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REVIEW PAPER

Is EIT-guided positive end-expiratory pressure titration for optimizing PEEP in ARDS the white elephant in the room? A systematic review with meta-analysis and trial sequential analysis

Soumya Sarkar[1] · Bharat Yalla[2] · Puneet Khanna[2] · Madhurjya Baishya[2]

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Abstract

Electrical Impedance Tomography (EIT) is a novel real-time lung imaging technology for personalized ventilation adjustments, indicating promising results in animals and humans. The present study aimed to assess its clinical utility for improved ventilation and oxygenation compared to traditional protocols. Comprehensive electronic database screening was done until 30th November, 2023. Randomized controlled trials**,** controlled clinical trials, comparative cohort studies, and assessments of EIT-guided PEEP titration and conventional methods in adult ARDS patients regarding outcome, ventilatory parameters, and P/F ratio were included. Our search retrieved five controlled cohort studies and two RCTs with 515 patients and overall reduced risk of mortality [RR = 0.68; 95% CI: 0.49 to 0.95; $I^2 = 0\%$], better dynamic compliance [MD = 3.46; 95% CI: 1.59 to 5.34; $I^2 = 0\%$] with no significant difference in PaO_2/FiO_2 ratio [MD = 6.5; 95%CI -13.86 to 26.76; $I^2 = 74\%$]. The required information size except PaO_2/FiO_2 was achieved for a power of 95% based on the 50% reduction in risk of mortality, 10% improved compliance as the cumulative Z-score of the said outcomes crossed the alpha spending boundary and did not dip below the inner wedge of futility. EIT-guided individualized PEEP titration is a novel modality; further well-designed studies are needed to substantiate its utility.

Highlights

Question: Is the EIT-guided PEEP titration in ARDS universally beneficial and effective?
Findings: This systematic review found better survivability, dynamic compliance, in ARDS patients, as the required information size was achieved for a power of 95%. There was no significant improvement in oxygenation and successful weaning incidence compared to conventional methods. However, the required information size for these contexts is yet to be achieved.
Meaning: EIT-guided PEEP titration in ARDS patients showed promising results and warranted further clinical trials.

Keywords Electrical Impedence Tomography (EIT) · Positive End-Expiratory Pressure (PEEP) · ARDS · Meta analysis · Trial Sequential Analysis

✉ Puneet Khanna
k.punit@yahoo.com

Soumya Sarkar
drsoumyasarkar@yahoo.co.in

Bharat Yalla
bharat.yalla1@gmail.com

Madhurjya Baishya
madhurjyabaishya121@gmail.com

1 Department of Anaesthesiology, AIIMS, Kalyani, India

2 Department of Anaesthesia, Pain Medicine & Critical Care, AIIMS, Ansari Nagar, New Delhi 110029, India

1 Introduction

Electrical impedance tomography (EIT) has been increasingly utilized in various clinical conditions, including ARDS, acute hypoxemia, [1–4] general anaesthesia, [5, 6] and postoperative cardiac surgery [7, 8].

It is an efficient, non-invasive,radiation-free, real-time bedside lung imaging technology to identify atelectasis, overdistension, and recruitment. It reconstructs impedance changes through the application of imperceptible currents and measurement of changes in voltage around the thorax, thereby allowing for individualized PEEP titration.

It assesses regional respiratory system compliance (Crs) changes by identifying cyclic opening & closing, regional overdistension, and early lung recruitment changes. EIT-derived regional ventilation delay inhomogeneity (SDRVD) correlates with alveolar cycling, offering a potential tool for adjusting ventilation settings. Its ability to estimate ventilation and perfusion depending upon impedance variations and real-time assessment of regional Crs changes, identifying atelectrauma and overdistension, makes it a comprehensive tool [9–12].

Mechanical ventilation is vital in acute respiratory distress syndrome (ARDS), which has morphological features such as regional atelectasis, overdistension, and lung inhomogeneities. Cyclic opening and closing of lung units pose risks like ventilator-induced lung injury (VILI) [13–15].

The stress–strain concept quantifies the harm caused by high lung volumes. Adjusting positive end-expiratory pressure (PEEP) based on global Crs aims to balance overdistension and cyclic opening/closing but lacks consistent benefits, possibly because global Crs inadequately predicts recruitability, especially in atelectasis dynamics [16–19].

Studies demonstrate that EIT-guided positive end-expiratory pressure (PEEP) titration is valuable for optimizing PEEP in animals and humans [20–22]. However, the question remains whether EIT-guided PEEP titration can enhance ventilation and optimize global oxygenation, which requires further investigation in this specific clinical context.

Thus, the current study aimed to assess the clinical utility of EIT-guided PEEP titration compared to traditional protocols in terms of better ventilation and oxygenation in adherence to the "Preferred reporting items of systematic review and meta-analysis" (PRISMA) statement [23].

