Higher PEEP for acute respiratory distress syndrome: a Bayesian meta-analysis of randomised clinical trials

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Ventilation with higher positive end expiratory pressure (PEEP) for acute respiratory distress syndrome (ARDS) may prevent atelectasis, improve oxygenation, and reduce the risk of ventilator-induced lung injury.[1] Three large, high quality randomised clinical trials (RCTs), however, failed to show mortality benefit of higher PEEP compared with lower PEEP.[2-4] A subsequent meta-analysis of individual patient data from these high quality RCTs suggested a survival benefit with higher PEEP in patients with moderate-to-severe hypoxemia.[5] In addition, subsequent conventional meta-analysis pointed toward some benefit of higher levels of PEEP.[6-8] Based on these findings, guidelines issuing a conditional recommendation in favour of higher PEEP for ARDS have been published.[9-11]

One large, high quality RCT that tested the effect of combining higher PEEP with a maximum recruitment strategy, also known as the open lung approach, found a higher mortality rate and more barotrauma with this approach.[12,13] Another RCT, which was stopped early because of the findings of the previous study, found no mortality benefit but more cardiac arrhythmias with higher PEEP and a maximum recruitment strategy.[14] In both studies, harm could have been caused by aggressive recruitment manoeuvres, potentially increasing the risk of barotrauma and causing hemodynamic instability.[14]

In view of these conflicting findings, there is substantial debate over how to interpret the current body of evidence and whether another RCT is needed to determine if higher PEEP benefits or harms patients with ARDS. To clarify the current state of evidence for higher versus lower PEEP, we conducted a systematic review and Bayesian meta-analysis to estimate the posterior probability of mortality benefit and harm with the use of higher PEEP in patients with ARDS. In addition, we addressed possible safety concerns relating to the use of a maximum recruitment strategy through a process of down-weighting trials that implemented this strategy.

ABSTRACT

Objective: Benefit or harm of higher positive end expiratory pressure (PEEP) for acute respiratory distress syndrome (ARDS) is controversial. We aimed to assess the impact of higher levels of PEEP in patients with ARDS under a Bayesian framework.

Design: Systematic review and Bayesian meta-analysis of randomised clinical trials comparing higher to lower PEEP in adult patients with ARDS.

Data sources: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from 1996 to 1 March 2020.

Review methods: We extracted data from high quality randomised clinical trials comparing higher to lower levels of PEEP in adult patients, using low tidal volume in both arms, and conducted a Bayesian meta-analysis using aggregate data from these studies.

Results: Eight clinical trials including 3703 patients (n = 1833 for higher PEEP, n = 1870 for lower PEEP) were included. Under a minimally informative prior, the posterior probability of benefit with higher PEEP was 65% (relative risk, 0.97 [95% credible interval, 0.78–1.14]). In patients with moderate-to-severe ARDS, the posterior probability of benefit with higher PEEP was 77% (relative risk, 0.94 [95% credible interval, 0.77–1.13]). Down-weighting studies that employed a maximum recruitment strategy by 100% increased the posterior probability of benefit to 92% under a minimally informative prior.

Conclusions: The probability of benefit or harm from routine use of higher PEEP for patients with ARDS ranges from 27% to 86%, and from 14% to 73% depending on one's prior, suggesting continued uncertainty and equipoise regarding the benefit of PEEP. If data from trials using a maximum recruitment strategy is discounted to some extent because of uncertainty over the appropriateness of this approach, the available evidence suggests that higher PEEP could be beneficial for moderate-to-severe ARDS. However, well powered randomised clinical trials are needed to confirm these findings.

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Methods

Design

We conducted a systematic review and Bayesian meta-analysis using aggregate data of studies comparing higher PEEP versus lower PEEP for ARDS.

Search strategy

For this review, higher PEEP included any strategy that resulted in PEEP higher than a comparator strategy used to determine PEEP. A recent systematic review comparing higher versus lower PEEP for ARDS was identified,[8] and we updated the search to include additional trials. We electronically searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials from 1996 to 1 March 2020. The search term combined medical subject headings and key words to identify studies of patients with ARDS. Additional details on the search term are provided online (Supporting Information).

Inclusion criteria

Studies that compared strategies to determine PEEP levels in adult patients with ARDS were included if they met the following criteria: adult patients; use of low tidal volume ventilation in both arms; demonstrated a difference in achieved PEEP levels between the groups; and RCT with low risk of bias, according to the Cochrane risk-of-bias tool. The definition of adult and the ARDS criteria were according to each trial. No language restrictions were applied.

Determining thresholds for minimum clinically important treatment effect

We considered the following relative risks (RRs) as possible thresholds for the minimum clinically important treatment effect for analysis: RR < 1.00; RR < 0.97; and RR < 0.90. These thresholds seemed reasonable in view of several considerations. First, the null hypothesis in the frequentist approach is no benefit (RR = 1.00), thus we estimated the probability of any benefit (RR < 1.00) to evaluate the equivalent hypothesis under Bayesian terms. Second, since increasing PEEP is a highly feasible intervention that comes at no additional financial cost, even small beneficial effects on mortality would be sufficient to justify its use. Indeed, a RR of 0.97 would be equivalent to an estimated 440 lives saved per year in United States (assuming 104 000 cases of ARDS annually, with 40% of these meeting the criteria for moderate-to-severe ARDS, and a baseline mortality rate of 35%).[15,16] To expand the possible detectable effects, we also computed the posterior probabilities at a RR of 0.90, equivalent to 1456 lives saved annually in US. Third, to understand the possible harm, we also report the probability of harm, defined as a RR > 1.00 (the null hypothesis).

