

SYSTEMATIC REVIEW



Positive end-expiratory pressure-induced recruited lung volume measured by volume-pressure curves in acute respiratory distress syndrome: a physiologic systematic review and meta-analysis

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Abstract

Purpose: Recruitment of lung volume is often cited as the reason for using positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) patients. We performed a systematic review on PEEP-induced recruited lung volume measured from inspiratory volume-pressure (VP) curves in ARDS patients to assess the prevalence of patients with PEEP-induced recruited lung volume and the mortality in recruiters and non-recruiters.

Methods: We conducted a systematic search of PubMed to identify studies including ARDS patients in which the intervention of an increase in PEEP was accompanied by measurement of the recruited volume (V_{rec} increase versus no increase) using the VP curve in order to assess the relation between V_{rec} and mortality at ICU discharge.

We first analysed the pooled data from the papers identified and then analysed individual patient level data received from the authors via personal contact. The risk of bias of the included papers was assessed using the quality in prognosis studies tool and the certainty of the evidence regarding the relationship of mortality to V_{rec} by the GRADE approach. Recruiters were defined as patients with a $V_{rec} > 150$ ml. A random effects model was used for the pooled data. Multivariable logistic regression analysis was used for individual patient data.

Results: We identified 16 papers with a total of 308 patients for the pooled data meta-analysis and 14 papers with a total of 384 patients for the individual data analysis. The quality of the articles was moderate. In the pooled data, the prevalence of recruiters was 74% and the mortality was not significantly different between recruiters and non-recruiters (relative risk 1.20 [95% confidence intervals 0.88–1.63]). The certainty of the evidence regarding this association was very low and publication bias evident. In the individual data, the prevalence of recruiters was 70%. In the multivariable logistic regression, V_{rec} was not associated with mortality but Simplified Acute Physiology Score II and driving pressure at PEEP of 5 cmH₂O were.

Conclusion: After a PEEP increment, most patients are recruiters. V_{rec} was not associated with ICU mortality. The presence of similar findings in the individual patient level analysis and the driving pressure at PEEP of 5 cmH₂O was

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associated with mortality as previously reported validate our findings. Publication bias and the lack of prospective studies suggest more research is required.

Keywords: Respiratory distress syndrome, adult/mortality, Respiratory distress syndrome, adult/therapy, Respiratory distress syndrome, adult/physiopathology, Positive-pressure respiration/therapeutic use, Alveolar recruitment, Lung recruitment, Positive end-expiratory pressure

Introduction

Lung protective mechanical ventilation is the cornerstone feature of ARDS management. It includes setting low tidal volumes (V_T) and maintaining plateau pressure (P_{plat}) ≤ 30 cmH₂O [1], to prevent much of the damage incurred to the injured ARDS lung by alveolar over-distension during mechanical ventilation. Positive end-expiratory pressure (PEEP) is the second main ventilator setting that aims at preventing lung derecruitment during expiration, thereby improving oxygenation and distribution of ventilation. These concepts, together with haemodynamic preservation, currently underlie the use of PEEP in ARDS.

In daily ICU practice, recruited lung volume is often not measured. Surrogates such as the changes in lung compliance and gas exchange are used instead. However, recruited lung volume can be measured at the bedside by using the volume-pressure (VP) curves available in almost every ICU ventilator. To the best of our knowledge, there has been no study of the relation between the recruited lung volume (V_{rec}) measured from the VP curves used to set PEEP and mortality in ARDS patients. We therefore performed a systematic review of the literature describing PEEP-induced recruited lung volume as

Take-home message:

We conducted systematic literature search in PubMed of studies on ARDS patients where recruited volume (V_{rec}) elicited by a PEEP increase was measured by inspiratory VP curve. Our analysis showed that, after a PEEP increment, most of the patients had a V_{rec} measured with VP curve greater than 150 ml. V_{rec} was not associated with ICU mortality but this may be affected by publication bias.

measured from inspiratory VP curves in ARDS patients, with the aim of estimating lung recruitability rate in association with mortality.

Two methods for bedside measurement of V_{rec} from VP curves were studied in the present systematic review, namely the occlusion technique and the low flow inflation technique. A description of these methods can be found in the ESM and also in Fig. 1.

Methods

Following registration in PROSPERO (CRD 420 2017 5380) the current systematic review was performed in order to study adult patients with ARDS as defined by the authors, in whom the effect of PEEP on recruited lung volume as assessed by bedside VP curves was investigated. We extracted V_{rec} , oxygenation, compliance and

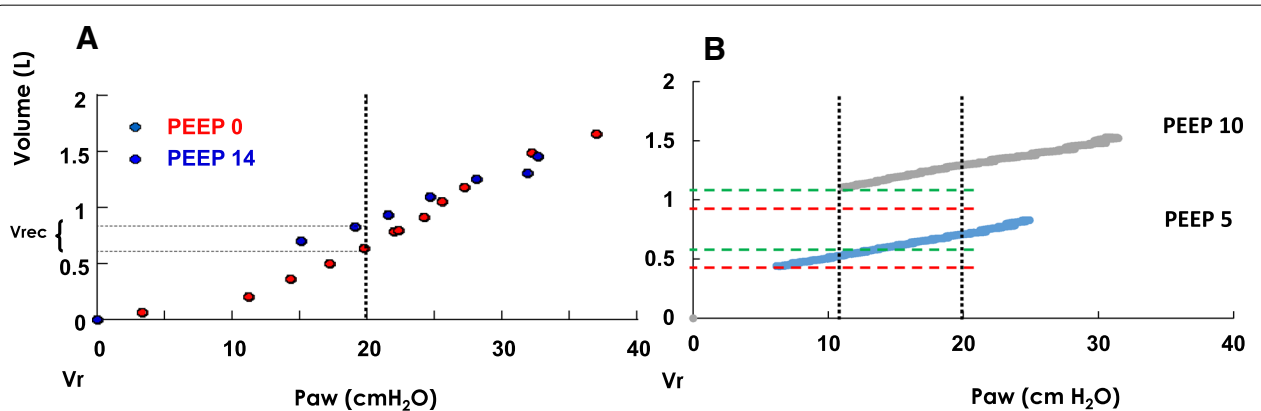


Fig. 1 The two methods to measure recruited volume (V_{rec}) from volume-pressure curve of the respiratory system that were investigated in present study. **a** Occlusion technique at different tidal volume (V_T). Airway pressure (P_{aw}) is recorded at different V_T during an end-inspiratory occlusion. Each dot is the plateau pressure at a given V_T . The procedure is done at PEEP 0 (red dots) and PEEP 14 cmH₂O (blue dots). Both curves are referred to the relaxation volume of the respiratory system at PEEP 0 (V_r). V_{rec} is the change in lung volume at a given pressure, i.e. 20 cmH₂O, between the 2 PEEP (broken horizontal black lines). **b** Low flow inflation technique. The respiratory system is insufflated from PEEP 5 (blue line) or PEEP 10 (grey line) at constant low flow (7 l/min). Volumes are referred to V_T at PEEP 0. V_{rec} can be obtained as the difference in lung volume at same 20 cmH₂O P_{aw} (broken horizontal green lines) or from PEEP 10 down to PEEP 5 (broken horizontal red lines)

mortality at ICU discharge or at last assessment from the included studies. We defined patients as recruiters when V_{rec} was >150 ml and as non-recruiters when V_{rec} was ≤ 150 ml. The primary end-point was ICU mortality in recruiters and non-recruiters. This threshold was selected because it has been previously used in the literature [2].