2 Methods

2.1 Literature search

The comprehensive search spanned various electronic databases (PubMed, Medline, and Embase), Google Scholar (https://scholar.google.com), preprint platforms MedRxiv (https://www.medrxiv.org), and Clinical trial database (https://ClinicalTrials.gov) until November 30, 2023, using the following keywords "EIT" OR " Electrical Impedance Tomography" AND " PEEP" OR " Positive End-Expiratory Pressure" AND " Acute Respiratory Distress Syndrome" OR "ARDS" OR "General Anesthesia" OR "Surgery". Using the above MeSH terminology, all the articles were screened & reviewed by BY and SS. Disagreements were sorted out by taking PK's opinions.

We adopted the PICO format for structuring the findings, where "P" denoted the population (Adults requiring mechanical ventilation due to ARDS), "I" referred to interventions (EIT-guided PEEP titration), "C" pertained to comparisons (conventional treatment), and "O" encompassed outcomes (P/F ratio, driving pressure, PEEP optimization, successful weaning).

2.2 Inclusion and exclusion criteria

Randomized controlled trials, controlled clinical trials, prospective and retrospective comparative cohort studies, case-control studies, comparing the clinical utility of EIT-guided PEEP titration with conventional management in patients with ARDS were included.

Case reports, narrative reviews, expert opinions, studies other than those in English, without appropriate control groups, were excluded.

2.3 Study selection and data extraction

SS and BY conducted independent screenings of abstracts to remove duplication and eliminate irrelevant articles. Eligible studies underwent full-text screening for inclusion criteria. A pre-designed data extraction sheet facilitated information collection such as the first author, publication year, study nature, country, patient count, P/F ratio, driving pressure, optimized PEEP, and successful weaning. Discrepancies were resolved through discussions with PK.

2.4 Risk of bias assessment

SS & PK independently determined any potential bias in the included RCTs using the “RoB 2.0″ [24] assessment tool, and non-randomized trials using the "Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I)” [25]. The disagreements were settled by discussing with MB.

2.5 Quality of the evidence

PK and SS evaluated each outcome individually as either "High" or "Moderate" or "Low" or "Very low" with the "Grading of Recommendations Assessment, Development and Evaluation (GRADE)" [26, 27] tool, comprising five downgrading factors: "study limitations, indirectness, imprecision, consistency of effect, and publication bias" and three upgrading factors: "dose-response relation, large magnitude of the effect, and plausible confounders or biases", and disagreements were resolved by MB.

2.6 Data synthesis

The meta-analysis was carried out by SS using Review Manager Software (RevMan V.5.4.1) & Trial sequential analysis (TSA) Copenhagen Trial Unit (Version 9.5.10 Beta, Copenhagen, Denmark) [28], The mean difference was utilized as the outcome measure for continuous variables & the log odds ratio for dichotomous variables. Outcome heterogeneity (tau^2) was estimated using I^2 statistic. Mild heterogeneity was considered for $I^2 < 30\%$, moderate for $I^2 = 30\%$ to 70%, and significant for $I^2 > 70\%$

Sensitivity analysis was conducted by removing one study at a time, noting effects on outcome heterogeneity. Funnel plot was used to assess publication bias.

3 Results

3.1 Basic characteristics

This review comprised five controlled cohort studies [29, 30, 33–35] and two randomized controlled trials, [31, 32] out of 341 screened publications. (Fig. 1) While three studies [29, 32, 35] included severe ARDS patients, two of them [30, 33] included mild, moderate, and severe ARDS, and one [31] had moderate and severe ARDS patients, as per Berlin definition. One of the studies included chronic obstructive pulmonary disease (COPD) [33], and the other one incorporated coronavirus disease (COVID-19) [34]-related ARDS patients.

While one study described 49% of patients required prone positioning, [30] in two studies, the prevalence was 2–4% [31, 35] in the EIT group compared to 41%, 0–3% in the control group. Two studies describe the use of inhaled nitric oxide in 54% and 66% of the patients who received EIT-guided PEEP optimization and 51.1% and 96.8% in the control group. 33.3% to 38.1% of patients in the EIT group received ECMO compared to 11.1 to 16.1% of patients in the control [31, 35].