Outcome

The outcome we used for this analysis was 28-day mortality when available, or the longest mortality endpoint reported when 28-day mortality was not available.

Specification of priors

By definition, priors are probability distributions that express one's beliefs about an outcome before some evidence is taken into account. We used priors to reflect varying degrees of beliefs about benefit or harm of higher PEEP. We used a minimally informative prior to produce results essentially dependent on data from the meta-analysis alone. In this prior, there is 90% probability of 0.50 < RR < 2.00. With the use of this prior, most of the results are based on the data of the included studies. Then, we defined three additional priors to represent archetypes of prior belief that PEEP effectively lowers mortality (enthusiasm), is ineffective (scepticism) or is harmful (pessimism). The enthusiastic prior distribution was centred at a RR of 0.75, based on the assumed RR of death used to power the Alveolar Recruitment for ARDS trial (RR ≤ 0.75) with a probability of RR > 1.00 of 5%. The sceptical prior distribution was centred at a RR of 1.00 and defined such that the probability that RR of death with higher PEEP used to power of one of the latest studies (RR ≤ 0.75) was only 5%.[12,13] The pessimistic prior distribution was centred at a RR of 1.20 based on the RR of death found in the Alveolar Recruitment for ARDS trial with a probability of RR < 1.00 of 5%. An enthusiastic prior was used because, given the available evidence, a negative result should be sufficiently strong to convince a reasonable enthusiast against the use of higher PEEP in ARDS, while a positive result given the sceptical prior should be sufficiently strong to convince a reasonable sceptic in favour of the use of higher PEEP in ARDS. A minimally informative half-Cauchy prior was used for the heterogeneity parameter in all analyses. Further details about the priors and probability density distributions for the RR specified by each prior distribution are available online (Supporting Information, eTable 1, Figure S1 and Figure S2).

Statistical analysis

We built separate Bayesian models for each of the prior distributions on the logarithm of the RR for higher PEEP. We then computed the probability of observing the data collected in the RCT for each possible value of RR. All models treated the numbers of deaths in the higher PEEP group and lower PEEP group as independent samples from binomial distributions and placed a uniform prior on the probability of death in the lower PEEP (p_c) group so that the probability in the higher PEEP group was RR × p_c. We used numerical integration to derive treatment effect estimates

and 95% credible intervals (CrIs) from the median and the 2.5th and 97.5th percentiles of the posterior distribution, and to estimate the posterior probabilities of treatment effects exceeding the proposed cut-offs.

We carried out three sensitivity analyses. In the first, we restricted the analysis to studies that used higher PEEP with recruitment manoeuvres in the intervention arm. One study only used recruitment manoeuvres in the first 80 patients and reported data for the first 85 patients assigned to higher PEEP separately from the remaining patients enrolled in the study.[2] Therefore, for this sensitivity analysis, data could be used from these 85 patients.

In the second sensitivity analysis, we sought to account for uncertainty and debate about the appropriateness of using a maximum recruitment strategy, defined as recruitment manoeuvres allowing increases in PEEP levels of up to 40 cmH_2O. To do so, we inflated the variances of the studies employing this strategy, effectively down-weighting the contribution of these studies to the pooled estimate of effect. We inflated the variances to varying degrees so that the effective sample sizes of these studies were reduced by 25%, 50%, 75% and 100% relative to their actual sample sizes; a full description of this process is available online (Supporting Information, eMethods).

For the third sensitivity analysis, we restricted the analysis to patients with moderate-to-severe ARDS, defined as PaO_2 to FiO_2 ratio (ratio between partial pressure of oxygen [arterial] and fraction of inspired oxygen) ≤ 200. We conducted this analysis owing to a previous meta-analysis of individual patient data that suggested a statistically significant mortality benefit in this subgroup.[5] For this analysis, we extracted data from three studies from the previous meta-analysis of individual patient data that stratified patients according to PaO_2 to FiO_2 ratio.[2-5] We estimated the heterogeneity of treatment effect of higher PEEP through a Bayesian heterogeneity of treatment effect model and present this as the Bayesian posterior probability of heterogeneity, which is the probability of a different effect in one of the subgroups.

