ANESTHESIOLOGY

High Positive End-expiratory Pressure (PEEP) with Recruitment Maneuvers *versus* Low PEEP during General Anesthesia for Surgery: A Bayesian Individual Patient Data Meta-analysis of Three Randomized Clinical Trials

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ABSTRACT

Background: The influence of high positive end-expiratory pressure (PEEP) with recruitment maneuvers on the occurrence of postoperative pulmonary complications after surgery is still not definitively established. Bayesian analysis can help to gain further insights from the available data and provide a probabilistic framework that is easier to interpret. The objective was to estimate the posterior probability that the use of high PEEP with recruitment maneuvers is associated with reduced postoperative pulmonary complications in patients with intermediate-to-high risk under neutral, pessimistic, and optimistic expectations regarding the treatment effect.

Methods: Multilevel Bayesian logistic regression analysis was performed on individual patient data from three randomized clinical trials carried out on surgical patients at intermediate to high risk for postoperative pulmonary complications. The main outcome was the occurrence of postoperative pulmonary complications in the early postoperative period. This study examined the effect of high PEEP with recruitment maneuvers *versus* low PEEP ventilation. Priors were chosen to reflect neutral, pessimistic, and optimistic expectations of the treatment effect.

Results: Using a neutral, pessimistic, or optimistic prior, the posterior mean odds ratio for high PEEP with recruitment maneuvers compared to low PEEP was 0.85 (95% credible interval, 0.71 to 1.02), 0.87 (0.72 to 1.04), and 0.86 (0.71 to 1.02), respectively. Regardless of prior beliefs, the posterior probability of experiencing a beneficial effect exceeded 90%. Subgroup analysis indicated a more pronounced effect in patients who underwent laparoscopy (odds ratio, 0.67 [0.50 to 0.87]) and those at high risk for postoperative pulmonary complications (odds ratio, 0.80 [0.53 to 1.13]). Sensitivity analysis, considering severe postoperative pulmonary complications only or applying a different heterogeneity prior, yielded consistent results.

Conclusions: High PEEP with recruitment maneuvers demonstrated a moderate reduction in the probability of postoperative pulmonary complication occurrence, with a high posterior probability of benefit observed consistently across various prior beliefs, particularly among patients who underwent laparoscopy.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative pulmonary complications frequently occur
- High positive end-expiratory pressure with recruitment maneuvers can protect the lungs against repetitive tidal recruitment but can potentially cause lung overdistension
- A recent individual patient data meta-analysis pooling the information from three large randomized clinical trials found that subjects ventilated with high positive end-expiratory pressure with recruitment maneuvers were less likely to develop postoperative pulmonary complications; however, this result was not significant at the standard *P* value threshold

What This Article Tells Us That Is New

- This *post hoc* Bayesian reanalysis of individual patient data from three large randomized clinical trials showed that using high positive end-expiratory pressure and recruitment maneuvers led to a high likelihood of a slight reduction in the probability of complications occurrence

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 6. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version.

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Postoperative pulmonary complications frequently occur, increasing mortality, hospital length of stay, and healthcare costs.[1] Although the protective role of low tidal volume has been established,[2] the effect of high positive end-expiratory pressure (PEEP) with recruitment maneuvers during intraoperative ventilation is less certain, because it can protect the lungs against repetitive tidal recruitment but can potentially cause lung overdistension.[3] A recent individual patient data meta-analysis pooled the information from three large randomized clinical trials to assess the effect of high PEEP and recruitment maneuvers *versus* low PEEP on postoperative pulmonary complications occurrence.[4] Subjects ventilated with high PEEP with recruitment maneuvers were less likely to develop postoperative pulmonary complications. However, this result was not significant at the standard *P* value threshold.

Several recent papers used a Bayesian approach to reanalyze data from previous anesthesiology and critical care randomized clinical trials with indeterminate frequentist results to gain further insights.[5–10] We aimed to reanalyze the individual patient data set from the previous REPEAT frequentist meta-analysis[4] with a Bayesian approach according to previously published recommendations.[7] We hypothesized that intraoperative high PEEP with recruitment maneuvers reduced the posterior probability of developing postoperative pulmonary complications.

Materials and Methods

Study Design and Context

The study is an individual patient data meta-analysis using a database pooling individual patients from three recent randomized clinical studies of intraoperative ventilation during general anesthesia for surgery.[4] This analysis's protocol and statistical analysis plan were previously published.[11] The data harmonization procedure is described in detail elsewhere.[12] Briefly, the three studies shared a similar intraoperative management and outcome definition and compared high PEEP (10 to 12 cm H_2O) with recruitment maneuvers to low PEEP (0 to 5 cm H_2O) without Rm. Of note, two of the studies were two-arm parallel trials, whereas one was a four-arm parallel trial with additional interventions in the early postoperative period. The primary analysis focused on the intraoperative intervention, *i.e.* the high PEEP with recruitment maneuvers strategy. The protocols of the three studies were approved by the institutional review boards of the participating hospitals and published previously.[13–15] The detailed characteristics of the studies are shown in supplemental table S1 (https://links.lww.com/ALN/D637).