Prevalence of tracheotomized patients ranges from 6-11% in the control group and 14–28% in patients with EIT

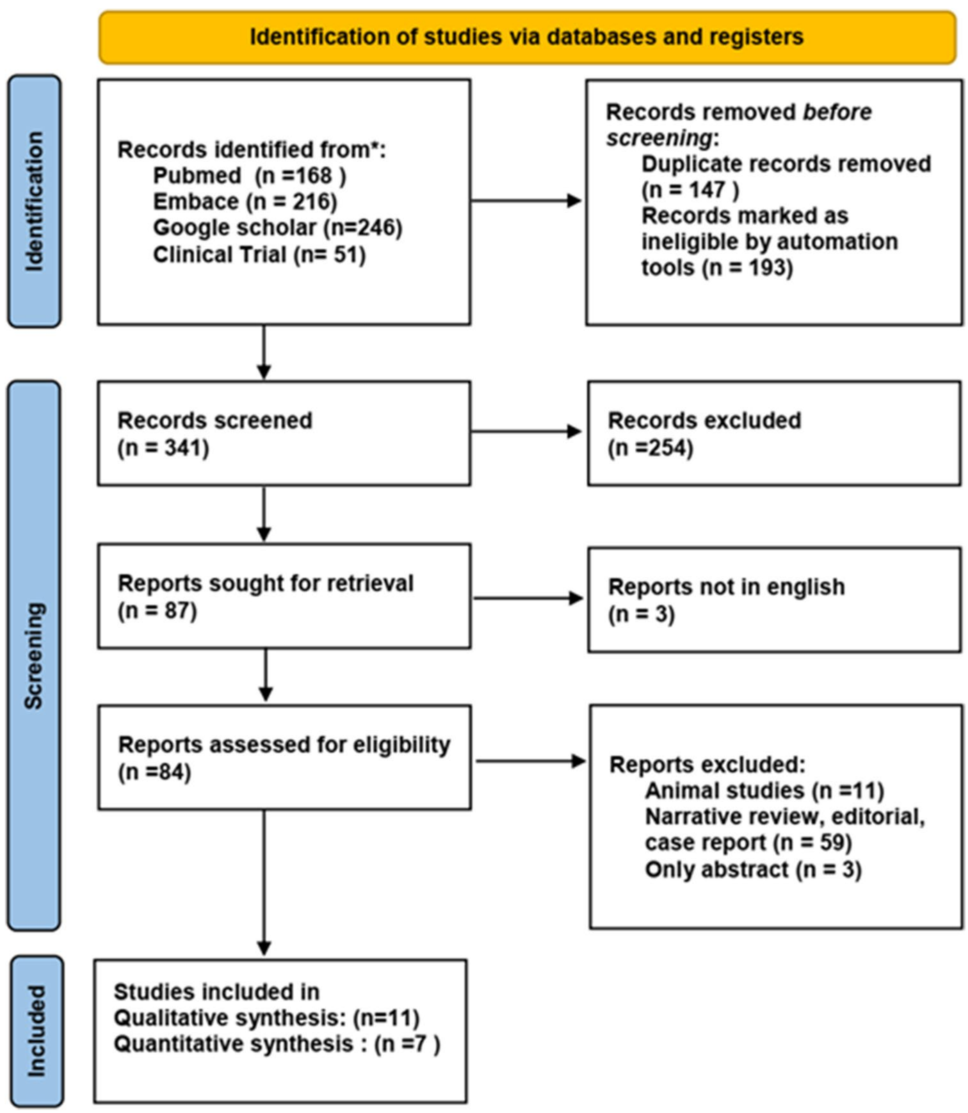


Fig. 1 PRISMA-2020-Flow-Diagram

Table 1 Characteristics of included studies

Sl. no	Study, Year	Nature	Country of origin	Population size	EIT protocol / interventions	Conclusion
1	Becher et al. [29] 2021	Prospective cohort, SC	Germany	20	Recruitability in respiratory mechanics was assessed using a sustained inflation manoeuvre with a Paw of 40 mbar, followed by a PEEP increase of 3 mbar. Crs was evaluated through EIT, and successful recruitment was defined by a > 3% increase in Crs in any of the four regions of interest. Alveolar cycling and over distension were diagnosed by changes in Crs with altered inspiratory pressure, guiding PEEP and tidal volume adjustments. If there was no evidence of recruitability or alveolar cycling during the last two hours, the PEEP was reduced by 2 mbar	Individualized ventilator settings through the EIT-based protocol improved oxygenation and decreased alveolar cycling, avoiding global over distension
2	He et al. [30] 2021	Prospective cohort, SC	China	117	Patients in pressure control mode experienced EIT-guided PEEP titration through an increase to 21 cmH2O (or 15 cmH_2O) for 5 min, and then decreased in 3 cmH_2O steps every 2 min till 0 cmH_2O. Optimal PEEP was chosen based on EIT-calculated regional collapse and over distension percentages during decremental PEEP trials. Selection aimed at balancing collapsed and over distended lungs, prioritizing the lowest global inhomogeneity index	Prompt application of personalized PEEP based on EIT had a 6% absolute reduction in mortality and c a quicker initial restoration of organ function
3	Hsu et al. [31] 2021	RCT,SC	Taiwan	87	Commencing at 5–8 cmH_2O, an incremental PEEP trial advanced in 2 cmH_2O steps for 2 min until a plateau pressure of 35 cmH2O or unstable blood pressure. Subsequently, a decremental trial, also in 2 cmH2O steps, returned to the initial range. EIT data analysis, using customized software, calculated regional compliance, cumulated collapse, and overdistension percentages. The chosen PEEP for the EIT group was determined by the intercept point of cumulated collapse and overdistension percentages, aiming for a balance between collapsed and overdistended lung. If the intercept occurred between two PEEP steps, the selected PEEP aligned with the step towards the lowest global inhomogeneity index, reflecting overall ventilation homogeneity	In moderate to severe ARDS, EIT-guided PEEP titration was associated with better driving pressure and increased survival rates than the pressure-volume (PV) curve method