We present overall quality of the evidence in a summary of findings table based on the GRADE approach. We conducted all analyses in R version 3.6.3 (R Foundation) using the R2jags (R package version 0.5-7) and bayesmeta packages.[17-19]

Results

Characteristics of the included studies

The initial search yielded 3867 articles and, of these, we excluded 3849 based on title and abstract because they did not meet the inclusion criteria. Subsequently, we assessed 18 studies as full text. Of these, we excluded four that did not report mortality data, two that assessed a co-intervention with tidal volume reduction, one that investigated only recruitment manoeuvre, one that did not achieve a difference of PEEP in both arms, one that was a preliminary report that was later reported as a final report, and one that had a high risk of bias. Thus, we included eight studies in our meta-analysis, which included 3703 patients (n = 1833 for higher PEEP, n = 1870 for lower PEEP).[2-4,12,14,20-22] A flowchart of study inclusion is provided online (Supporting Information, Figure S3) and characteristics of the included studies are shown in Table 1. PEEP levels in the included studies, a summary of the risk of bias in the studies as assessed by the Cochrane risk-of-bias tool, and the RR of each study according to mortality in the control group are available online (Supporting Information, eTable 2, Figure S4, Figure S5).

Bayesian meta-analysis

Under the minimally informative prior, the estimated median RR for 28-day mortality with the use of higher PEEP was 0.97 (95% CrI, 0.78 to 1.14) (Table 2 and Figure 1). The probabilities of mortality benefit (RR < 1.00) and harm (RR > 1.00) with higher PEEP were 65% and 35%, respectively, and the probability of a RR < 0.90 was 20%. Under an enthusiastic prior, the posterior probabilities of RR < 1.00 and RR > 1.00 were 86% and 14%, respectively, while under a sceptical prior they were 64% and 36% and under a pessimistic prior they were 27% and 73% (Table 2 and Figure 1).

Sensitivity analyses

The studies employing an open lung approach are described online (Supporting Information, eTable 3).[2,4,12,14,20-22] Considering only studies employing the open lung approach, the estimated median RR for 28-day mortality with the use of higher PEEP was 0.93 (95% CrI, 0.70 to 1.16) and the probability of any mortality benefit (RR < 1.00) with higher PEEP was 73% (Table 2 and Supporting Information, Figure S6). Under an enthusiastic prior, the probability of any mortality benefit increased to 93%, while under a sceptical prior it was 70% and under a pessimistic prior it was 26% (Table 2 and Supporting Information, Figure S6). The probability of a lower RR in the open lung approach subgroup, compared with the non-open lung approach subgroup, was 52% (Supporting Information, Figure S7).

In one sensitivity analysis, we re-assessed the Bayesian meta-analysis after down-weighting studies that used a maximum recruitment strategy.[12,14,20,22] Under a minimally informative prior, the probability of any mortality benefit with the use of higher PEEP was 80% when completely

Table 1. Characteristics of studies included in the meta-analysis

Study	Centres	Location(s)	PaO_2 to FiO_2 ratio*	Intervention			Control			Primary outcome	Outcome used in meta-analysis
				N	PEEP	Tidal volume†	N	PEEP	Tidal volume†		
Brower 2004[2]	23	United States	< 300	276	Higher PEEP, FiO_2 chart without RM‡	6	273	Lower PEEP, FiO_2 chart	6	Hospital mortality	Hospital mortality
Meade 2008[4]	30	Canada, Australia and Saudi Arabia	≤ 250	475	Higher PEEP, FiO_2 chart with RM	6	508	Lower PEEP, FiO_2 chart	6	Hospital mortality	28-day mortality
Mercat 2008[3]	37	France	< 300	385	Titrated to P_{plat} of 28–30 cm-H_2O without RM	6	382	5–9 cm-H_2O	6	28-day mortality	28-day mortality
Talmor 2008[21]	1	United States	< 300	30	Titrated to P_L of 0–10 cmH_2O with RM	6	31	Lower PEEP, FiO_2 chart	6	PaO_2 to FiO_2 ratio at Day 3	28-day mortality
Hodgson 2011[20]	1	Australia	< 200	10	Titrated according to SpO_2 with RM	6	10	Lower PEEP, FiO_2 chart	6	Inflam-matory biomarkers	Hospital mortality
Kacmarek 2016[22]	20	Brazil, Spain, Chile, United States and South Korea	≤ 200	99	Titrated according C_{RS} with RM	6	101	Lower PEEP, FiO_2 chart	6	60-day mortality	28-day mortality
Cavalcanti 2017[12]	120	Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain and Uruguay	≤ 200	501	Titrated according C_{RS} with RM	6	509	Lower PEEP, FiO_2 chart	6	28-day mortality	28-day mortality
Hodgson 2019[14]	35	Australia, Ireland, Saudi Arabia, New Zealand and United Kingdom	≤ 200	58	Titrated according to SpO_2 with RM	6	57	Lower PEEP, FiO_2 chart	6	Ventila-tor-free days at Day 28	28-day mortality

ARDS = acute respiratory distress syndrome. C_{RS} = respiratory system compliance. FiO_2 = fraction of inspired oxygen. PaO_2 partial pressure of oxygen (arterial). PEEP = positive end expiratory pressure. P_L = transpulmonary pressure. P_{plat} = plateau pressure. RM = recruitment manoeuvre. SpO_2 = oxygen saturation as measured by pulse oximetry. * Measure of ARDS severity. † Reported in mL/kg predicted body weight. ‡ First 80 patients received RMs.

discounting maximum recruitment strategy trials (Table 2 and Figure 2). Under an enthusiastic prior, the probability of any mortality benefit was 93%, under a sceptical prior it was 80% and under a pessimistic prior it was 35% (Table 2 and Figure 2).