Literature search

Two collaborators (ET and CG) performed a comprehensive search of the Pubmed database from inception to 19/07/2019 for relevant papers. The search was updated on 20/05/2020 to ensure full capture of the available literature. The keywords used were: "acute respiratory distress syndrome", "acute lung injury", "positive end expiratory pressure", "continuous positive airway pressure", "Positive-Pressure Respiration/methods", "lung recruitment", "alveolar recruitment", "recruited lung volume" and "PEEP-induced recruitment". We also used a 'snowballing' method, using study references to find additional studies to be included.

Study selection

The citations identified in the preliminary search were screened in duplicate by the same investigators to assess fulfilment of inclusion criteria in three stages: first by title, then by abstract review and finally in full text review. Only articles reporting V_{rec} elicited by PEEP and measured with either the VP curve or nitrogen wash out in ARDS patients were selected. Disagreements regarding fulfilment of inclusion criteria were resolved by discussion between the two researchers performing screening. Animal studies, studies in which recruitment was performed by other means than PEEP (e.g. recruitment manoeuvres or high frequency oscillation ventilation), pediatric studies, case reports, bench studies, reviews, abstracts and articles not in the English language were excluded.

Data extraction

The relevant data were extracted independently and in duplicate to a predefined form (ET and CE). Disagreements were resolved by discussion. Extracted data included patient characteristics (e.g. age, gender, height, weight, predicted body weight [PBW]), disease details (cause and number of days since onset of ARDS, simplified acute physiology score [SAPS] II), ventilation parameters (oxygen arterial partial pressure [PaO_2] to inspired fraction [FiO_2] ratios, FiO_2 , PEEP, compliance, P_{plat} , driving pressure, total respiratory rate [RR] and V_{T}), V_{rec} and mortality at ICU discharge or at last assessment. If in the original papers V_{rec} was available only as graphs, the GetData Graph Digitizer software (getdata-graph-digitizer.com) was used to transform it to numeric values.

The corresponding authors of the original papers were also contacted directly to obtain individual patient-level data regarding the above listed variables as well as the respiratory mechanics and ventilator settings at two specific levels of PEEPs: 5 and 15 cmH_2O .

Quality assessment

The Quality In Prognosis Studies (QUIPS) tool was used to assess the risk of bias in the included papers [3]. The QUIPS checklist examines the risk of bias across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Two authors (ET and CG) independently assessed the risk of bias of each article included in the meta-analysis, using the QUIPS tool. For each domain we considered the full list of potential issues suggested by the tool. These were then taken together to inform an overall judgment of potential bias for each domain and to classify the risk in this domain as either high, moderate or low. This process was repeated for each of the 6 domains in each of the papers included (see Supplemental material 2). We also considered the items 1, 2 and 6 of the QUIPS tool for rating the prevalence of recruiters. The same two authors then assigned an overall judgment regarding the quality of the study; this too was classified as either high, moderate or low. The overall risk of bias was assigned the quality of the domain with the highest risk of bias assessment (conservative approach).

Statistical analysis

The statistical analysis was divided into two parts. In the first part, we analyzed the data obtained directly from previously published papers (pooled data analysis). In the second part, we analysed the individual patient-level data.

Pooled data analysis

The data extracted for the pooled data analysis were mean and standard deviation (SDs) or counts ($\pm 95\%$ confidence intervals [CI]s). Data provided in the included papers as median and quartiles were converted to mean (\pm SDs) [4]. Forest plots were constructed using the random effects model since heterogeneity was expected. For the same reason the Cochran's Q test and I^2 were used to quantify data heterogeneity.

The prevalence of recruiters was presented as percent among the total number of patients. To compare continuous and dichotomous outcome variables in recruiters and non-recruiters, their mean difference and relative risks were used, respectively. The mortality in recruiters and non-recruiters was expressed as relative risk (95% CI).

Funnel plots were created for the articles retrieved in order to identify potential publication bias. Finally,

several subgroup analyses were performed to assess the stability of our model when taking into account potential sources of confounding and heterogeneity. These included the PEEP levels used in the VP curve to measure V_{rec} (5 cmH₂O versus 15 cmH₂O), the PaO₂/FiO₂ ratio, the cause of ARDS, the timing of paper publication in relation to the ARMA trial (before or after) [1] and the overall risk of bias assessment (low versus moderate versus high).

Following GRADE methodology the certainty in the relationship between V_{rec} and mortality in the pooled data was rated [5]. Data from observational studies were initially designated as low certainty evidence. The degree of certainty was downgraded for concerns related to individual study risk of bias, inconsistency, indirectness, imprecision or publication bias and additional concerns. Disagreements were resolved by discussion.

Individual data analysis

In the individual data analysis variables were presented as median (1st and 3rd quartiles). The extracted variables were compared between recruiters and non-recruiters, and between survivors and non-survivors at ICU discharge by using non-parametric tests. The association between V_{rec} and patient outcome was assessed using the area under curve (AUC) of the receiving operating characteristics (ROC) analysis.

We performed a multivariable logistic regression analysis of survival to ICU discharge as the dependent variable (enter method). Variables were selected as follows: Variables with a P value < 0.20 in the univariate comparisons between groups were eligible as independent covariates [6] and were required to reach this P value in each univariate analysis to be included in the multivariable logistic regression analysis. Some of the variables that met this criterion had obvious co-linearity and mathematical coupling (e.g. driving pressure, compliance, P_{plat} , PEEP) and were expected to have a high rate of missing values. Therefore, we prioritized variables based on prior clinical knowledge, our first choice being the driving pressure because it has been shown to be most strongly predictive of mortality in ARDS [7]. We forced V_{rec} as a covariate in the model regardless of whether it was significant in the univariate comparisons. To handle missing data as recommended for a rate was greater than 50% [8], the missing driving pressure values (where this occurred) were replaced once with a low value and once with a high value for both PEEP 5 and PEEP 15. The low value was the first quartile and the high value was the third quartile of the existing data. The results are presented with the final ORs and 95% CIs for each covariate.

Statistical analyses were performed using R [R version 3.5.2 (2018-12-20)] with the meta, pROC and epi2 packages [9].