Table 1 (continued)

Sl. no	Study, Year	Nature	Country of origin	Population size	EIT protocol / interventions	Conclusion
4	Jimenez et al. [32] 2023	RCT,SC	USA	12	PEEP was gradually reduced by 2 cmH_2O every 5–10 min until a 10% decline in delta end-expiratory lung impedance in dorsal regions was identified by EIT, reaching 5 cmH_2O PEEP or encountering hemodynamic instability/hypoxemia. The final PEEP level was determined based on the intersection point between lower overdistension and collapse percentages	Adjusting positive end-expiratory pressure (PEEP) based on electrical impedance tomography (EIT) in moderate to severe ARDS had a reduction in mechanical power, primarily attributed to a reduction in elastic-dynamic power
5	Liu et al. [33] 2022	Prospective, cohort,SC	China	54	PEEP was incrementally adjusted from 5 to 20 cm H_2O every 30 min; considering hemodynamic factors in COPD patients, PEEP was capped at 16 cm H_2O. Parameters were assessed every 30 min, and the best PEEP was identified using the global inhomogeneity index for the entire lung was calculated. The PEEP associated with the lowest GI index value, representing the nadir of the curve, was identified as the optimal PEEP determined by EIT based on the GI index. EIT assessed ventilation distribution, and the Center of Ventilation (CoV) calculated ventilation homogeneity in Four horizontal parallel regions of interest along the ventral-dorsal axis	The requirement of PEEP in COPD-associated ARDS with EIT guidance was lower than that of the ARDSnet protocol, resulting in improved ventilation, mechanical power, cardiac index, oxygen delivery, and fewer hemodynamic issues
6	Somhorst et al. [34] 2012	Retrospective cohort, SC	Netherland	150	During a decremental PEEP trial, an EIT belt with surface electrodes was positioned at the 4th–5th intercostal parasternal space for continuous regional ventilation monitoring. PEEP was adjusted using EIT's titration tool, starting from baseline as per the high PEEP-FiO2 table, reaching 10 cmH2O above baseline or a minimum of 24 cmH2O. Driving pressure was unchanged, and PEEP was maintained for at least one minute. The reduction occurred in 2 cmH2O steps every 30 s PEEP. PEEP was reduced in steps until evident collapse, confirming the lowest sustainable PEEP without hypotension or desaturation. The final PEEP was set at the intersection point of curves, indicating relative alveolar overdistention and collapse	PEEP trial guided by EIT led to a significant PEEP adjustment in 63% of patients, indicating the importance of that individualized PEEP settings

guided PEEP optimization group. The protocol for EIT application also varied across the studies (Table 1).

None of them had any serious concerns about the risk of bias (Fig. 2).

3.2 Meta-analysis

3.2.1 Mortality

The mortality risk was lower with EIT-guided PEEP optimization in five studies with 298 patients [Risk ratio (RR) = 0.68; 95% CI: 0.49 to 0.95; $I^2 = 0\%$; $p = 0.02$). (Fig. 3a).

Trial sequential analysis: The required information size was estimated at 276 for a power of 95% based on the 50% relative risk reduction for mortality. The cumulative Z-score crossed the alpha spending boundary and did not dip below the inner wedge of futility, indicating a significant effect size has been achieved. (Supplementary Fig. 1).

3.2.2 Dynamic compliance

A meta-analysis of seven studies involving 515 patients found better dynamic compliance with EIT-guided PEEP optimization by an average of 3.46 ml/cm H_2O (95% CI: 1.59 to 5.34; $I^2 = 0\%$; $p < 0.003$) compared to the conventional methods. (Fig. 3b).

Trial sequential analysis: The required information size was estimated at 510 for a power of 95% based on the 10% improved dynamic compliance. The cumulative Z-score crossed the alpha spending boundary and did not dip below the inner wedge of futility, indicating a significant effect size has been achieved. (Supplementary Fig. 2).