The studies that we considered in the sensitivity analysis on moderate-to-severe ARDS patients are described online (Supporting Information, eTable 4).[2-5,12,14,20,22] After restricting our analysis to patients with moderate-to-severe ARDS, the estimated median RR for 28-day mortality under a minimally informative prior was 0.94 (95% CrI, 0.77 to 1.13) and the probability of RR < 1.00 was 77% (Table 2 and Supporting Information, Figure S8). Under an enthusiastic prior, the probability of any mortality benefit increased to 90%, while under a sceptical prior it was 75% and under a pessimistic prior it was 37% (Table 2 and Supporting Information, Figure S8). The probability of heterogeneity of treatment effect according to severity of ARDS (mild versus moderate-to-severe) was 62% (Supporting Information, Figure S12).

In patients with moderate-to-severe ARDS, the posterior probability of any mortality benefit and after completely

Table 2. Probability of treatment effects estimated by a Bayesian meta-analysis according to varying prior beliefs on mortality benefit from higher levels of PEEP in patients with ARDS

Prior belief	Posterior median RR (95% credible interval)	Probability of treatment effect for a specific threshold			
		RR < 1.00	RR < 0.97	RR < 0.90	RR > 1.00
Overall meta-analysis					
Minimally informative	0.97 (0.78 to 1.14)	65%	49%	20%	35%
Enthusiastic	0.91 (0.73 to 1.06)	86%	74%	41%	14%
Sceptical	0.97 (0.82 to 1.12)	64%	46%	14%	36%
Pessimistic	1.04 (0.92 to 1.21)	27%	13%	1%	73%
Sensitivity analysis considering only studies performing open lung approach					
Minimally informative	0.93 (0.70 to 1.16)	73%	62%	36%	27%
Enthusiastic	0.86 (0.67 to 1.04)	93%	87%	64%	7%
Sceptical	0.95 (0.78 to 1.14)	70%	56%	26%	30%
Pessimistic	1.06 (0.90 to 1.27)	26%	14%	2%	74%
Sensitivity analysis down-weighting clinical trials using a maximum recruitment strategy*					
Minimally informative					
25% down-weighting	0.97 (0.82 to 1.13)	65%	51%	18%	35%
50% down-weighting	0.97 (0.81 to 1.13)	67%	53%	20%	33%
75% down-weighting	0.95 (0.80 to 1.13)	72%	58%	25%	28%
100% down-weighting	0.91 (0.72 to 1.14)	80%	71%	46%	20%
Enthusiastic					
25% down-weighting	0.93 (0.77 to 1.08)	83%	72%	39%	17%
50% down-weighting	0.93 (0.77 to 1.07)	84%	74%	41%	16%
75% down-weighting	0.92 (0.76 to 1.06)	87%	78%	46%	13%
100% down-weighting	0.87 (0.70 to 1.04)	93%	88%	67%	7%
Sceptical					
25% down-weighting	0.98 (0.84 to 1.12)	64%	47%	13%	36%
50% down-weighting	0.97 (0.84 to 1.12)	66%	50%	14%	34%
75% down-weighting	0.96 (0.83 to 1.11)	71%	55%	19%	29%
100% down-weighting	0.93 (0.78 to 1.11)	80%	69%	35%	20%
Pessimistic					
25% down-weighting	1.03 (0.91 to 1.18)	29%	15%	1%	71%
50% down-weighting	1.03 (0.91 to 1.19)	31%	17%	2%	69%
75% down-weighting	1.03 (0.90 to 1.20)	34%	20%	3%	66%
100% down-weighting	1.03 (0.88 to 1.25)	35%	24%	6%	65%
Sensitivity analysis considering only patients with moderate-to-severe ARDS*					
Minimally informative					
No down-weighting	0.94 (0.77 to 1.13)	77%	64%	31%	24%

(*Continues*)

Table 2. Probability of treatment effects estimated by a Bayesian meta-analysis according to varying prior beliefs on mortality benefit from higher levels of PEEP in patients with ARDS (*continued*)

Prior belief	Posterior median RR (95% credible interval)	Probability of treatment effect for a specific threshold			
		RR < 1.00	RR < 0.97	RR < 0.90	RR > 1.00
25% down-weighting	0.94 (0.78 to 1.11)	77%	65%	32%	23%
50% down-weighting	0.93 (0.78 to 1.11)	79%	67%	34%	21%
75% down-weighting	0.92 (0.77 to 1.10)	84%	74%	42%	16%
100% down-weighting	0.86 (0.70 to 1.06)	92%	87%	67%	8%
Enthusiastic					
No down-weighting	0.89 (0.72 to 1.04)	90%	82%	52%	10%
25% down-weighting	0.90 (0.75 to 1.05)	91%	83%	53%	9%
50% down-weighting	0.90 (0.75 to 1.04)	92%	85%	55%	8%
75% down-weighting	0.88 (0.75 to 1.03)	95%	89%	62%	5%
100% down-weighting	0.83 (0.69 to 0.98)	99%	97%	84%	1%
Sceptical					
No down-weighting	0.95 (0.80 to 1.12)	75%	60%	23%	25%
25% down-weighting	0.95 (0.81 to 1.10)	76%	62%	24%	24%
50% down-weighting	0.94 (0.81 to 1.10)	78%	64%	27%	22%
75% down-weighting	0.93 (0.80 to 1.09)	83%	71%	34%	17%
100% down-weighting	0.88 (0.74 to 1.06)	92%	85%	58%	8%
Pessimistic					
No down-weighting	1.04 (0.90 to 1.24)	37%	22%	4%	63%
25% down-weighting	1.02 (0.89 to 1.19)	37%	23%	4%	63%
50% down-weighting	1.02 (0.89 to 1.20)	39%	25%	5%	61%
75% down-weighting	1.01 (0.87 to 1.21)	41%	28%	7%	59%
100% down-weighting	1.01 (0.84 to 1.28)	42%	31%	12%	58%