Patients

The studies included patients with an intermediate risk of developing postoperative pulmonary complication as assessed by the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score[16] who underwent major abdominal surgery. No additional exclusion criteria were added for this analysis.

Data Collected

Baseline characteristics, as well as intraoperative data and postoperative pulmonary complications occurrence, were collected. Of note, for postoperative pulmonary complications, the follow-up was available up to 5 postoperative days for every patient and up to 7 days in one study.[14]

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Definitions

Postoperative pulmonary complications are defined as a collapsed composite of mild and severe respiratory failure, acute respiratory distress syndrome, pulmonary infection, pleural effusion, atelectasis, pneumothorax, and bronchospasm. The definition of the individual components of the composite is shown in supplemental table S2 (https://links.lww.com/ALN/D637).

Outcomes

The outcome of this analysis was the proportion of patients developing one or more postoperative pulmonary complication.

Statistical Methods and Analysis

We used all of the available data without any *a priori* power calculations and carried out a one-stage approach meta-analysis by fitting a multilevel Bayesian logistic model using the *brms* R package,[17] including the effect of the PEEP strategy as population (fixed) effect and the study and site as a random effect modeling heterogeneity of effect across different studies. The site was introduced as a nested effect for the study (supplemental fig. S1, https://links.lww.com/ALN/D637).

Prior Distributions

Priors were set for the fixed effect, *i.e.,* the effect of PEEP strategy, standard deviations of the random effects, and the correlation structure of the random effects. We defined a neutral, a pessimistic, and an optimistic prior probability distribution with moderate belief strength to cover the full range of possible beliefs for the effect of the PEEP strategy as previously recommended and shown in detail in table 1.[7] We used normal distributions for the effects on the log odds scale (supplemental fig. S2, https://links.lww.com/ALN/D637). This allows the null effect to be centered at zero and a symmetrical distribution, which can be transformed back to odds ratios by exponentiating the log odds values. We assigned some strength to our prior beliefs to be weakly informative; *i.e.*, we set them so that we cannot rule out an eventual benefit but can mostly rule out large effect sizes for the intervention and acknowledge a non-negligible chance of the intervention being harmful.[4]

Table 1. Defining Priors to Explain What We Expect the Intervention Will Achieve and How Strong These Assumptions Are

	Belief		
Strength	**Neutral**	**Optimistic**	**Pessimistic**
Weak	We do not know much about the intervention effect. We will use a normal distribution with a mean of 0 and a large SD. The extreme case will be a “flat” prior with an infinite SD. Example: N ~ (0, 5)	We believe the intervention is beneficial, but we have no reason to exclude that it can be harmful. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 30% probability of harm (*i.e.*, OR > 1, log odds > 0).	We believe the intervention is harmful, but we rule out a benefit. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 30% probability of benefit (*i.e.*, OR < 1, log odds < 0).
Moderate	We do not know whether the intervention may be beneficial or harmful, but we exclude that the effect is large. We will use a normal prior with a mean of 0 and an SD to retain only 2.5% of probability of large effect of more than OR > 2 or OR < 0.5. Example: N ~ (0, 0.355). *We used this prior for the analysis.*	We believe the intervention is beneficial, but we cannot exclude that there is a certain chance that it can be harmful. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 15% probability of harm (OR > 1, log odds > 0. *We used this prior in the analysis using averaged effect size estimate from the three original studies (OR = 0.51, log odds = −0.67).*	We believe the intervention is harmful, but we cannot exclude that there is a certain chance that it can be beneficial. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 15% probability of benefit (*i.e.*, OR < 1, log odds < 0). *We used this prior in the analysis using averaged effect size estimate from the three original studies (OR = 1/0.51, log odds = 0.67).*
Strong	We strongly believe that the intervention does not have an effect. We will use a normal prior with a mean of 0 and an SD to retain only 2.5% of probability of large effect of more than OR > 1.5 or OR < 0.66. Example: N ~ (0, 0.205)	We believe the intervention is beneficial, but there is a very low chance for it to be harmful. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 5% probability of harm (OR > 1, log odds > 0).	We believe the intervention is harmful, but there is a very low chance for it to be beneficial. We will use a normal distribution with a mean at the expected effect and an SD to retain at least a 5% probability of benefit (*i.e.*, OR < 1, log odds < 0.

This table is based on an example to study the intervention effect on a harmful binary outcome, meaning that positive ratios represent harm. In this context, we usually express our initial guess as an effect ratio; for instance, the odds ratio (OR) using the log of this ratio that allows to use normal distribution to model it. Such distribution will be defined by the mean (location) and the standard deviation (SD; scale) and parameterized according to our set of beliefs. For instance, a log odds of 0 represents no effect, *i.e.*, an OR of 1, and a log odds greater than 0 represents higher odds for the event. The normal distributions are reported as N ~ (mean, SD). The *weakly* pessimistic prior was initially chosen to retain a 0.30 probability of benefit [Pr(OR < 1)]; however, because this returned an almost flat prior due to the great variance needed to retain that probability density for benefit with an average of OR of 1.98 that mirrors the effect from the optimistic prior, we opted for a symmetric prior retaining 0.15 probability of benefit, as previously used in a recent study.[8]