3.2.3 Oxygenation

There is no substantial improvement in PaO_2/ FiO_2 with EIT-guided PEEP optimization compared to conventional methods, [Mean Difference (MD) = 6.5; 95%CI -13.86 to 26.76; $I^2 = 74\%$; $p = 0.53$] found in 515 patients of seven studies (Fig. 4a).

Trial sequential analysis: The required information size was estimated at 879 for a power of 95% based on the observed change of mean PaO_2/ FiO_2 by at least 10. (Supplementary Fig. 3).

3.2.4 Successful weaning

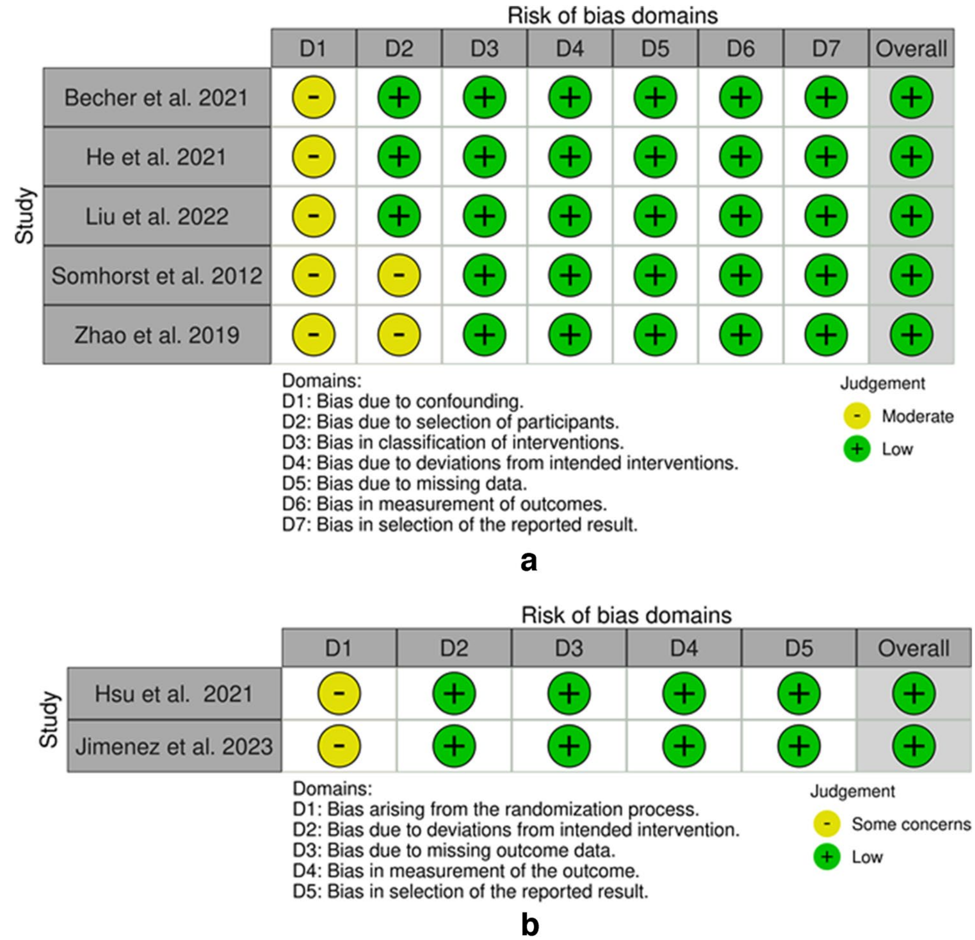
There is no substantial improvement in successful weaning incidence with EIT-guided PEEP optimization than conventional methods, [Odds Ratio (OR) = 6.5; 95%CI 0.07 to 3.01 to, $I^2 = 51\%$; $p = 0.32$] found in 259 patients of three studies (Fig. 4b).

Table 1 (continued)

Sl. no	Study, Year	Nature	Country of origin	Population size	EIT protocol / interventions	Conclusion
7	Zhao et al. [35] 2019	Prospective cohort, SC	Taiwan	55	EIT electrode belt, with 16 electrodes placed around the thorax, recorded continuous images at 20 Hz. Ventilator data was synchronized with EIT, and PEEP titration was performed by starting at 5–8 cmH2O, progressing in 2 cmH_2O increments until the plateau pressure reached 35 cmH2O or any haemodynamic instability. Subsequently, a stepwise decrease in PEEP was conducted with 2 cmH_2O/ steps for 2 min. EIT data analysis, using customized software, calculated regional compliance, collapse, and overdistension percentages to determine the optimal PEEP level	EIT-guided PEEP titration in severe ARDS patients was safe, and showed improved outcomes compared to pressure–volume curves

SC: Single centre; *Paw*: peak airway pressure; *PEEP*: positive end-expiratory pressure; *Crs*: Regional compliance; *EIT*: Electrical impedance tomography