ARDS = acute respiratory distress syndrome. PEEP = positive end expiratory pressure. RR = relative risk. * Down-weighting refers to a deliberate reduction in the influence (weight) of trials using an open lung approach with maximum recruitment in the Bayesian meta-analysis by artificially increasing the variance of these studies.

down-weighting trials with a maximum recruitment strategy was 92% under a minimally informative prior, 99% under an enthusiastic prior, 92% under a sceptical prior, and 42% under a pessimistic prior (Table 2 and Figure 3).

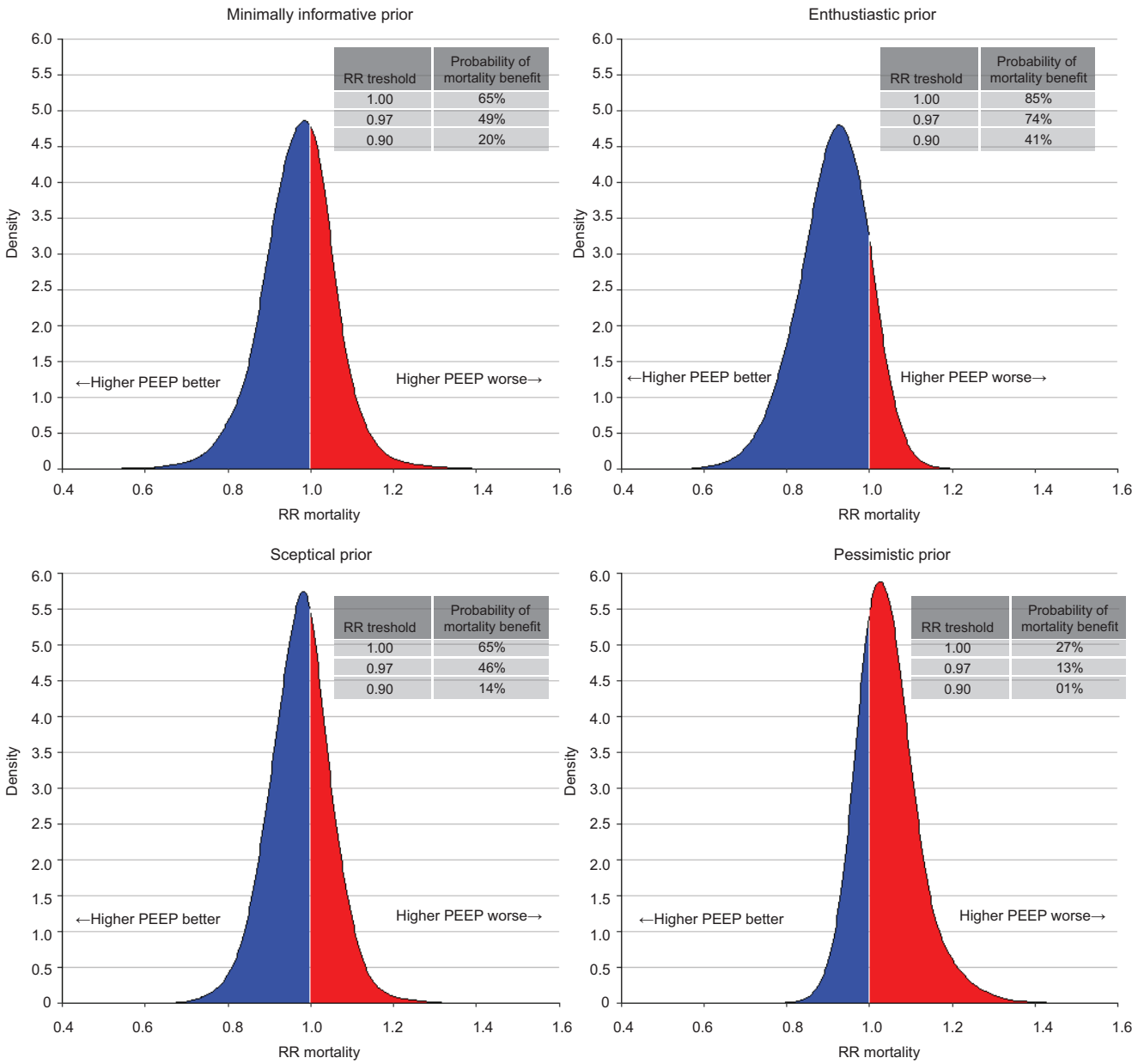
The overall quality of the evidence in the studies we included in this meta-analysis was low. A summary of our findings on study quality is presented online (Supporting Information, eTable 5).