Results

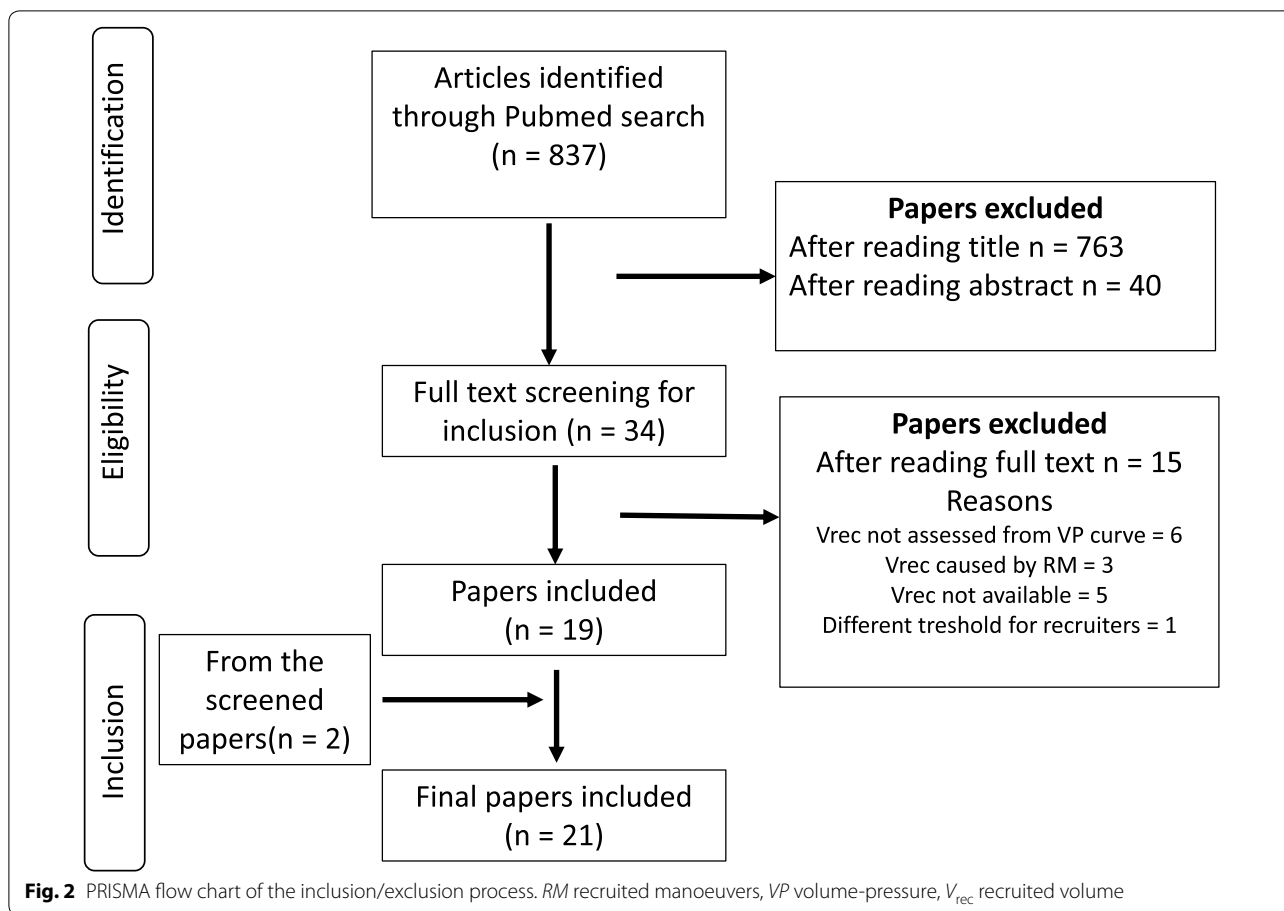
Study selection and individual data

We identified 837 papers in the Pubmed search (Fig. 2). Among these, 803 articles were excluded based on title and abstract and another 15 of the 34 remaining papers were excluded following full text review. After inclusion of two papers retrieved from the references of previously selected articles [10, 11] a total of twenty-one papers fulfilled inclusion criteria [10–30] (Table 1). The 21 retrieved articles were all observational studies. Five of the 21 papers provided the data in a format that did not enable pooled data extraction [10–13, 24]. As these five articles could not be included in the pooled analysis, we contacted the authors and they provided us with their individual patient data, which were included in the individual data analysis. For the pooled data meta-analysis we used sixteen papers for a total of 308 patients (Table 1). The median number of patients per paper was 18 (10–23). Individual patient-level data were available in 6 of the published articles [22, 24, 26–28, 30] and were provided directly by the authors of 8 papers [10–13, 16–18, 20] [12, 13, 16–18, 20] (Table 1). Therefore, individual data were available for 384 patients included in 14 papers (Table 1). As shown in Table 1 ESM (Supplemental material 1) the rate of missing values ranged between 2% (V_{rec}) to 61% (driving pressure and compliance) for the papers included in the individual data meta-analysis. Eighteen papers used the Berlin definition [31] or the previous American-European Consensus Conference (AECC) [32] criteria for ARDS (Table 1). Three papers published before the AECC definition, used the authors' definition of ARDS (Table 1).

Assessment of risk of bias (Quality in Prognostic Studies [QUIPS] tool): All papers were rated as having a moderate to low risk of bias in the domains of study participation, study attrition, prognostic factor measurement and statistical analysis and reporting (Table 2 and Supplemental material 2). The risk of bias was rated as low to moderate in 12/21 papers for the domain of outcome measurement and in 17/21 papers for the domain of study confounding (Table 2). The overall risk of bias was rated as low in 3 papers, moderate in 9 and high in 9 papers (Table 2).

Baseline data

The baseline data of patients in each paper are displayed in Table 3 ESM (Supplemental material 1) and summarized in each study in Table 4 ESM (Supplemental



material 1) for the pooled analysis and in Table 5 ESM (Supplemental material 1) for the individual data analysis. The distribution of most of the values used in converted form for the pooled and individual analyses approximated normal (Tables 4 ESM and 5 ESM Supplemental material 1).

Pooled analysis of recruiters versus non-recruiters

Among the 308 patients included in the 16 papers used for the pooled analysis, the overall prevalence of recruiters was 74% (95% CI 64–84%) (Fig. 3). The overall between-study heterogeneity was 85% (Fig. 3). The mean difference in compliance at baseline between recruiters and non-recruiters was 13.83 ml/cmH₂O (95% CI 0.14–27.52) ($P=0.048$) (Table 3), i.e. compliance was significantly higher in recruiters than in non-recruiters. Otherwise the two groups did not differ in any of the independent variables studied including mortality and days in ARDS before the investigation (Table 3). Funnel plots showed bias in favor of publication supporting an association between recruitability and mortality;

nine articles were within and seven were outside the CIs (Fig. 1 ESM Supplemental material 1).