Fig. 2 **a** ROBINS-I assessment for the included non-randomized cohort studies, **b** ROB-2 assessment for the included randomized controlled studies



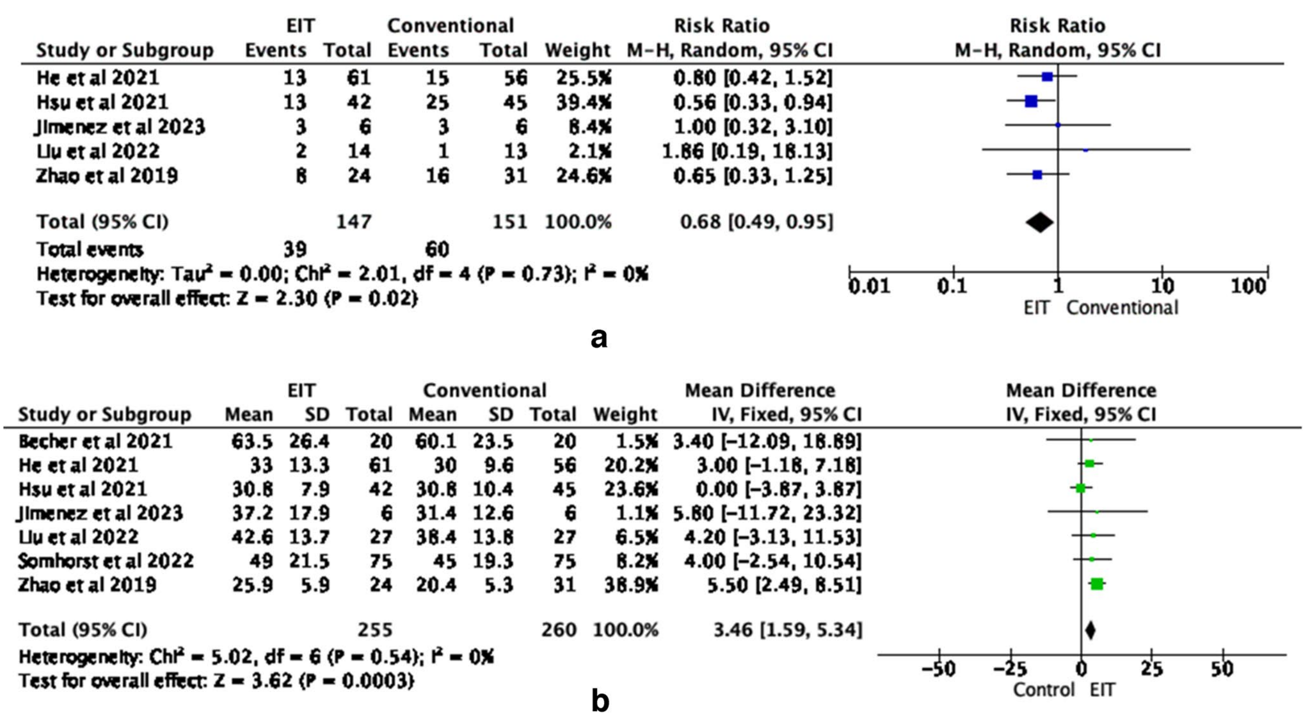


Fig. 3 The impact of EIT-guided individualized PEEP titration on overall mortality (**a**), and dynamic compliance (**b**) in ARDS patients