Discussion

In this meta-analysis, we used a Bayesian approach to assess the posterior probability of mortality benefit and harm with higher versus lower PEEP for ARDS. The posterior probability of mortality benefit with higher PEEP ranged from 27% to 86% depending on the level of prior pessimism or enthusiasm. The posterior probability of benefit with higher PEEP increased considerably when studies using a maximum recruitment strategy were down-weighted, particularly in patients with moderate-to-severe ARDS. We conclude that there is considerable equipoise on the benefit or harm of PEEP and that a potential benefit of higher PEEP has not been ruled out. Further studies employing an optimal higher PEEP strategy in appropriately selected patients (ie, those for whom prior enthusiasm for higher PEEP is warranted) are required to resolve this uncertainty.

The impact of higher PEEP for ARDS has long been debated. While a meta-analysis of individual patient data from three large studies and two conventional meta-analyses found a potential benefit with the use of higher PEEP for moderate-to-severe ARDS,[5,6,8] no individual study showed that higher PEEP improved survival.[2-4,12,14,20-22] The

Figure 1. Posterior density of RR for the meta-analysis under a minimally informative prior, an enthusiastic prior, a sceptical prior and a pessimistic prior*

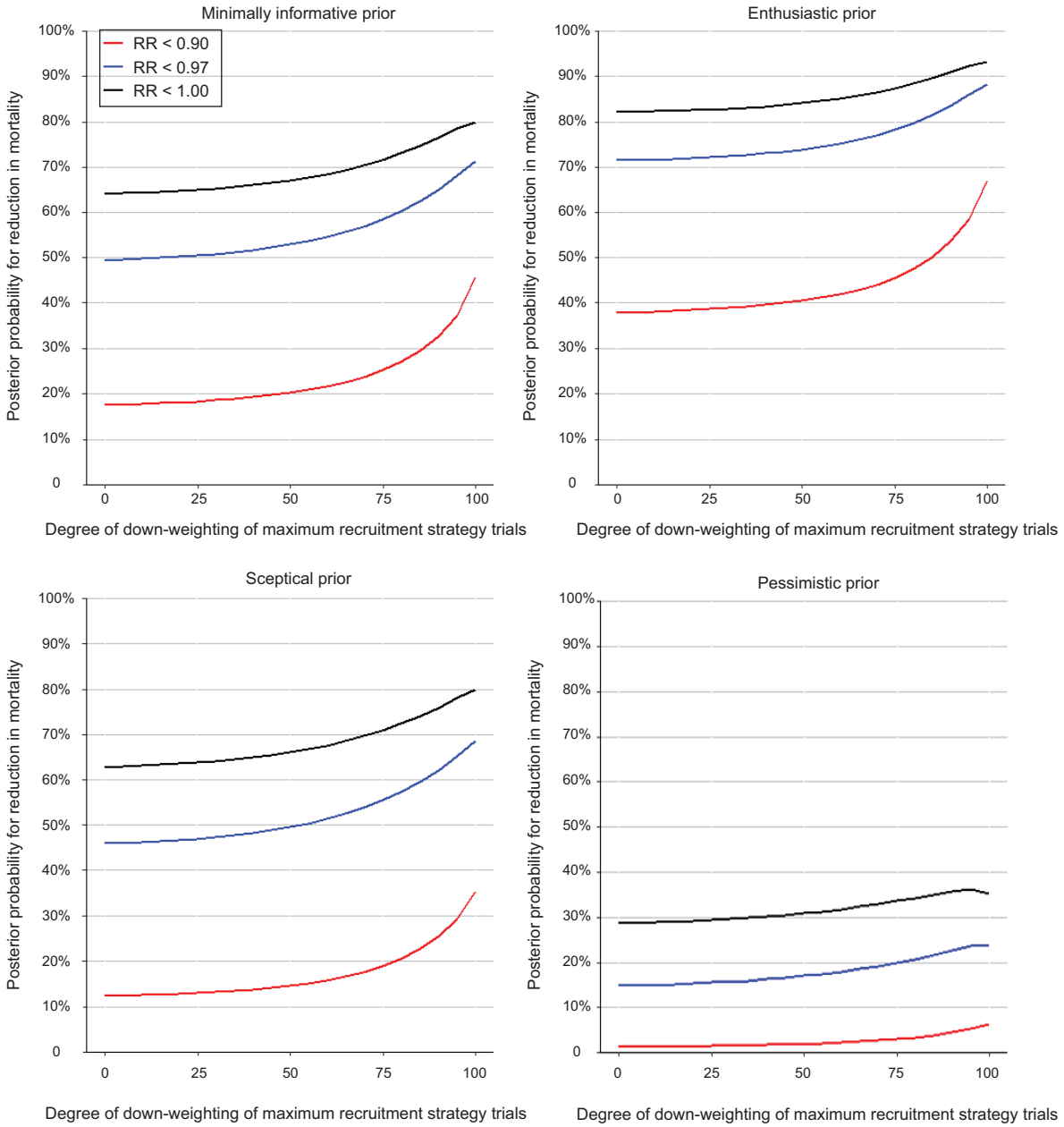


PEEP = positive end expiratory pressure. RR = relative risk. * Full posterior density from the Markov chain Monte Carlo approach. The red area represents RR > 1, where higher levels of PEEP increase mortality.

subsequent negative results of the two most recent studies even provide evidence that PEEP could be harmful.[12,14] Indeed, a recent global study of ventilation practice in ARDS demonstrated that clinicians typically use lower PEEP, even when hypoxaemia is severe.[16] This finding reflects widespread scepticism about the benefit of higher PEEP for ARDS. Therefore, it is important to examine whether continued equipoise about the potential benefit of higher PEEP is justified.