The prior distribution for the standard deviations of the random effects, *i.e.* the intervention heterogeneity across studies, was defined as a half-normal distribution with a mean of 0 and a SD = 0.5; this yields prior probabilities of 52% in the reasonable category, 27% in the fairly high category, and 5% in the extreme category (supplemental fig. S3, https://links.lww.com/ALN/D637).[18] Furthermore, the prior distribution for the correlation matrix of the random effects was based on the Lewandowski–Kurowicka–Joe distribution with an η parameter of 2 (supplemental fig. S4, https://links.lww.com/ALN/D637).[19]

We also looked at how different beliefs about the intervention affected the main results as postulated in previously published recommendations.[7] We did this by treating the estimates from different priors' models as if they were separate studies and fitting an aggregate data Bayesian meta-analysis. This helped us see how much these beliefs influenced the results because the heterogeneity of this meta-analysis is the influence of the priors, because there is no other sampling difference. We used a weekly informative neutral prior similar to the one we used in the main analysis for the effect size and a DuMouchel prior for heterogeneity. We chose such heterogeneity prior following the recommendations on Bayesian reanalysis;[7] the DuMouchel prior has been shown to provide good coverage for this kind of analysis, not deviating much from uniform priors while providing some regularization.[20]

We chose the region of practical equivalence as the interval between odds ratios of 0.9 and 1.1. The region of practical equivalence is usually defined based on the context of the study and specific use; it is set based on previous knowledge, expert opinions, or thinking about how parameter values practically affect the outcome; parameters within region of practical equivalence are seen as having similar effects, and any differences between them might not be seen as important in a clinical context.[21] The extent of the 95% posterior highest density interval overlap with region of practical equivalence helps to understand the chances of an intervention being helpful or harmful. In addition, we defined a threshold for severe harm at an odds ratio of 1.25.

We used the threshold suggested by previously published recommendations in a critical care setting[7] because we considered that our clinical scenario bears sufficient similarities. We drew 7,000 samples from the posterior distribution after fitting the models with *brms* Hamiltonian Markov No U-turn sampler using each of the previously defined priors and determined how much of the posterior probability density laid in the region of practical equivalence interval or exceeded the threshold for severe harm and determined the posterior probability density of treatment effect using estimated marginal means with the *emmeans* package for R (version 1.8.5).[22]

We reported the effect of the intervention both as a marginal effect and as a conditional effect. For the conditional effect, we conditioned on a new random effect simulated by drawing posterior samples from the random effect mixture distribution of trials and sites. In other words, this conditional effect draws random values from the joint posterior distribution to reflect the observed uncertainty within and across all subjects for the random effects included in the model, thus allowing assessment of the effect of the intervention for hypothetical or unobserved scenarios as an additional assessment of the heterogeneity. Furthermore, we compared the interval of the region of practical equivalence with the 95% posterior highest density interval, as previously recommended, to see whether the highest density interval posterior probability density falls outside the region of practical equivalence.

We performed the following preplanned subgroup analyses by refitting the multilevel logistic regression model by adding an interaction term between treatment and a subgroup of interest and reporting the effect estimated by pairwise contrasts in the groups of interest. We carried out these analyses for the effect of high PEEP and recruitment maneuver *versus* low PEEP in (1) type of surgery, *i.e.*, laparoscopic *versus* open surgery; (2) risk for postoperative pulmonary complications, *i.e.*, ARISCAT score less than 45 *versus* greater than or equal to 45; and (3) body mass index less than 30 *versus* greater than 30. Next, we evaluated potential heterogeneity due to the different design of one of the studies.[14] Therefore, we assessed the effect of (4) type of PEEP selection, *i.e.*, fixed *versus* titrated, in the high PEEP and recruitment maneuver cohort and the (5) use of a postoperative element as part of the tested intervention, *i.e.*, applied postoperative continuous positive airway pressure (CPAP) *versus* standard oxygen support.

We performed sensitivity analyses by (1) refitting the model and using only severe postoperative pulmonary complications as the primary outcome; (2) varying the heterogeneity prior to a half-Cauchy prior[18]; and (3) assessing prior-data conflicts by examining the perturbation on posterior distributions of parameters by power-scaling priors with the R *priorsense* package.[23] We could not perform the previously planned analysis including only patients with lung collapse before the intervention as previously specified,[11] because we could not identify such a group with the available data. All analyses used R software (version 4.2.3, Core Team, Vienna, Austria).

Results

The pooled database contained 3,836 patients: 1,913 high PEEP and recruitment maneuver patients and 1,923 low PEEP patients. Demographic, perioperative, and care-delivery characteristics were well balanced at baseline between high PEEP and recruitment maneuver and low PEEP patients (supplemental table S3, https://links.lww.com/ALN/D637). Intraoperative and ventilatory variables and differences between groups by every outcome component are shown in supplemental tables S4 and S5 (https://links.lww.com/ALN/D637).

