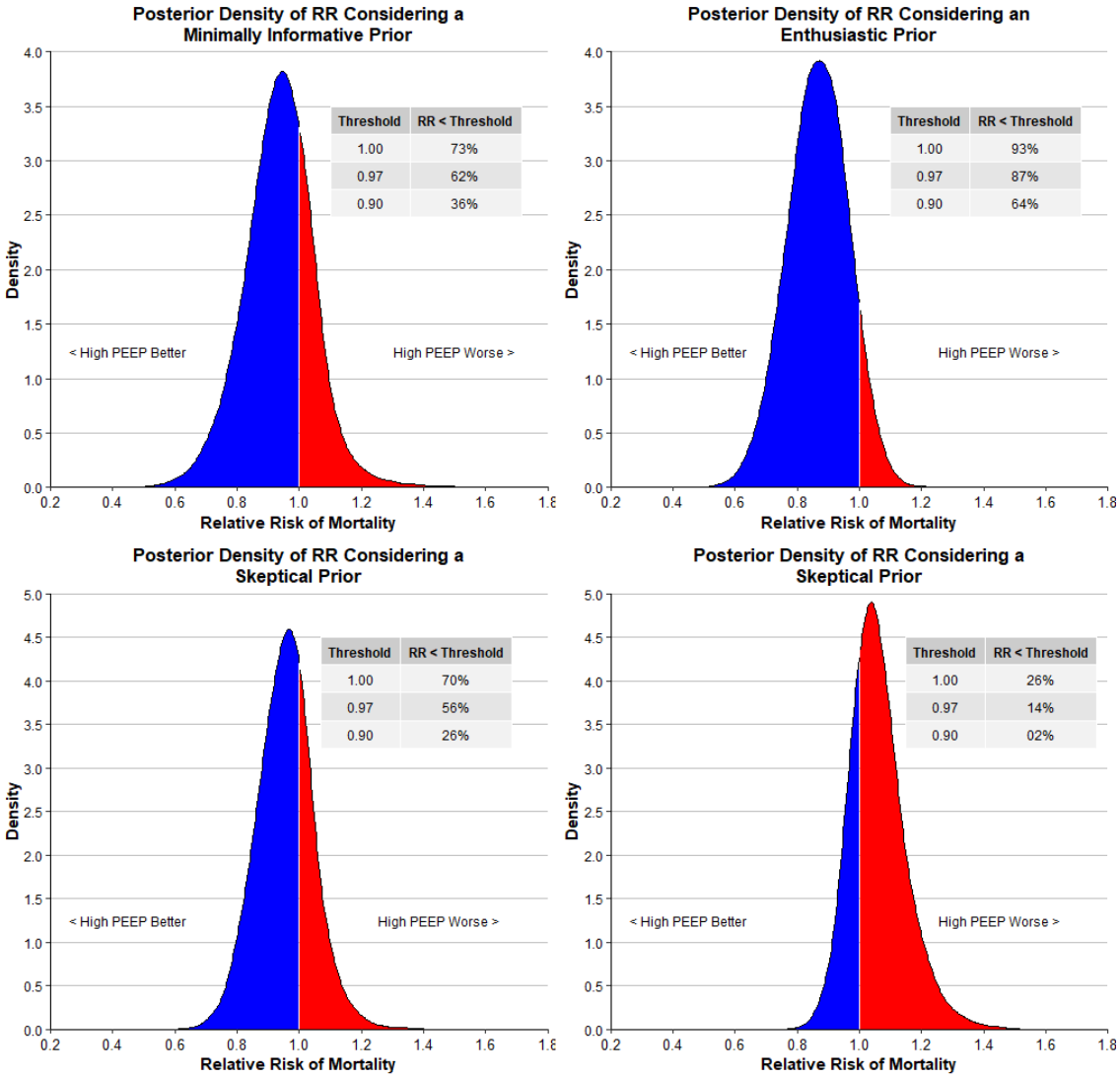
Quality according to the *Cochrane Risk of Bias Tool*

Figure S5 – Relative risk of each study according to the mortality in the control group