Subgroup analyses on pooled data

The prevalence of recruiters was 80% and 89% when V_{rec} was measured between PEEP 5 and 15 cmH₂O vs. between PEEP 0 and 10 cmH₂O, respectively (Table 4 and Fig. 2 ESM Supplemental material 1). The prevalence of recruiters was 94% and 65% in studies where PaO₂/FiO₂ was greater than vs. lower than 150 mmHg, respectively (Table 4 and Fig. 4). The prevalence of recruiters was 75% and 66% in articles where primary ARDS accounted for by more vs. less than 50% of the cases, respectively (Table 4 and Fig. 4 ESM Supplemental material 1). The prevalence of recruiters was 61% and 77% for those papers published before vs. after the ARMA trial release, respectively (Table 4 and Fig. 5 ESM Supplemental material 1). The prevalence of recruiters was 70% in articles with an overall low risk of bias vs. 75% in those with a moderate risk of bias and 72% in those with a high risk of bias according the QUIPS tool (Table 4 and Fig. 6 ESM Supplemental material 1). The relative risk of ICU

Table 1 Characteristics of the 21 included articles

Rank	First author	Year of publication	Used in pooled data analysis (No of patients)	Available individual data (No of patients)	Delta PEEP used in the assessment of V_{rec}	Method used for obtain V_{rec}	ARDS definition	Type of study
1	Ranieri	1991	Yes (8)	No	0–15	Static	Author definition	Observational
2	Valta	1993	Yes (9)	Yes (9) ^a	Other	Static	Author definition	Observational
3	Ranieri	1994	Yes (19)	Yes (19) ^a	0–15	Static	Author definition	Observational
4	Ranieri	1995	Yes (9)	Yes (9) ^a	0–10	Static	AECC	Observational
5	Chelucci	2000	Yes (6)	Yes (6) ^a	Other	Static	AECC	Observational
6	Maggiore	2001	Yes (16)	No	5–15	Low flow	AECC	Observational
7	Koutsoukou	2002	No	Yes (13) ^a	0–10	Low flow	AECC	Observational
8	Grasso	2005	Yes (19)	No	Other	Low flow	AECC	Observational
9	Demoule	2006	Yes (17)	Yes (17) ^a	0–10	Static	AECC	Observational
10	Lu	2006	Yes (19)	No	0 to 15	Low flow	AECC	Observational
11	Thille	2007	No	Yes (71) ^b	Other	Low flow and static	AECC	Observational
12	Patroniti	2010	Yes (10)	No	5–15	Low flow	AECC	Observational
13	Bouhemad	2011	Yes (40)	Yes (41) ^b	0–15	Low flow	AECC	Observational
14	Dellamonica	2011	Yes (30)	Yes (30) ^b	5–15	Low flow	AECC	Observational
15	Wallet	2013	Yes (14)	Yes (14) ^b	5–15	Low flow	AECC	Observational
16	Stahl	2015	Yes (25)	No	Other	Other	AECC	Observational
17	Chiumello	2016	Yes (22)	No	5–15	Other	Berlin definition	Observational
18	Yonis	2018	No	Yes (65) ^b	5–15	Low flow	Berlin definition	Observational
19	Aguirre-Bermeo	2018	No	Yes (20) ^b	0–10	Other	Berlin definition	Observational
20	Chen	2020	Yes (45)	Yes (45) ^b	5–15	Low flow	Berlin definition	Observational
21	Guérin	2020	No	Yes (25) ^b	5–15	Low flow	Berlin definition	Observational

No number, PEEP positive end expiratory pressure, V_{rec} recruited volume, ARDS acute respiratory distress syndrome, AECC American-European Consensus Conference

^a Individual data reported in the original article, ^bindividual data obtained after email contact with the author

death for recruiters vs. non-recruiters was 1.20 (95% CI 0.88–1.63) (Fig. 5).

GRADE assessment of certainty of evidence

We assessed the certainty of the evidence with regards to the relation of V_{rec} with mortality at ICU discharge to be overall very low (Table 5).

Individual data meta-analysis

Prevalence of recruiters versus non-recruiters

Among the 384 patients included in the 14 papers used for the individual data meta-analysis the prevalence of recruiters was 70% (266/380 patients with data available for V_{rec}).

Comparison of recruiters to non-recruiters

At the threshold of $P < 0.20$, age, baseline $\text{PaO}_2/\text{FiO}_2$, compliance at PEEP15, and V_T (ml/kg/ P_{BW}) were higher in recruiters whilst days in ARDS, P_{plat} at PEEP5 and at PEEP15, driving pressure at PEEP5, baseline respiratory rate and SAPSII were lower in recruiters than in non-recruiters (Table 6).

Overall mortality

Fourteen studies contributed to the individual data analysis on mortality at ICU discharge (Tables 6ESM and 4ESM Supplemental material 1). ICU mortality was 44% (152/344 patients with data on mortality available).

Comparison of survivors to non-survivors

Several variables met the threshold of $P < 0.20$ in the comparison between survivors and non-survivors. These included the proportion of primary ARDS proportion, compliance at PEEP15 and tidal volume (ml) (all higher in survivors) and baseline FiO_2 , baseline PEEP, P_{plat} at PEEP5 and PEEP15, driving pressure at PEEP5 and PEEP15, respiratory rate and SAPSII (all lower in survivors) (Table 7).

The relative risk of mortality in recruiters was 1.05 (0.86–1.30). The performance of V_{rec} for prediction of ICU mortality was poor (AUC ROC 0.52, 95% CI 0.46–0.58). The ROC curve did not suggest any other specific threshold to be tested (Fig. 6).

Table 2 Assessment of the risk of bias in each included paper according to the quality in prognosis study tool

Study Number	Author	Year of publication	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Con- founding	Statistical Analy- sis and Reporting	Overall risk of bias
1	Ranieri	1991	M	L	L	H	H	L	H
2	Valta	1993	M	H	L	H	H	L	H
3	Ranieri	1994	M	L	M	H	H	L	H
4	Ranieri	1995	M	L	M	H	H	L	H
5	Chelucci	2000	M	L	M	H	H	L	M
6	Maggiore	2001	M	L	M	L	M	L	M
7	Koutsoukou	2002	M	L	L	H	M	L	H
8	Grasso	2005	L	L	M	H	M	L	H
9	Demoule	2006	L	L	L	L	M	L	M
10	Lu	2006	M	L	L	H	M	L	H
11	Thille	2007	M	L	L	L	M	L	M
12	Patroniti	2010	M	L	L	L	M	L	M
13	Bouhemad	2011	L	L	L	L	M	L	M
14	Dellamonica	2011	M	L	L	H	M	L	H
15	Wallet	2013	L	L	L	L	L	L	L
16	Stahl	2015	M	L	L	H	M	L	H
17	Chiumello	2016	M	L	L	L	M	L	M
18	Yonis	2018	M	L	L	L	M	L	M
19	Aguirre-Bermeo	2018	L	L	L	L	M	L	M
20	Chen	2020	L	L	L	L	L	L	L
21	Guérin	2020	L	L	L	L	L	L	L

L low risk of bias, M moderate risk of bias, H high risk of bias

Multivariable logistic regression on ICU mortality

Three variables were selected as covariates for the multivariable logistic regression analysis on ICU mortality because they had reached a P value < 0.20 in the univariate comparison between both survivors and non-survivors and recruiters versus non-recruiters. These variables were baseline respiratory rate, driving pressure at PEEP5 and SAPSII. In addition, as planned, we forced V_{rec} (as a continuous variable) into the model. In accordance with our preplanned analysis strategy driving pressure PEEP 15 was also entered into specific models. We did it too because we felt it may be wrong to impute only the driving pressure at a low PEEP because of the literature. The low and high cut-off values of 8 and 13 cmH₂O for the driving pressure at PEEP5 and 9 and 14 cmH₂O for the driving pressure at PEEP15 were used to replace the missing values. V_{rec} was not significantly associated with ICU mortality in any model (Table 8 and Table 6 ESM in Supplemental material 1). The single variables significantly associated with ICU mortality were SAPSII and driving pressure at PEEP 5 (Table 8). However, in models that included both driving pressures at PEEP5 and at PEEP15 the driving pressure at PEEP 15 was consistently significantly associated with ICU mortality (Table 6 ESM Supplemental material 1).