The posterior mean effect of high PEEP and recruitment maneuver on the occurrence of postoperative pulmonary complications was 0.85 (95% credible interval, 0.71 to 1.02), 0.87 (0.72 to 1.04), and 0.86 (0.71 to 1.02) for the models fitted with neutral, pessimistic, and optimistic priors, respectively. The posterior probability of a beneficial effect was more than 90% regardless of the prior (table 2; figs. 1 and 2). The conditional effects estimated by considering the random effect of trial and site have similar posterior means but a wider 95% credible interval and some posterior probability of harm, *i.e.*, more than 10% regardless of prior (supplemental table S6 and figs. S5 and S6, https://links.lww.com/ALN/D637). The posterior probability density comprised in the region of practical equivalence was always less than 30%. The prior choice had little influence on the results; the estimated heterogeneity I^2 from the aggregate estimate meta-analysis was 0.107. Therefore, approximately 10% of the variance was caused by the priors (supplemental fig. S7, https://links.lww.com/ALN/D637).

The effect of high PEEP and recruitment maneuver *versus* low PEEP had a higher posterior probability of benefit in the laparoscopic surgery group compared to the open surgery group. High PEEP and recruitment maneuver was slightly more likely to be beneficial in the high-risk ARISCAT cohort. We did not find any differences between the other subgroups (table 3). As for the main analysis, the conditional effects reported a similar posterior mean with wider 95% credible intervals and some posterior probability of harm (supplemental table S6 and figs. S8 to S12, https://links.lww.com/ALN/D637). We found that the posterior distributions changed little when we used only severe postoperative pulmonary complications as the outcome or when we used a different prior for heterogeneity (table 3; fig. 3). In addition, the *post hoc* prior sensitivity did not report any conflicts for the intervention estimates.

Discussion

We applied a Bayesian analysis framework on a large, harmonized data set to estimate the effect of high PEEP and recruitment maneuver ventilation on the occurrence of postoperative pulmonary complications compared to a strategy based on low PEEP, an approach that allows for flexible hypothesis testing, the intuitive use of probabilities.[24–28] Our results showed that (1) using high PEEP and recruitment maneuver led to a slight reduction in the posterior probability of complications occurrence; (2) this benefit was highly likely in general, although (3) it can be less likely to benefit depending on the variability of patients. Moreover, (4) the different prior distributions did not influence the results. Subgroups and sensitivity analyses showed that (5) the effect of the high PEEP and recruitment maneuver was more beneficial in the laparoscopic and high ARISCAT risk score patients' groups, and no effect was associated with the use of postoperative CPAP or an individualized high PEEP instead of a fixed high PEEP.

The physiologic basis of mechanical ventilation studies in the operating room is that general anesthesia with muscle paralysis causes airway and lung collapse. This can lead to injury due to the excessive pressure or volume applied to the shrunk parenchyma or to the shear force occurring in cyclically opening regions.[29] The use of high PEEP with recruitment maneuvers is intended to counteract these deleterious effects. However, apart from a recent meta-analysis of mainly small studies in which the authors acknowledged some publication bias,[30] several large randomized clinical trials yielded indeterminate results on the benefit of such a ventilatory strategy. Our results based on a different statistical framework provide a reasonable belief that a high PEEP and recruitment maneuver strategy can be beneficial. The magnitude of this benefit, although not negligible based on the prespecified region of practical equivalence criteria, is probably small. We applied a region of practical equivalence criterion suitable for similar clinical contexts

Table 2. Average Effect Estimates from Main Model for Primary Outcome

Belief	Prior Subject Matter Justification	Odds Ratio (95% Credible Interval)*	Absolute Risk Reduction* (95% Credible Interval)	Probability Mass in the Region of Practical Equivalence	Probability of Benefit Odds Ratio < 1 (Odds Ratio < 0.8; > 1.25)
Neutral	There is no previous firm evidence to believe the intervention is good or bad, but large effect sizes can be reasonably ruled out.	0.85 (0.71 to 1.02)	−3% (−6 to 0%)	25%	96% (23%; 0%)
Pessimistic	The intervention is believed to be harmful, but there are few data, and an eventual benefit cannot be ruled out.	0.87 (0.72 to 1.04)	−3% (−5 to 0%)	30%	93% (18%; 0%)
Optimistic	The intervention is believed to be good, but a non-negligible chance of harm must be acknowledged.	0.86 (0.71 to 1.02)	−3% (−6 to 0%)	25%	96% (25%; 0%)

The region of practical equivalence was defined by an odds ratio interval of 0.9 and 1.1.