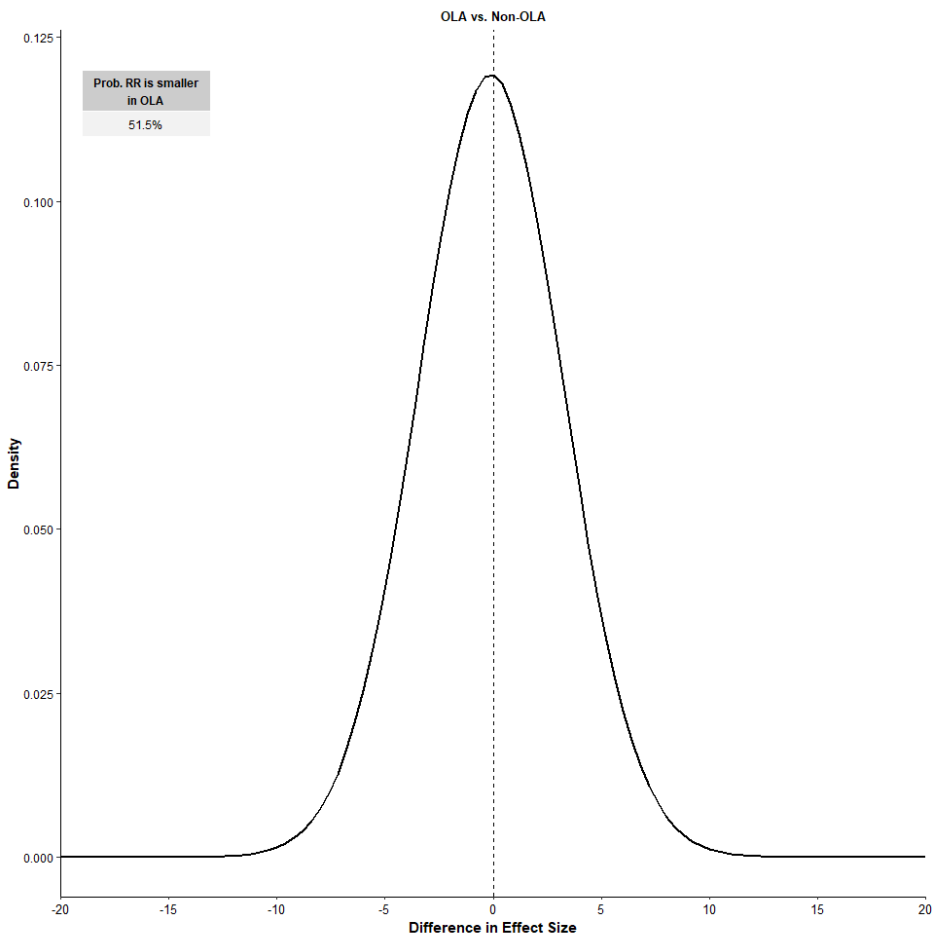
Control group is the low PEEP group.

Figure S6 – Posterior density of relative risk for the meta–analysis considering only studies performing open lung approach under a A) minimally informative, B) an enthusiastic prior, C) a skeptical prior, and D) a pessimistic prior



Full posterior density from the Markov chain Monte Carlo approach. The red area is where RR > 1 and higher levels of PEEP increase mortality