We found that the probability of any mortality benefit from higher PEEP was highly dependent on the priors used, which suggests that the question of whether higher PEEP is

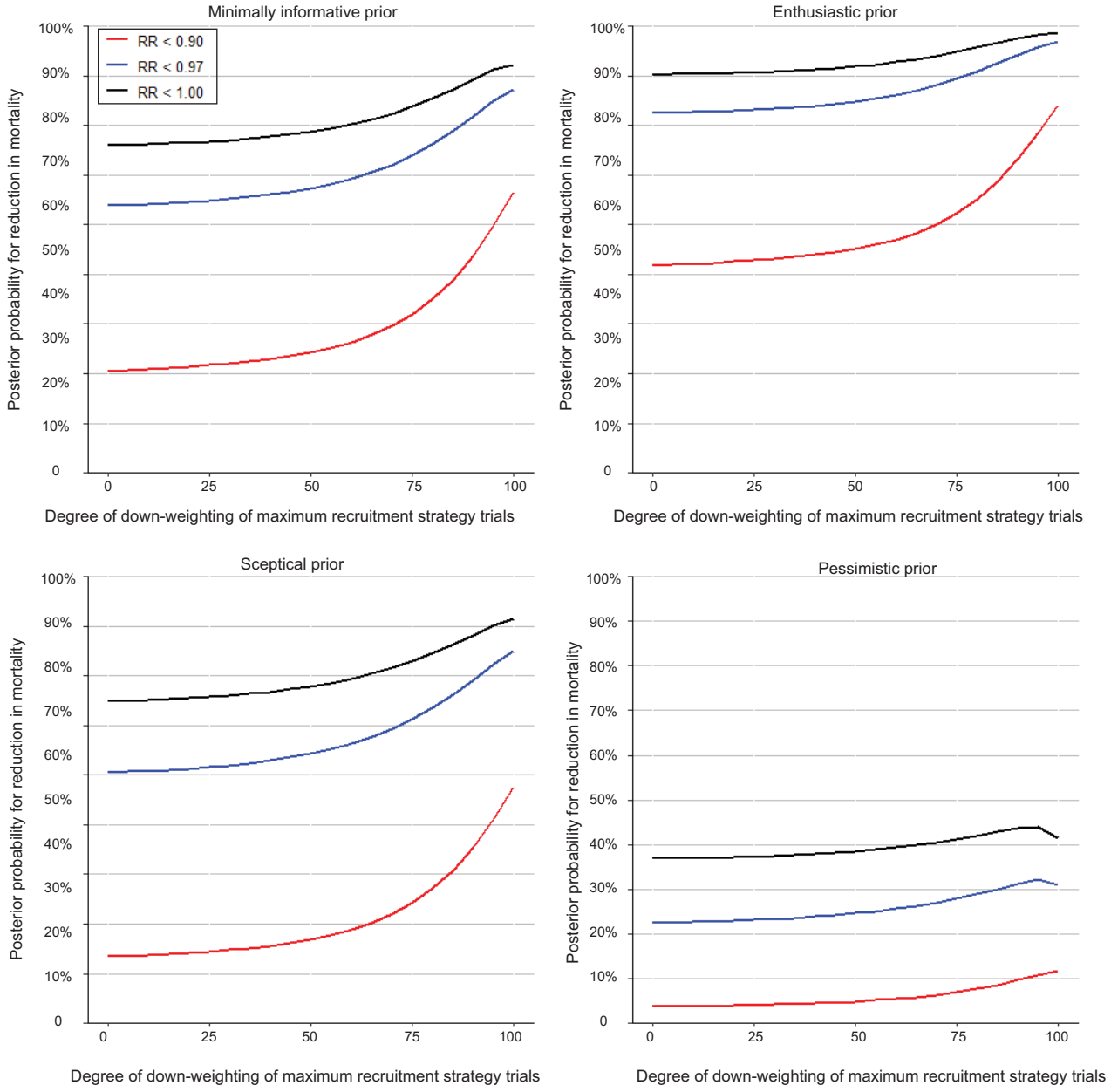
Figure 2. Posterior probability of a reduction in mortality with higher PEEP given the results of the meta-analysis of patients with ARDS under a minimally informative prior, an enthusiastic prior, a sceptical prior and a pessimistic prior*



ARDS = acute respiratory distress syndrome. PEEP = positive end expiratory pressure. * Decreasing weights were applied to trials that used a maximum recruitment strategy by increasing the sample variances for the estimated logarithms of the relative risks. Each plot shows the resulting estimated posterior probability that the relative risk of mortality is lower than each threshold value.