*This risk reduction is a simple estimation derived from the posterior draws of the predictor transformed by the inverse-link function with only the intervention as previously described.[8]

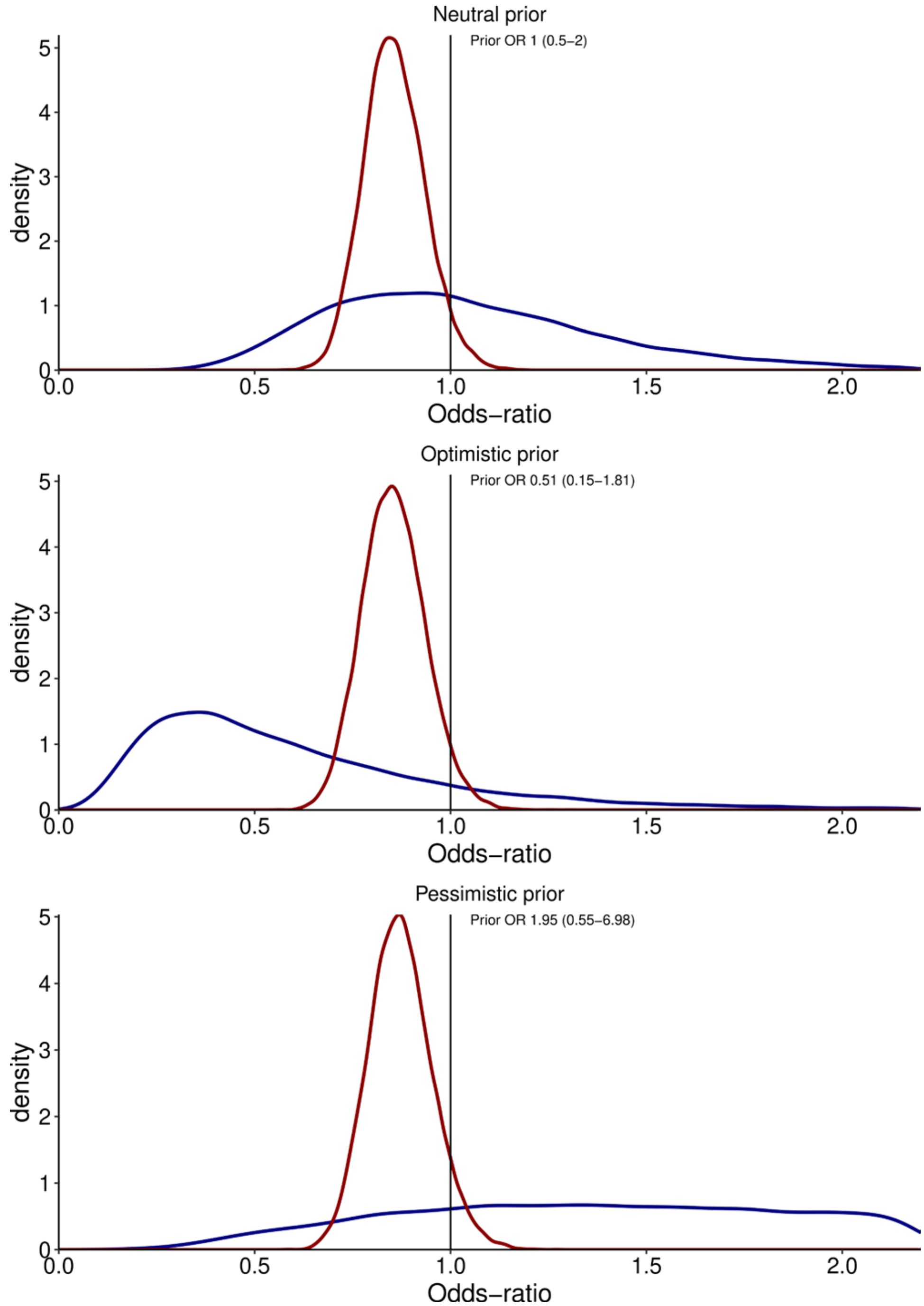

Fig. 1. Prior and posterior distributions for the high positive end-expiratory pressure and recruitment maneuver intervention are reported in the odds ratio (OR) scale. *Blue lines*, prior distribution; *red lines*, posterior distribution of the effect.

and discovered that approximately 25% of the posterior probability density lies within this interval. A similar density is observed for a significant benefit (odds ratio less than 0.8), whereas no density is found above an odds ratio of 1.25. Ultimately, the essence of Bayesian analysis lies in the full posterior distribution, akin to a map illustrating probabilities across various parameter values. Making decisions based on different parameters or combinations thereof using regions of practical equivalence occurs after evaluating this primary information. In addition, we should try to avoid making strict yes or no decisions, because we might ignore how important or uncertain a parameter value really is. This type of thinking can lead to misunderstandings and confusion.[31,32]