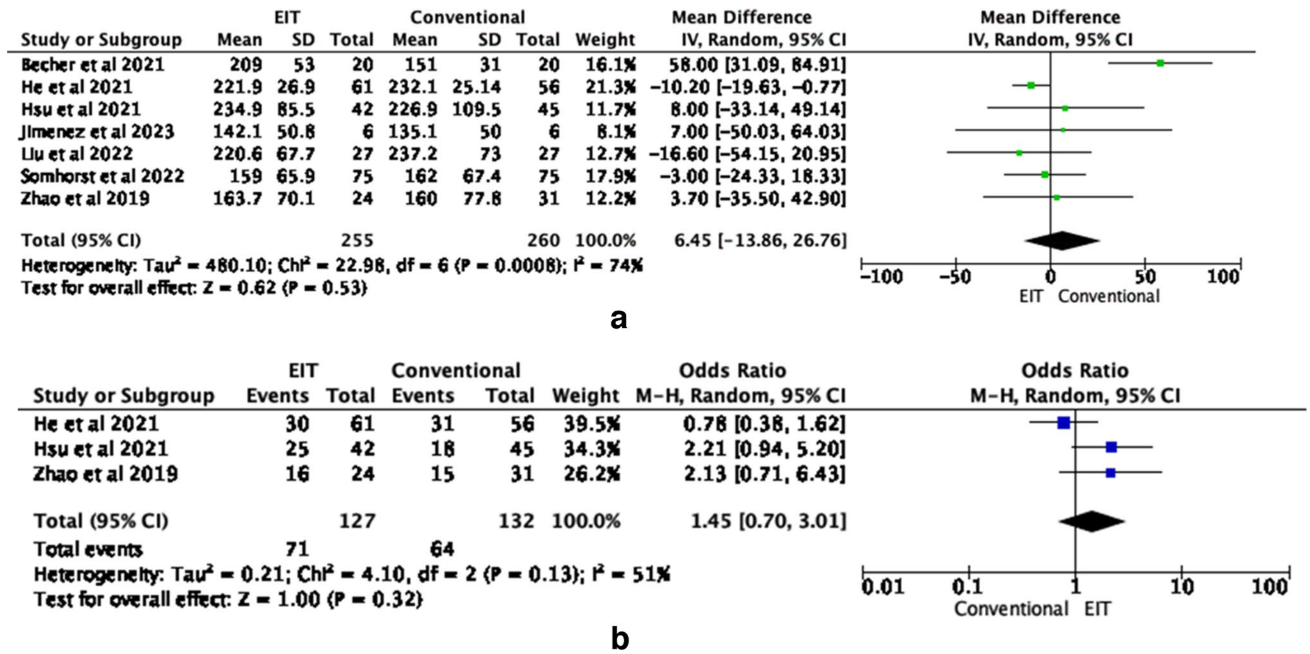


Fig. 4 The impact of EIT-guided individualized PEEP titration on PaO_2/FiO_2 ratio (**a**), and successful weaning (**b**)

3.2.5 Driving Pressure

No significant difference in the requirement of driving pressure was found in the groups of 515 patients from seven studies. [MD = -0.3; 95%CI -0.99 to 0.37; $I^2 = 82\%$; $p = 0.38$] (Supplementary Fig. 4a).

3.2.6 Optimized PEEP

No significant difference in the requirement of PEEP was found in the groups across 461 patients in six studies. [MD = 0.95; 95%CI -0.40 to 2.29; $I^2 = 96\%$] (Supplementary Fig. 4b).

3.3 Quality of evidence

The evidence regarding the utility of EIT-guided PEEP titration in ARDS patients in terms of mortality and dynamic compliance is of low quality owing to considerable indirectness, and PaO_2/FiO_2, successful weaning, driving pressure, optimized PEEP, is of very low quality additionally due to inconsistency, imprecision. (Table 2).

3.4 Publication bias

An assessment of publication bias regarding dynamic compliance suggests its unlikelihood, as indicated by the absence of Funnel plot asymmetry through the Egger's Regression and Begg & Mazumdar Rank Correlation ($p = 0.98$ and $p = 0.56$, respectively). (Supplementary Fig. 5).

4 Discussion

This systematic review found reduced risk of mortality, better dynamic compliance with no significant improvement in oxygenation and successful weaning with EIT-guide PEEP titration in ARDS patients than conventional methods.

A recent systematic review of 202 participants found a higher PaO_2/FiO_2 ratio [standardized mean difference (SMD) = 0.636; 95% CI 0.364 to 0.908.] with no significant change in compliance compared to alternative PEEP titration strategies [SMD = -0.085; 95% CI -0.342 to 0.172.]. However, it needed to assess the generalizability of the findings and the adequate size of the population for identifying the effect with optimum power calculation [36].

An impressive 94% positive predictive value for better oxygenation during prone ventilation was reported using electrical impedance tomography to monitor collapse in dependent lung areas [37].

Another multicentric study on COVID-19 patients reported that median EIT-based PEEP varied across groups: 10, 13.5, and 15.5 cm H_2O for low, medium, and high recruit ability, respectively ($P < 0.05$) [38].

Table 2 GRADE evidence profile of EIT-guided PEEP titration

Out come	No. of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence (Grade)	Relative effect
	Total no	Intervention	Control							
Mortality	298	147	151	No	No	Yes	No	None	Low ⊕⊕⊝⊝	OR = 0.56 (95%CI:0.33 to 0.93)
Dynamic Compliance	515	255	260	No	No	Yes	No	None	Low ⊕⊕⊝⊝	MD = 3.46 (95%CI: 1.59 to 3.34)
PaO_2/FiO_2	515	255	260	No	Yes	Yes	Yes	None	Very low ⊕⊝⊝⊝	MD = 6.45 (95%CI: -13.8 to 26.7)
Successful weaning	259	127	132	No	Yes	Yes	Yes	None	Very low ⊕⊝⊝⊝	OR = 1.45 (95% CI: 0.7 to 3.01)
Driving pressure	515	255	260	No	Yes	Yes	Yes	None	Very low ⊕⊝⊝⊝	MD = -0.31 (95% CI:-0.99 to 0.37)
PEEP optimization	461	228	233	No	Yes	Yes	Yes	None	Very low ⊕⊝⊝⊝	MD = 0.95 (95% CI:-0.40 to 2.29)