beneficial or harmful has not been definitively resolved.[23-26] In patients with moderate-to-severe ARDS, the posterior probability of clinically relevant mortality benefit with higher PEEP was relatively high (> 90%) after down-weighting trials employing a maximal recruitment strategy. This suggests that higher PEEP is likely to be beneficial in this subgroup, consistent with the previous meta-analysis of individual patient data, provided that the higher PEEP is titrated based

Figure 3. Posterior probability of a reduction in mortality with higher PEEP given the results of the meta-analysis of patients with moderate-to-severe ARDS under a minimally informative prior, an enthusiastic prior, a sceptical prior and a pessimistic prior*



ARDS = acute respiratory distress syndrome. PEEP = positive end expiratory pressure. * Decreasing weights were applied to trials that used a maximum recruitment strategy by increasing the sample variances for the estimated logarithms of the relative risks. Each plot shows the resulting estimated posterior probability that the relative risk of mortality is lower than each threshold value.

on a strategy other than a maximum recruitment strategy.[5] These findings suggest that a future trial of higher versus lower PEEP may be warranted.

The use of varying priors is especially relevant for evaluating the benefit of PEEP because its benefit or harm probably varies considerably between patients — some patients accrue putatively beneficial lung recruitment, while others are exposed to harmful overdistention and haemodynamic

impairment.[27] This physiological response may determine clinical outcome.[28] While priors are ordinarily employed to describe the plausible range of values for the population-average treatment effect in a clinical trial, at the bedside a clinician may form a highly enthusiastic or sceptical prior regarding benefit for an individual patient depending on the patient's potential (based on a clinical assessment) for lung recruitment. The clinician's prior for an individual patient may therefore vary substantially given the widely varying potential for lung recruitment in patients with ARDS.[29] Future trials of higher versus lower PEEP should ideally focus on patients in whom there is prior enthusiasm for potential benefit (ie, those with significant potential for lung recruitment).[30]

A recent clinical trial assessed the impact of personalised mechanical ventilation tailored to lung morphology in ARDS patients, although our meta-analysis did not include this study.[31] In this study, a standard control group receiving ventilation according to the Acute Respiratory Distress Syndrome Network protocol was compared with a group for whom an approach based on lung morphology was used, where patients with focal ARDS received a tidal volume of 8 mL/kg predicted body weight, with low PEEP and prone position, and patients with non-focal ARDS received a tidal volume of 6 mL/kg predicted body weight, along with recruitment manoeuvres and high PEEP. The authors found that a personalisation of mechanical ventilation did not decrease mortality in patients with ARDS, even though misclassification of a large number of patients may have blurred possible benefit or harm. We did not include this study in our meta-analysis because the comparison was not restricted to PEEP.

Despite potential benefits in oxygenation and respiratory mechanics, the use of higher levels of PEEP could lead to adverse events.[32] Depending on the level used and on patient characteristics, higher levels of PEEP could lead to overinflation of non-dependent alveoli, increase in dead space and increased risk of barotrauma. From a haemodynamic perspective, higher levels of PEEP have important effects on the right ventricle, including decreased right ventricular preload, increased right ventricular afterload, intraventricular septum displacement causing decreased left ventricular compliance, increased pulmonary vascular resistance, and increased intracranial pressure.

Our meta-analysis has limitations. First, as in any meta-analysis, the results are built on the underlying internal and external validity of the original studies. Second, PEEP used in the control groups of some studies may not be representative of usual care in all settings. Third, the inclusion and exclusion criteria, recruitment manoeuvres (if used), and PEEP titration strategies were not homogeneous among the included studies. Fourth, the decision to down-weight the results of the trials using a maximum recruitment strategy could be interpreted as an arbitrary decision. However, this decision was made a priori based on the substantial debate in the field regarding the open lung approach tested in these trials. Fifth, our meta-analysis was not pre-registered, although all analyses were pre-planned. Sixth, one of the included studies was a small, single centre study focused on a physiological approach of PEEP titration based on measurements of oesophageal pressure.[21] This technique is not widely available in daily practice, and the study had additional limitations such as the physiological primary outcome. Seventh, recent studies suggest that ventilation in ARDS patients should take into account the different phenotypes among patients with ARDS, but we did not consider this in our study.[33]

Conclusions

The probability of benefit or harm from routine use of higher PEEP for patients with ARDS ranges from 27% to 86%, and from 14% to 73% depending on one's prior, suggesting continued uncertainty and equipoise regarding the benefit of PEEP. If data from trials using a maximum recruitment strategy are discounted to some extent because of uncertainty over the appropriateness of this approach, the available evidence suggests that higher PEEP could be beneficial for patients with moderate-to-severe ARDS. However, well powered RCTs are needed to confirm these findings.

Competing interests

Ary Serpa Neto has received personal fees from Dräger outside of the submitted work. Marcelo Gama de Abreu has received grants and personal fees from Drägerwerk and GlaxoSmithKline, and personal fees from GE Healthcare outside of the submitted work. Ewan Goligher has received travel reimbursement and speaker honoraria from Getinge outside of the submitted work.

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