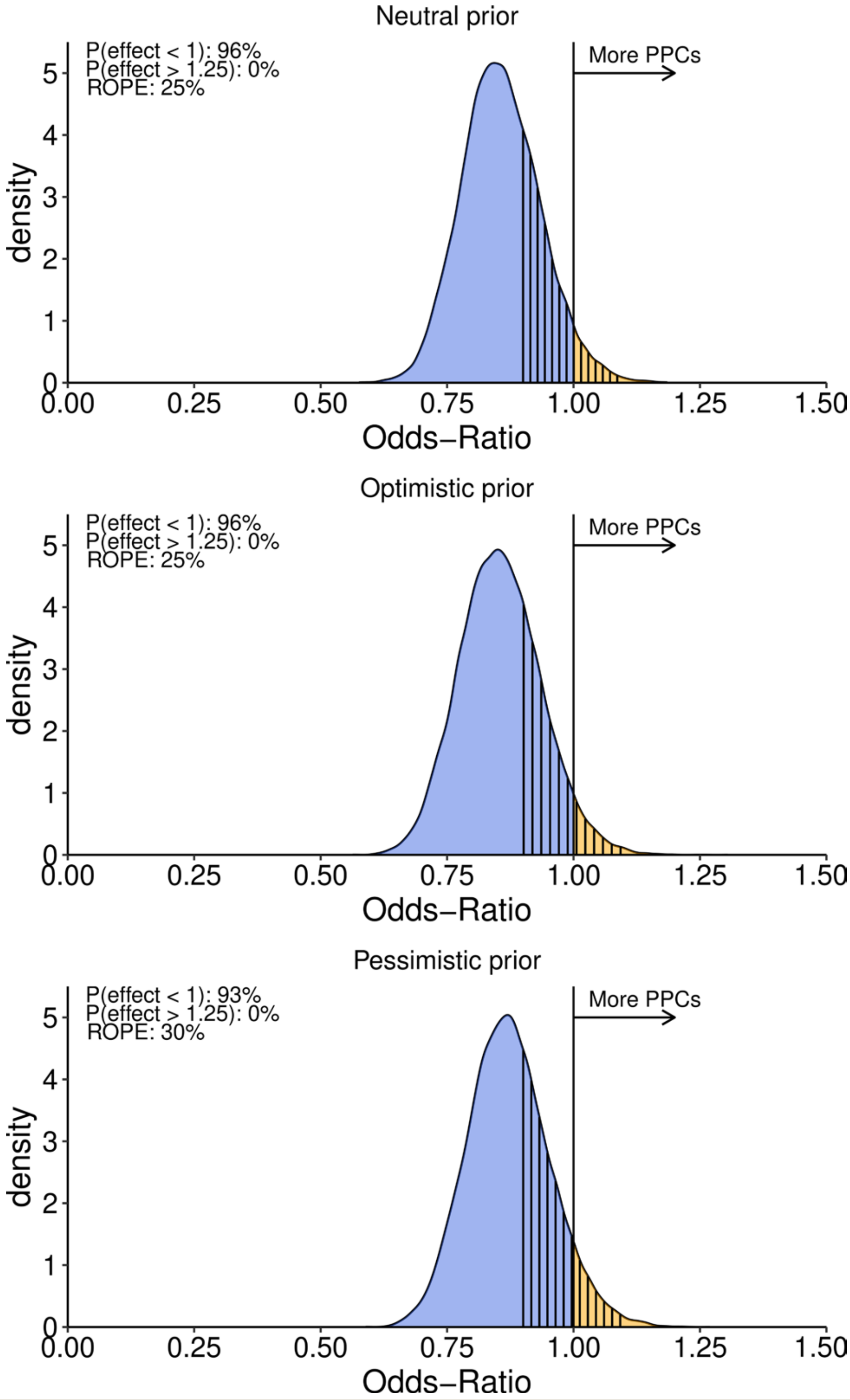

Fig. 2. Posterior distributions of the effects of high positive end-expiratory pressure and recruitment maneuver on the probability of postoperative pulmonary complication occurrence with a highlighted probability of benefit area. *Blue area*, probability density for the benefit threshold (odds ratio, less than 1); *orange area*, probability density for the harm threshold (odds ratio, greater than 1); *dark orange area*, probability density for the harm threshold (odds ratio, greater than 1.25); *black vertical lines*, region of practical equivalence boundaries (odds ratio, 0.9 to 1.1). PPC, postoperative pulmonary complications; ROPE, region of practical equivalence.