Discussion

This is the first systematic review and meta-analysis on PEEP-induced recruited lung volume in ARDS patients. Our main finding was that at the threshold tested V_{rec} was very prevalent but was not associated with mortality. However, the certainty of the evidence with regards to this association was very low. We also identified significant publication bias in studies reporting in favor of significant associations between V_{rec} and mortality using proportions and found that the number of studies reporting risk ratios was too low to enable assessment of publication bias. These findings suggest that the existing literature does not really suffice to determine the relation of V_{rec} with patient outcomes.

Most papers assessing V_{rec} used a cut-off of 150 ml to differentiate between "recruiters" and "non-recruiters". While this recruited lung volume appears clinically meaningful, such dichotomization makes little biological sense. We used recruited lung volume as a continuous variable in the individual data analysis. Although both analyses indicated that recruitment of lung volume as a result of increased PEEP does not seem to modify important effect measures in any meaningful way, the uncertainty regarding these conclusions remains significant due to the small amount of aggregated data available.

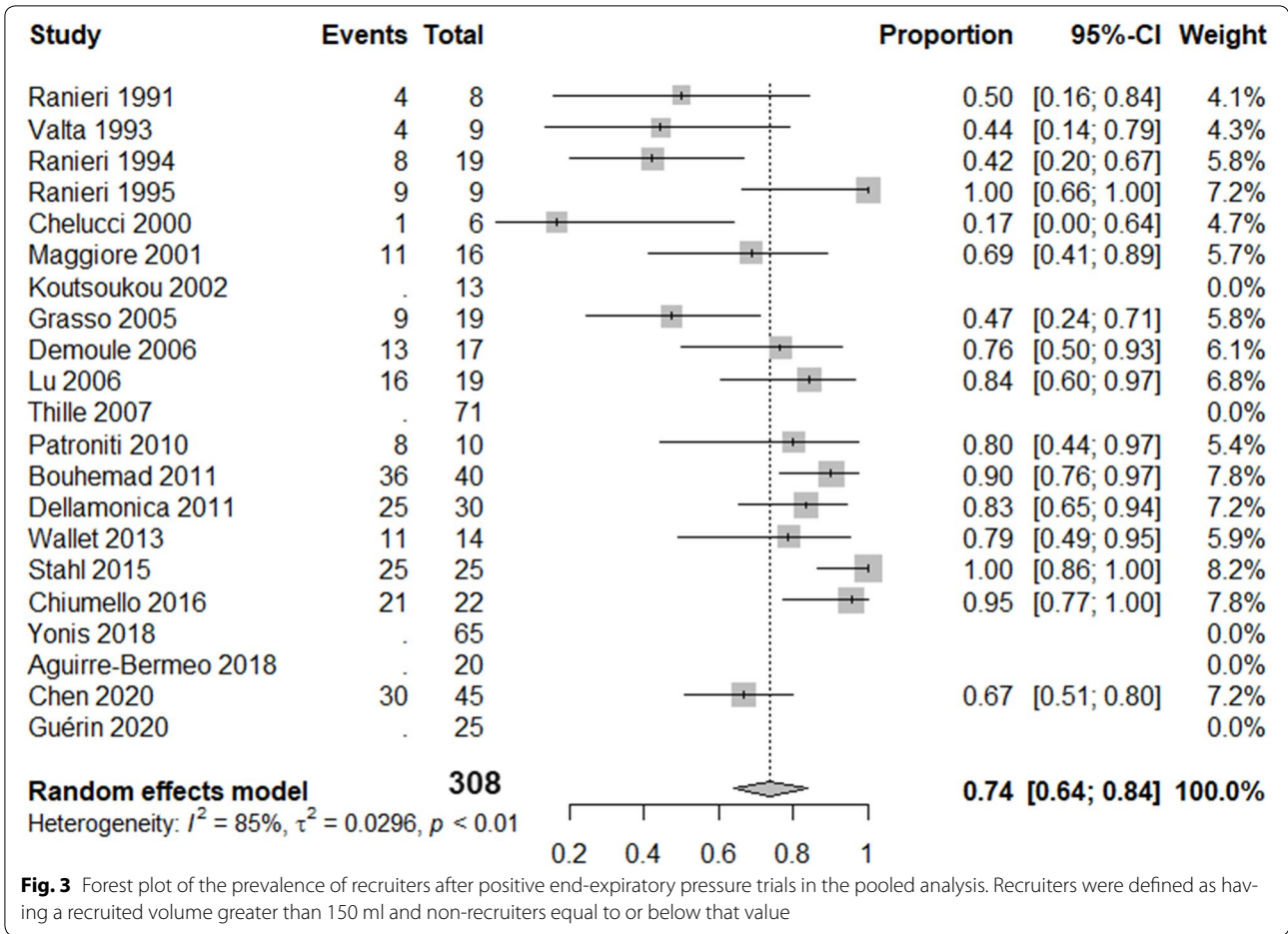


Fig. 3 Forest plot of the prevalence of recruiters after positive end-expiratory pressure trials in the pooled analysis. Recruiters were defined as having a recruited volume greater than 150 ml and non-recruiters equal to or below that value

Table 3 Comparison between recruiters and non recruiters in the pooled data analysis

	No of studies	No of recruiters	No of non-recruiters	RR or MD (recruiters vs non-recruiters)	95% confidence intervals	P value	I^2 (%)
Age, years	5	41	28	MD -1.18	- 8.16; 5.81	0.741	0
Male gender	4	27	23	RR 1.34	0.88; 2.03	0.177	0
Primary ARDS	7	50	44	RR 0.79	0.54; 1.15	0.214	15
Days of ARDS before experiment	3	23	21	MD -1.27	- 2.54; 0.01	0.051	0
PaO ₂ /FiO ₂ , mmHg	5	45	35	MD 0.72	- 12.5; 14.19	0.917	0
PEEP, cmH ₂ O	3	23	21	MD 0.12	- 2.41; 2.65	0.927	0
Compliance, ml/cmH ₂ O	4	36	25	MD 13.83	0.14; 27.52	0.048	0
Mortality	3	25	14	RR 1.20	0.88; 1.63	0.256	0

RR relative risk, MD mean difference, ARDS acute respiratory distress syndrome, PaO₂ arterial partial pressure of oxygen, FiO₂ inspired fraction of oxygen, PEEP positive end expiratory pressure, I^2 statistical heterogeneity

This issue, concomitant with the existence of clear publication bias, suggests that the prognostic value of V_{rec} may have been unjustifiably inflated.