CI: confidence interval; *GRADE*: Grading of Recommendations Assessment, Development, and Evaluation; *MD*: Mean difference; *OR*: Odds ratio; *PEEP*: Positive end-expiratory pressure

One of the reasons behind the conflicting outcome regarding oxygenation in our study is multifactorial. Primarily, the disease severity of included patients varied from mild to severe ARDS along with COPD and COVID-19. The use of the prone position was also not uniform and standardized. This itself can influence a wide variety of primary outcomes. ARDS is an acute hypoxemic state caused by the sudden development of diffuse injury to the terminal respiratory units with exudative pulmonary oedema. The application of PEEP to recruit the collapsed alveoli is crucial. However, determining the optimal PEEP striking a balance between preventing over-distension and de-recruitment while avoiding hemodynamic compromise remains a complex task.

Thirdly, the duration of EIT intervention was also variable, ranging from a few hours to two days. Frequent EIT-guided PEEP titration was not done, unlike ARDS net tables, where PEEP was variable according to the FiO_2. Moreover, application EIT-guided PEEP titration was based on finding the intercept point between the overall collapse and distension curves, and the selection of this point was subjective, which can be a source of PEEP discrepancy. At the same time, the control groups included either the ARDS net tables or pressure-volume loops (by calculating the maximal hysteresis/setting the PEEP above the lower inflexion point).

Another critical issue is the difference in the operator experience. EIT is a complex technique compared to other techniques for setting optimal PEEP. Secondly, the position of the EIT belt affects its measurement. The impedance changes are measured in a lens-shaped slice of the thorax. As a result, it cannot visualize the ventilation distribution of the whole lung, which is a major drawback. The PEEP level with the best regional compliance differs for cranial and caudal lung regions in mechanically ventilated patients. While performing a decremental PEEP trial to find the optimal PEEP in the caudal lung regions, the diaphragm can enter the measurement field, producing artefacts and causing erroneous results [39].

Various methods are available for titrating PEEP through EIT, which include the overexpansion and collapse (OD/CL) method, end-expiratory lung impedance (EELI) method, GI index method and regional ventilation delay (RVD) method [33]. However, a consensus on the best EIT-derived parameter has yet been reached.

Zhao et al. demonstrated that the global inhomogeneity (GI) index positively correlated with PEEP adjustment with global dynamic compliance and intra-tidal compliance method [20].

EIT reflects regional changes better, i.e. recruitment of dependent and non-dependent lung areas can be visualized separately, compared to the latter techniques, which do not provide any information on ventilation distribution. For the same reason, overall lung compliance is expected to increase, corresponding to the decline in driving pressures.

Heines et al. concluded that the difference in EIT-based PEEP and clinician set PEEP was clinically relevant in 28% of the patients, whereas the EIT-based PEEP disagreed with the PEEP settings according to the ARDS network [39].

PEEP plays an integral part in the acute phase of ARDS by preventing the collapse of recruited airways, thereby improving oxygenation. It minimizes ventilator-associated lung injury (VALI) in the long term by preventing repeated alveolar collapse/distension cycle (atelectotrauma). As a result of this effect, optimal PEEP can contribute to weaning success by minimizing VALI. The studies included in our review did not demonstrate weaning success by EIT-guided PEEP titration. This can be explained by these studies being underpowered to demonstrate a significant difference.

5 Strengths & limitation

The present study comprises the most considerable population reported so far with the necessary minimum population required size for identifying the effect.

Diverse populations and protocols contribute to significant heterogeneity; some of the studies have retrospective control and are prone to selection bias. Moreover, the minimum population required size was not achieved to identify a relevant change in oxygenation and successful weaning.

6 Conclusion

Electrical impedance tomography-guided individualized lung protective ventilation strategies are required to improve the overall outcome, with further requirements of prospective multicenter randomized control trials to demonstrate its utility.

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Author contributions Dr Soumya Sarkar (SS): Search strategy, Study selection, Data extraction, Data synthesis, Risk of bias assessment, quality of the evidence assessment, Manuscript drafting and editing. Dr Bharat Yalla (BY): Search strategy, Study selection, Data extraction. Dr Puneet Khanna (PK): Conceptualization, study selection, Risk of bias assessment, quality of the evidence assessment and editing. Dr Madhurjya Baishya (MB): Risk of bias assessment, quality of the evidence assessment.

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Data availability Data openly available in a public repository & derived data is available on request.

Compliance with Ethical Standards

Competing interests The authors declare no competing interests.

Institutional ethical committee approval Not Applicable.

Prior presentations Nil.

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