Table 3. Subgroups and Sensitivity Analyses

Pairwise Comparison	Subgroup	Odds Ratio (95% Credible Interval)*	Region of Practical Equivalence Probability, %	Probability of Benefit or Harm, %		
				Odds Ratio < 1	Odds Ratio < 0.8	Odds Ratio > 1.25
Subgroup analyses						
High PEEP and RM *versus* low PEEP	Laparoscopic surgery	0.67 (0.50 to 0.87)	0	99	90	0
		0.67 (0.50 to 0.87)	0	99	90	0
		0.67 (0.50 to 0.85)	0	99	91	0
	Open surgery	1.01 (0.79 to 1.23)	66	48	2	3
		1.01 (0.79 to 1.27)	62	46	3	4
		0.98 (0.76 to 1.22)	62	56	4	2
	High ARISCAT risk	0.80 (0.53 to 1.13)	22	88	50	1
		0.80 (0.53 to 1.13)	23	88	49	1
		0.79 (0.54 to 1.12)	21	89	52	1
	Intermediate ARISCAT risk	0.90 (0.73 to 1.07)	46	87	13	1
		0.90 (0.74 to 1.10)	50	85	11	1
		0.88 (0.71 to 1.06)	37	91	18	1
	Body mass index < 30 kg m^{-1}	0.88 (0.67 to 1.13)	40	83	24	1
		0.89 (0.66 to 1.16)	42	79	21	1
		0.84 (0.62 to 1.08)	29	89	35	1
	Body mass index > 30 kg m^{-1}	0.84 (0.66 to 1.07)	27	91	34	1
		0.85 (0.65 to 1.06)	28	91	33	1
		0.84 (0.64 to 1.06)	26	91	38	1
Postoperative CPAP *versus* no postoperative CPAP	High PEEP and RM	1.19 (0.73 to 1.78)	28	21	3	42
		1.20 (0.71 to 1.79)	27	21	3	42
		1.22 (0.74 to 1.85)	25	18	3	46
	Low PEEP	1.14 (0.79 to 1.57)	34	21	2	31
		1.15 (0.77 to 1.57)	34	22	2	32
		1.14 (0.79 to 1.58)	34	22	2	30
Individualized PEEP *versus* fixed high PEEP†	High PEEP and RM	1.14 (0.71 to 1.70)	32	27	4	34
		1.14 (0.72 to 1.71)	32	27	4	34
		1.14 (0.70 to 1.68)	32	26	2	34
Sensitivity analyses						
Severe postoperative pulmonary complications		0.84 (0.69 to 1.01)	21	96	30	0
		0.87 (0.70 to 1.06)	34	91	20	0
		0.86 (0.69 to 1.04)	28	93	26	0
Different heterogeneity prior		0.86 (0.71 to 1.01)	25	96	23	0
		0.87 (0.72 to 1.03)	33	93	18	0
		0.86 (0.70 to 1.01)	26	95	24	0

The region of practical equivalence is the probability distribution between 0.9 and 1.1 odds ratio.

*Results for the posterior means and posterior probabilities are reported according to the prior distribution from top to bottom: neutral, pessimistic, and optimistic. †This comparison is carried out in the cohort receiving high PEEP and RM because no patient in the low PEEP cohort received it.

ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; RM, recruitment maneuver.

Furthermore, the effects of the intervention estimated conditional on a new random effect reflecting the uncertainty within and across subjects show how the estimate distributions widen even to contain some posterior probability of harm. Hence, high PEEP and recruitment maneuver should not be a one-size-fits-all solution, but when and how to apply them should be carefully chosen. A partial explanation of these results comes from subgroup analysis. For instance, the effect of high PEEP and recruitment maneuver is more beneficial in specific groups such as laparoscopic surgery and high-risk ARISCAT patients, whereas in obesity, there is only a small interaction effect.

In addition, lung injury is ultimately related to the amount of stress and strain applied to the parenchyma during the mechanical ventilation process,[33] and ventilation must be tailored to minimize it. Thus, applying high PEEP, recruitment maneuvers, or both can be beneficial as long as they decrease lung strain. This could not always be the case because, on the one hand, they can reduce the strain dynamic component by applying the same tidal volume to a greater number of alveoli thanks to recruitment and the pressure to keep them open, but on the other, they can increase the static strain by administering more force to the lung scaffold.[34] Other parameters, such as driving pressure, have been proposed to guide ventilation during general anesthesia, although its physiologic rationale is still being debated and laid out,[35] and specific randomized clinical trials to evaluate its effect are ongoing.[36] Also, other more comprehensive measurements of the total force, *i.e.*, the mechanical power applied to the lung during ventilation, have been described. Results from *post hoc* analysis show that this