The combination of negative results of large trials investigating higher versus lower PEEP [33] and studies showing an increased risk with the use of very high PEEP

[34] highlights the need for a bedside tool for assessing individual alveolar recruitment potential. Esophageal pressure has been put forward as one such tool [35] but to date there is no evidence of clinical benefit of its use [36]. The measurement of V_{rec} with the VP curve is easy to carry out at the bedside. However, our findings raise

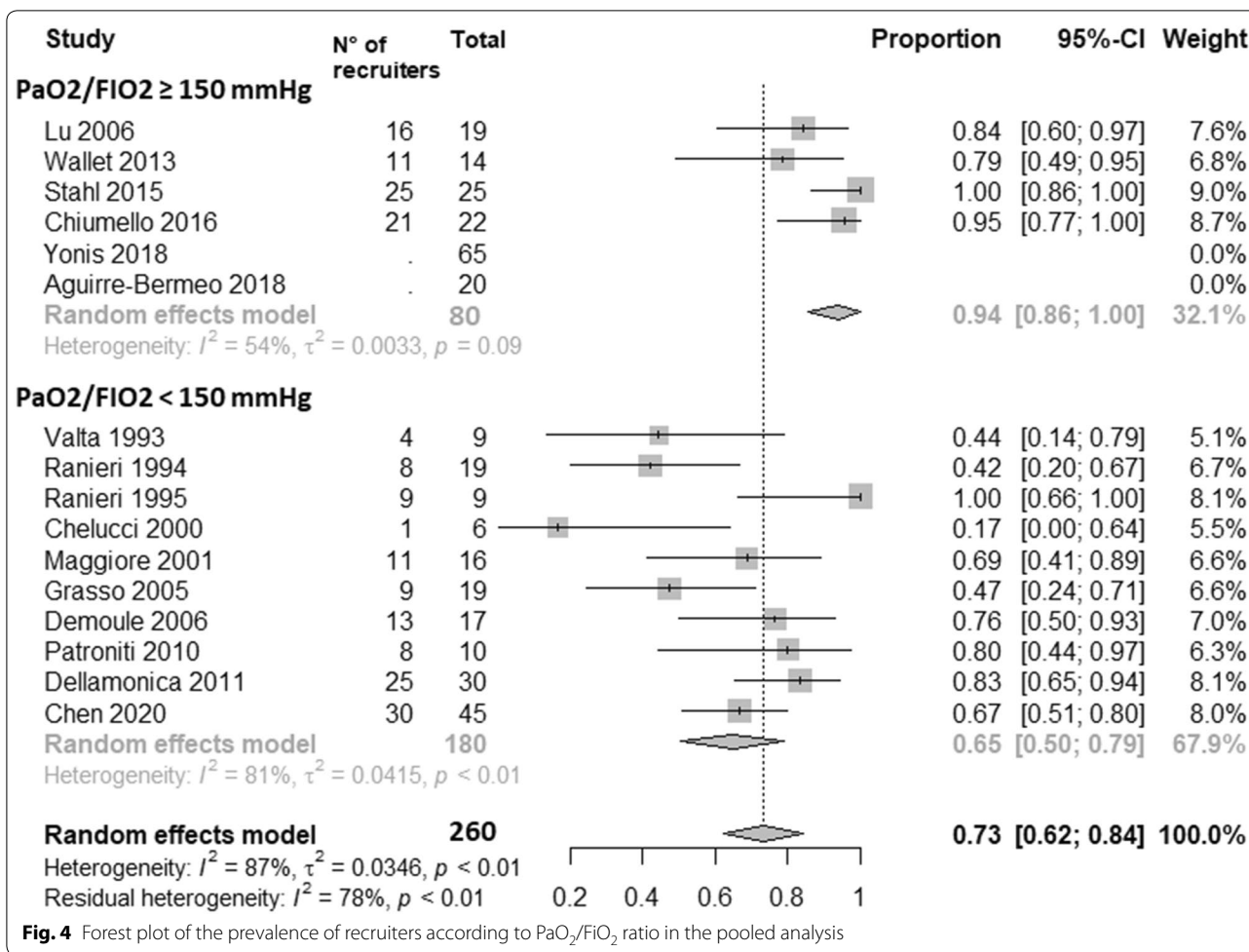


Fig. 4 Forest plot of the prevalence of recruiters according to PaO₂/FiO₂ ratio in the pooled analysis

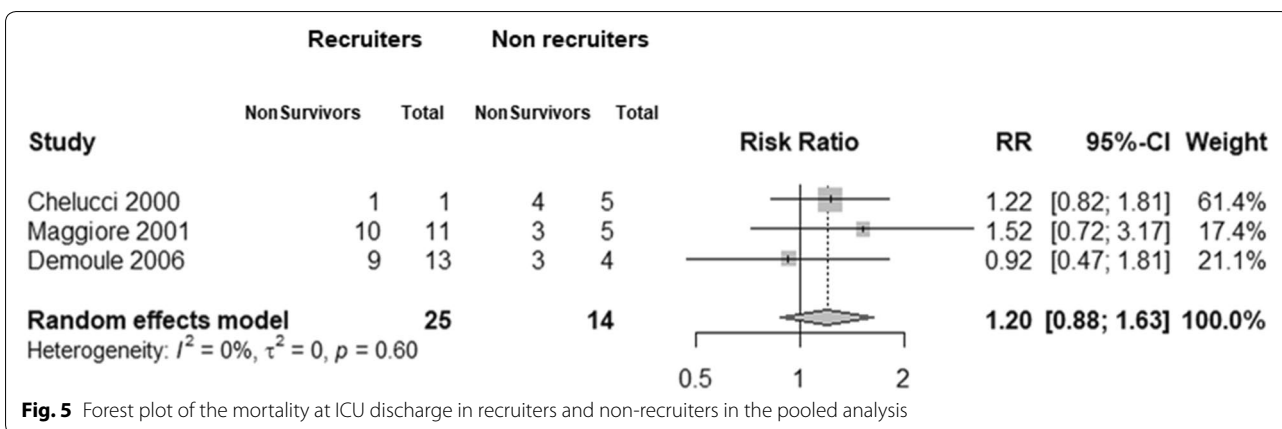


Fig. 5 Forest plot of the mortality at ICU discharge in recruiters and non-recruiters in the pooled analysis

important questions regarding the justification for using "recruitability" versus "non-recruitability" as a criterion for enrolment to clinical trials or for post-hoc stratification. Recent advances to assess lung recruitability at the

bedside [11, 17] share the same approach, and hence have the same implication as the VP curve explored in present study.

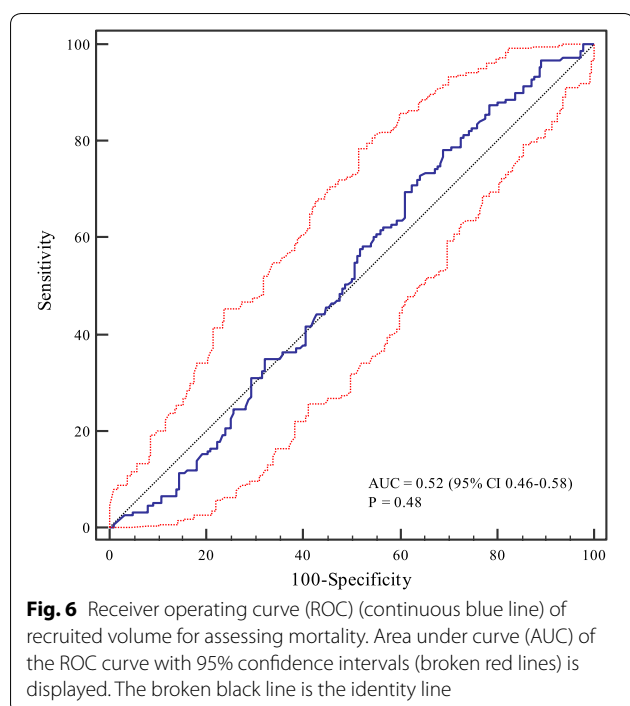


Fig. 6 Receiver operating curve (ROC) (continuous blue line) of recruited volume for assessing mortality. Area under curve (AUC) of the ROC curve with 95% confidence intervals (broken red lines) is displayed. The broken black line is the identity line