Figure S7 – Heterogeneity of treatment effect in each of the subgroups assessed



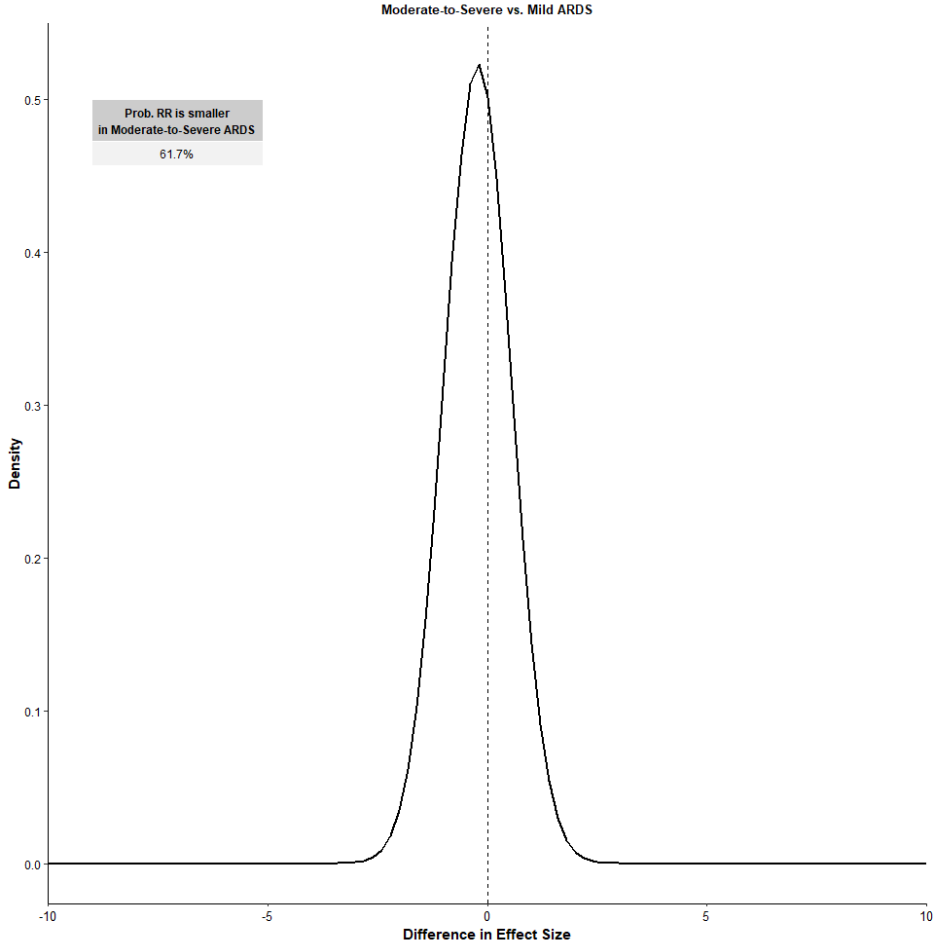
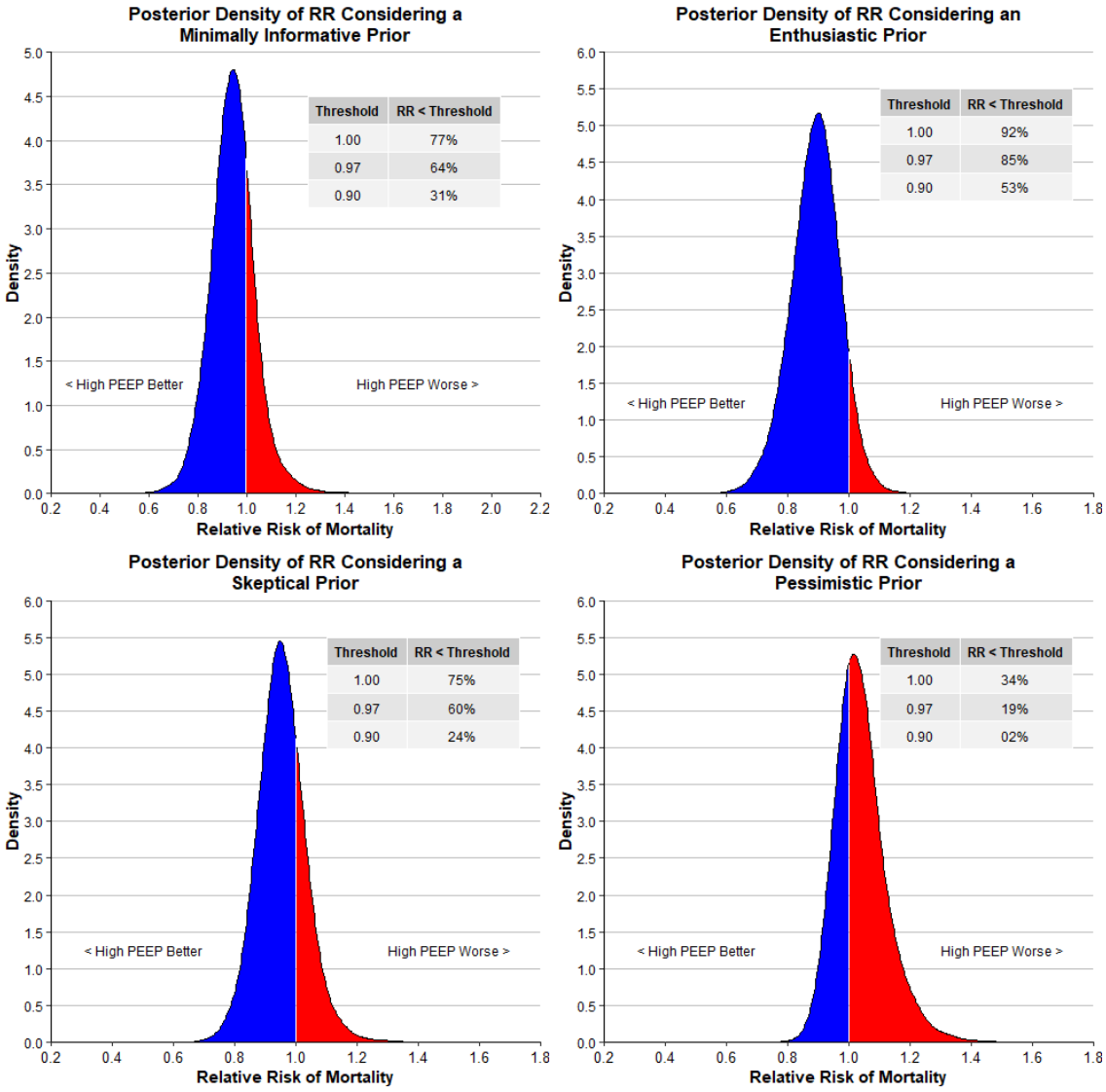


Figure S8 – Posterior density of relative risk for the meta–analysis considering only patients with moderate–to–severe ARDS under a) minimally informative, B) an enthusiastic prior, C) a skeptical prior and D) a pessimistic prior



Full posterior density from the Markov chain Monte Carlo approach. The red area is where RR > 1 and higher levels of PEEP increase mortality.