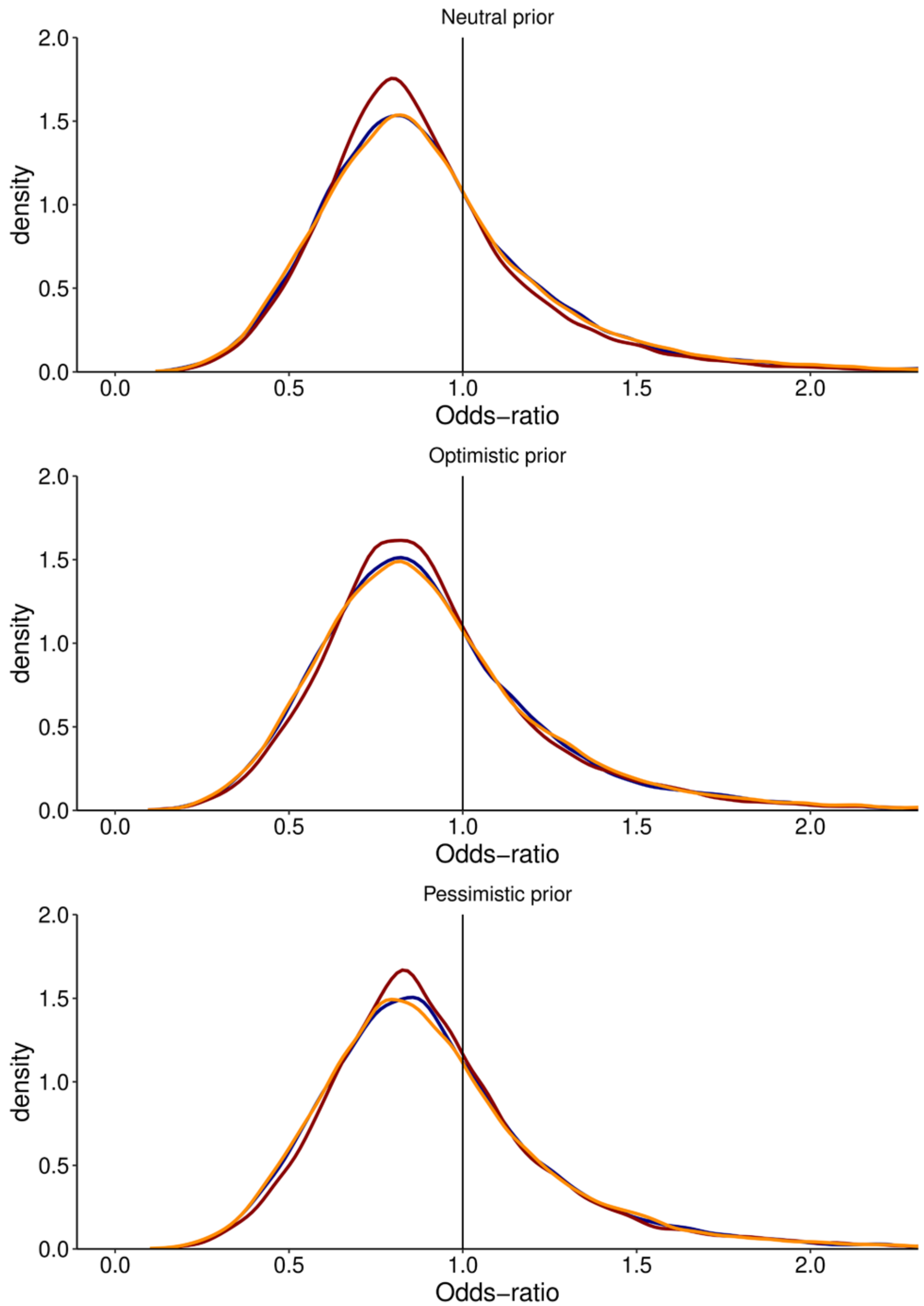

Fig. 3. Sensitivity analysis results for the posterior probability distributions for the effect of high positive end-expiratory pressure and recruitment maneuvers on the probability of postoperative pulmonary complications occurrence. Reported are the effect estimates conditionally on a new random effect for a new hypothetical scenario. *Blue lines*, different heterogeneity prior; *red lines*, only severe postoperative complications as the outcome; *orange lines*, main model.

can be a promising measurement,[37] but we are not aware of any study specifically designed to test whether this parameter can reduce postoperative pulmonary complications.

Several limitations of this study must be acknowledged. First, although our database was previously harmonized, a non-negligible heterogeneity between studies cannot be ruled out. Although we introduced a random effect in the model to precisely account for potential between studies differences, the effect of high PEEP and recruitment maneuver may be different in particular clinical scenarios or patients with specific preoperative medications that cannot be ascertained by this study. Second, we chose to focus on individual patient data from large randomized clinical trial, leaving out some small studies. We could have switched to aggregate data meta-analysis and potentially had some difference in the point estimates, although with the trade-off of losing data granularity. As in our previous frequentist analysis, we decided to concentrate on the binary composite main outcome. However, it is important to note that this type of outcome has limitations, such as increased heterogeneity. Moreover, because the studied intervention combined the use of recruitment maneuvers and high PEEP, we cannot isolate the individual role of each component, and the synergistic or antagonistic effect in specific clinical situations could not be investigated. In addition, data on dynamic and static strain, such as functional residual capacity estimation or stress index, were not collected in the original studies thus, we cannot elucidate when the PEEP effect changes from beneficial to injurious by adding only overdistension. Moreover, although we did not observe any effect from other types of intervention, such as postoperative CPAP or the individualized setting of PEEP according to the pulmonary compliance after the recruitment maneuver, these interventions were administered in only one of the three studies; thus, our results should be interpreted with caution. Finally, we could not carry out the prespecified subgroup analysis on patients who presented atelectasis before the intervention administration because no data could identify such a group reliably. This must be investigated in future studies because the application of PEEP, and recruitment maneuvers in particular, seem sensible if a significant amount of collapsed parenchyma is present.

In conclusion, intraoperative mechanical ventilation with high PEEP and recruitment maneuvers slightly reduces the risk of occurrence and adverse postoperative pulmonary events as compared to low PEEP. This effect is likely not generalizable and is more pronounced in patients undergoing laparoscopy or at high risk of complications.

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Competing Interests

Dr. Zampieri received consulting fees from Baxter (Deerfield, Illinois). Dr. Gama de Abreu received consulting fees from Zoll (Chelmsford, Massachussets), and Drager Medical (Lubeck, Germany), and Ambu Inc. (Copenhagen, Denmark), and honoraria for lectures from Merck Sharpe Dohme (Readington, New Jersey). Dr. Neto received honorary from Drager Medical for lectures and own stocks in Endpoint Health (Palo Alto, California).

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Supplemental Digital Content

Additional tables, figures, and R code, https://links.lww.com/ALN/D637

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