Physiological meaning of V_{rec}

V_{rec} as measured from the VP curve of the respiratory system reflects the amount of air that enters previously non-aerated lung regions as a result of PEEP increase [29]. It may also include some overdistension of previously normally aerated lung. By contrast, lung CT scan measures the amount of non-aerated tissue that becomes aerated as a result of the increase in PEEP. Comparison of these methods showed they do not correlate [14]. Contrary to Chiumello et al. [14], Lu et al. [21] found a tight correlation between V_{rec} and recruited lung

volume measured by CT. Part of this discrepancy could be explained by the fact that Lu et al. defined recruited lung volume on CT by the amount of gas penetrating not only non-aerated lung area but also poorly ventilated lung regions [21]. They also pointed out that the morphology of lung involvement (focal vs. diffuse) may affect the degree of correlation of the two techniques [21].

Relationship between V_{rec} and mortality

We found no association between V_{rec} and mortality at the predefined threshold we used. This threshold was selected from the literature and had a large prevalence in our study. The lack of a significant relationship between V_{rec} and mortality may be explained by a lack of power of present study, prevalence of focal and diffuse ARDS, and the threshold definition for V_{rec} . This threshold was selected because it has been previously used by other investigators. Moreover, the ROC curve did not suggest any other value to be tested for assessing mortality further. Interestingly, the amount of 150 ml was the lowest value of V_{rec} observed in patients used by Chiumello et al. to compare V_{rec} to CT-based recruited lung volume [14]. Furthermore, at this value of 150 ml of V_{rec} the amount of recruited lung volume can range between 0 and 350 g [14] and with this latter value patients would be defined as higher recruiters [37]. Mortality is increased in patients with higher versus lower percentage of potentially recruitable lung, i.e. 41 vs. 15% ($P < 0.05$), respectively [37]. The lack of prognostic role of V_{rec} may also reflect that the included studies were not designed and did not aim to assess mortality. However, that driving pressure at PEEP 15 was a significant independent predictor of ICU mortality in present study adds reliability to our analysis.

Table 4 Sensitivity subgroup analysis for prevalence of recruiters in the pooled data meta-analysis

	No of articles	Proportion of recruiters (95% CI)	ρ^2 (%)	P value
Articles with V_{rec} measured from PEEP 5 to 15 cmH ₂ O	6	0.80 (0.69; 0.91)	66	0.01
Articles with V_{rec} measured from PEEP 0 to 10 cmH ₂ O	2	0.89 (0.67; 1.00)	72	0.06
Articles with $\text{PaO}_2/\text{FiO}_2 \geq 150$ mmHg	4	0.94 (0.86; 1.00)	54	0.09
Articles with $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg	10	0.65 (0.50; 0.79)	81	<0.01
Articles with more than 50% of primary ARDS	9	0.75 (0.63; 0.87)	80	<0.001
Articles with more than 50% of secondary ARDS	6	0.66 (0.45; 0.86)	82	<0.001
Articles published before ARMA trial	4	0.61 (0.25; 0.96)	89	<0.01
Articles published after ARMA trial	12	0.77 (0.67; 0.87)	85	<0.01
Articles with low overall low risk of bias	62	0.74 70 (0.62 59; 0. 8782)	690	< 0.36
Articles with overall moderate or high risk of bias	106	0.73 75 (0.60 59; 0. 8791)	8583	<0.01
Articles with overall high risk of bias	9	0.72 (0.56–0.88)	89	<0.01

No number, CI confidence intervals; V_{rec} recruited volume, PEEP positive end expiratory pressure, PaO_2 arterial partial pressure of oxygen, FiO_2 inspired fraction of oxygen, ARDS acute respiratory distress syndrome, ARMA the acute respiratory syndrome network

Prevalence of recruiters

The prevalence of recruiters was large in our study, at the threshold used. We found only a small difference in the prevalence of recruiters in the pooled versus the individual data. This difference could be due to the inclusion of different papers into the two analyses.

Subgroup analysis of the pooled data revealed some of the sources of the significant heterogeneity observed between studies. Some of the heterogeneity stemmed from differences in the level of PEEP applied. The prevalence of recruiters was also clearly related to the initial patient PaO₂/FiO₂ and to the risk of bias as assessed by the QUIPS tool. Our findings differ from those of several previous studies. Our subgroup analysis showed that the subgroup of articles with a mean PaO₂/FiO₂ > 150 mmHg had a higher percentage of recruiters. This could be due to the fact that the high V_{rec} found in patients with a high

PaO₂/FiO₂ does not reflect recruitment alone, but also includes some component of over-distension. This discrepancy could also be a chance finding, as is often the case when multiple subgroup analyses are conducted.

There is no threshold to define recruiters based on CT scan. In the studies that investigated the CT-based lung recruitment the authors used the median value of the observed data to define recruiters and non-recruiters. Across studies the percentage of potentially recruitable lung varies between 13% [37] and 42% [38] depending on definition of lung recruitment, range of pressure investigated and whether ARDS was early or late. When lung recruitment was defined as a ≥ 10% decrease of non-aerated lung tissue between PEEP and zero PEEP 62% of the patients studied were recruiters [39].

Table 5 Certainty of evidence for the relationship between ICU mortality and recruited lung volume

Certainty assessment							Effect (relative risk 95% CI)	Certainty
Number of studies	Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
21	Observational	Serious	Not serious	Not serious	Serious	Publication bias strongly suspected	1.20 (95% CI 0.88–1.63)	Very low

Table 6 Univariate comparison between recruiters and non-recruiters in the individual data meta-analysis

	Recruiters (N = 266)	Non-recruiters (N = 112)	P value
Age, years	62 (46–71)	58 (48–68)	0.189
Male gender	173/241 (72)	73/92 (79)	0.223
Primary ARDS	167/265 (63)	66/112 (59)	0.490
ARDS days before experiment	3 (2–4)	4 (2–5)	0.012
Baseline PaO ₂ /FiO ₂ , mmHg	148 (109–184)	136 (104–164)	0.199
Baseline FiO ₂ , %	60 (50–80)	60 (50–70)	0.399
Baseline PEEP, cmH ₂ O	10 (8–14)	10 (8–13)	0.532
Compliance at PEEP 5, ml/cmH ₂ O	35 (28–47)	36 (25–44)	0.279
Compliance at PEEP 15, ml/cmH ₂ O	34 (26–46)	30 (21–43)	0.123
P _{plat} at PEEP 5, cmH ₂ O	17 (14–19)	19 (17–25)	0.003
P _{plat} PEEP 15, cmH ₂ O	28 (26–30)	29 (27–31)	0.107
Driving pressure at PEEP 5, cmH ₂ O	10 (8–13)	11 (9–17)	0.023
Driving pressure at PEEP 15, cmH ₂ O	11 (9–14)	13 (10–15)	0.368
Respiratory rate, breaths/min	25 (22–30)	28 (25–30)	0.019
Tidal volume, ml	412 (370–450)	400 (350–450)	0.551
Tidal volume, ml/kg/PBW	6 (6–7)	6 (6–6)	0.025
Body mass index, kg/m ²	29 (24–33)	28 (24–32)	0.997
Simplified Acute Physiology Score II	43 (31–59)	49 (39–65)	0.015

Values are median (1st–3rd quartiles) or counts (percentage-point per group)

ARDS acute respiratory distress syndrome, PaO₂ partial pressure of oxygen, FiO₂ inspired fraction of oxygen, PEEP positive end expiratory pressure, P_{plat} plateau pressure, P_{BW} predicted body weight

Table 7 Univariate comparison between survivors and non-survivors at ICU discharge in the

Variable	Survivors N = 192	Non survivors N = 152	P value
Individual data meta-analysis			
Age, years	61 (46–69)	63 (45–71)	0.340
Male gender, %	139/187 (74)	100/140 (71)	0.615
Primary ARDS	138/191 (72)	90/152 (59)	0.012
ARDS days before experiment	3 (2–5)	3 (2–5)	0.658
Baseline PaO ₂ /FiO ₂ , mmHg	155 (120–186)	150 (114–186)	0.419
Baseline FiO ₂ , %	50 (50–71)	60 (50–75)	0.161
Baseline PEEP, cmH ₂ O	10 (8–12)	12 (10–15)	0.003
Compliance at PEEP 5, ml/cmH ₂ O	36 (27–47)	34 (28–43)	0.533
Compliance at PEEP 15, ml/cmH ₂ O	35 (26–47)	32 (23–39)	0.057
P _{plat} at PEEP 5, cmH ₂ O	17 (14–19)	18 (16–23)	0.034
P _{plat} at PEEP 15, cmH ₂ O	28 (25–30)	30 (26–31)	0.011
Driving pressure at PEEP 5, cmH ₂ O	10 (8–13)	11 (9–13)	0.094
Driving pressure at PEEP 15, cmH ₂ O	11 (9–14)	13 (10–15)	0.027
V _{rec} , ml	247 (131–404)	243 (149–352)	0.574
Respiratory rate, breaths/min	25 (22–30)	26 (24–30)	0.108
Tidal volume, ml	420 (360–450)	400 (357–440)	0.077
Tidal volume, ml/kg/PBW	6 (6–7)	6 (6–6)	0.472
Body mass index, kg/m ²	29 (24–32)	28 (24–34)	0.587
Simplified acute physiology score II	44 (31–58)	46 (36–65)	0.100

ARDS acute respiratory distress syndrome, PaO₂ partial pressure of oxygen, FiO₂ inspired fraction of oxygen; PEEP positive end expiratory pressure; P_{plat} plateau pressure; V_{rec} recruited volume, P_{BW} predicted body weight

Values are median (1st–3rd quartile) or counts (percentage-point per group)

Table 8 Multivariable logistic regression analysis in which missing values of driving pressure PEEP 5 have been imputed (1st quartile for low value and 3rd quartile for high value) and driving pressure PEEP5 was entered alone (not together with driving pressure PEEP 15)

Models Covariates	Low value for driving pressure PEEP5 ^a		High value for driving pressure PEEP5 ^b	
	OR (95% CI)	P value	OR (95% CI)	P value
V _{rec} per 1 ml	1.00 (1.00–1.00)	0.843	1.00 (1.00–1.00)	0.893
Respiratory rate per 1 breath/min	1.02 (0.95–1.09)	0.616	1.02 (0.95–1.10)	0.564
SAPSII per 1-point	1.03 (1.01–1.06)	0.008	1.03 (1.01–1.06)	0.008
Driving Pressure at PEEP 5 per 1 cmH ₂ O	1.15 (1.04–1.29)	0.009	1.14 (1.03–1.28)	0.015

V_{rec} recruited lung volume; SAPSII simplified acute physiology score, PEEP positive end-expiratory pressure

^a Imputation of missing values by replacing missing values by 8 cmH₂O, ^b imputation of missing values by replacing missing values by 13 cm H₂O

Limitations

Our study has several limitations. It was registered in PROSPERO 9 months after the first search due to an excessive time lag in the PROSPERO answer. Some discrepancies are now present between the version submitted to PROSPERO and the current version. These discrepancies partly come from the request of the reviewers to use the QUIPS tool to assess the risk of bias and be clearer for the time of assessment of mortality (ICU

discharge in the current version and not ICU discharge or at the last assessment). We added in the current version a subgroup analysis based on risk of bias in the studies. Lacking RCTs, our analysis is based on observational data. Such data is by nature prone to bias by uncontrolled confounders. Some of the papers we included are dated before widespread use of several important therapeutic mechanical ventilation strategies. This could explain why, as shown in Fig. 3, older articles had a lower percentage

of recruiters when compared to the more recent ones. The data in the present study did not enable investigation of airway opening pressure (AOP) which may also affect the determination of V_{rec} [40]. However, since we extracted data on V_{rec} at a pressure of 20 cmH₂O, it is likely that this level would be greater than AOP on average [40]. Lung recruitability has been suggested to decrease over time. As temporal data was not provided by the authors we were therefore unable to assess the effect of this variable on V_{rec} . Based on previously published data we felt that driving pressure is a variable than cannot be ignored in this analysis. Despite the consistent finding in our sensitivity analysis, our result regarding this variable should be interpreted with caution due to the amount of missing data imputed. An analysis with this amount of missing data is concerning and may be of limited value (and potentially misleading). Finally selection of covariates was performed based on a *P* value of 0.20. While this method has the advantage of relatively broad inclusion as benefits an exploratory study such as ours and a threshold of 0.157 (corresponding to selection based on the Akaike information criterion) is often used, variable selection bias remains a possibility. The primary reason for this is a limitation due to the risk of chance findings in the screening process which may inflate the risk of random errors. This is the reason that statistical variable selection is generally recommended against [41].

Conclusion

We found that after a PEEP increment most patients had a $V_{rec} > 150$ ml measured with VP curve, and that V_{rec} was not associated with ICU mortality. In the pooled data the certainty of evidence with regards to this association was overall very low as all of the studies identified were observational and had quality limitations. Two of our results suggest this association is valid nonetheless: the fact that the findings were present in the individual patient level analysis and our finding that driving pressure at PEEP of 5 cmH₂O was associated with mortality as previously reported. Conversely, the presence of significant publication bias towards studies reporting significant associations between V_{rec} and mortality and using proportions rather than risk ratios and, as well as the paucity of studies reporting risk ratios, suggest that the existing literature still does not suffice to determine the relation of V_{rec} to outcome.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-06226-9>) contains supplementary material, which is available to authorized users.

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Acknowledgements

The authors would like to thank H. Aguirre-Bermeo, L. Chen, J. Dellamonica, A. Koutsoukou, J.J. Rouby, and A. Thille for sharing their data. The authors are grateful to the ESICM systematic review group for assistance received in data analysis and presentation.

Funding

This study has received no external funding.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 4 May 2020 Accepted: 20 August 2020

Published online: 11 September 2020

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