



Surgical and Bronchoscopic Lung Volume Reduction for Severe Emphysema: A Systematic Review and Network Meta-analysis

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Abstract

Background Along with lung volume reduction surgery (LVRS), bronchoscopic lung volume reduction is a treatment option for end-stage emphysema. However, comparisons among interventions remain insufficient.

Methods We searched on PubMed, CENTRAL, Embase, and Web of Science. We included randomized controlled trials with outcomes measuring mid-term mortality within 6 months, changes in forced expiratory volume in one second (FEV₁), St. George's Respiratory Questionnaire (SGRQ), six-minute walk distance (6MWD) from baseline, adverse event related to procedures, and long-term mortality within 5 years. Bayesian network meta-analysis was performed. The certainty was assessed by CINeMA.

Results Twenty-five randomized controlled trials involving 4,283 patients were included, identifying seven types of procedures and standard of care. Mid-term mortality increased in LVRS and endobronchial valve (EBV) (LVRS, risk ratio [RR] 3.26, 95% CrI 1.98–6.21, low certainty; EBV, RR 2.06 95% CrI 1.07–4.36, moderate certainty). LVRS showed the largest improvements: change in FEV₁ (187.2 mL, 95% CrI 166.4–209.6), 6MWD (42.2 m, 95% CrI 33.2–50.5), and SGRQ (–13.29 points, 95% CrI –27.25–0.75). Among bronchoscopic procedures, high efficacy was noted in EBV and endobronchial coil (EBC) for FEV₁ changes (EBV, 111.8 mL, 95% CrI 92.2–136.2; EBC, 74.1 mL, 95% CrI 47.6–101.7). Pneumothorax increased in these two procedures (EBV, RR 12.75, 95% CrI 5.52–35.48; EBC, RR 4.95, 95% CrI 1.12–40.90).

Conclusion LVRS offers high efficacies but is accompanied by increased mid-term mortality. EBV and EBC also showed effectiveness; however, they increased pneumothorax, and EBV slightly increased mortality. For accurate assessment, long-term survival data of BLVR are needed.

Keywords Emphysema · Chronic obstructive pulmonary disease · Bronchoscopy · Surgery · Meta-analysis

Abbreviations

6MWD	Six-minute walk distance	MCMC	Markov Chain Monte Carlo
BLVR	Bronchoscopic lung volume reduction	NMA	Network meta-analysis
CINeMA	Confidence in network meta-analysis	RCT	Randomized controlled trial
COPD	Chronic obstructive pulmonary disease	RoB	Risk of bias
CrI	Credible interval	RR	Risk ratio
EBC	Endobronchial coil	RV	Residual volume
EBV	Endobronchial valve	SAB	Stent for airway bypass
ELS	Endoscopic lung sealant	SGRQ	St. George's respiratory questionnaire
FEV ₁	Forced expiratory volume in 1 s	SoC	Standard of care
IBV	Intrabronchial valve	SUCRA	Surface under the cumulative ranking curve
LVRS	Lung volume reduction surgery	TVA	Thermal vapor ablation
MD	Mean difference		
MCID	Minimum clinically important difference		

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Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of death worldwide, results in more than three million deaths annually [1, 2]. Chronic exposure to irritants, including tobacco smoke and pollution, triggers inflammation that causes irreversible damage to the lung structure. Emphysema, characterized by the enlargement of alveoli, often leads to air trapping, compromised oxygen exchange, and exertional respiratory distress [3]. Inhaled long-acting muscarinic antagonists, long-acting beta agonists, and corticosteroids are key medical treatment options for this disease, controlling partially reversible bronchial obstruction and inflammation. Additionally, smoking cessation, rehabilitation programs, and vaccinations are frequently offered to patients with advanced COPD [1, 3, 4]. However, these therapies are not always sufficient to manage advanced COPD accompanied by severe emphysematous changes, because none of these therapies directly modify emphysematous changes of the alveoli.

Mechanical lung volume reduction (LVR) is one of the treatment strategies for patients with end-stage emphysema and improves dyspnea by reducing hyperinflation and residual volume (RV). Lung volume reduction surgery (LVRS) was established in the 1990s [5]. The National Emphysema Treatment Trial (NETT), the largest randomized controlled trial (RCT) of LVRS conducted in 2003 with 1218 patients, demonstrated improvements in exercise capacity but did not contribute to improved survival outcomes [6]. NETT highlighted the importance of patient selection based on emphysema type and baseline exercise capacity, and it prompted the development of safer surgical techniques and bronchoscopic lung volume reduction procedures. Since then, various bronchoscopic procedures, such as endobronchial valves (EBV) [7], intrabronchial valves (IBV) [8], endobronchial coils (EBC) [9], bronchoscopic thermal vapor ablation (TVA) [10], stents for airway bypass (SAB) [11], and emphysematous lung sealant (ELS) [12], have been developed. However, in most studies, patients were randomly allocated into either the novel intervention or medical treatment arms; making direct comparisons of these newly developed treatments rare. The first RCT was conducted comparing EBV directly with LVRS in 2023 [13], but it found no significant differences in improving gas trapping and relieving dyspnea symptoms between two interventions.

Network meta-analysis (NMA) is the preferred research approach for ranking several volume reduction procedures and providing clinically useful data. To our knowledge, two frequentist network meta-analyses evaluating bronchoscopic lung volume reduction procedures, each including

10 and 13 trials, presented partially inconsistent results with each other in 2020 [14, 15]. Subsequently, the number of RCTs on this topic more than double by 2023. The current systematic review and Bayesian NMA were designed to compare and rank the efficacy and safety of lung volume reduction procedures, including LVRS, for severe emphysematous COPD.

Methods

Overview

This research was conducted based on the analysis of previously published data and did not involve the use of independent patient data. As a result, it did not necessitate approval from the Institutional Review Board or Ethics Committee of any institution.

This study employs a network meta-analysis (NMA) to account for the interdependency of effect estimates in multi-arm RCTs, following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for NMA [16]. The protocol was registered on PROSPERO on September 19, 2023 (CRD42023462007).

Study Search

First, the candidate article list was generated from four electronic databases, PubMed, Web of Science, Cochrane CENTRAL, and EMBASE. The search period encompassed all available years up to September 10th, 2023. The search formulas are presented elsewhere (S-Table 1). Additionally, the GOLD document 2023 [17] and published review articles shown in the supplementary file (S-Table 2) were manually reviewed.

Two review authors (N.H. and S.Y.) initially selected potentially eligible studies from the list based on the titles and abstracts. The final decision was then made through a full-text review. Any discrepancies between the review authors were resolved through discussion.

Study Design and Publication Type

Only English language research articles presenting data from RCTs were included. Consequently, non-English articles, observational studies, and study protocols were excluded. A conference abstract was accepted when sufficient data were available. Secondary analysis of data from RCTs was accepted, even if the analysis was designed in a post hoc manner.

Patients

The primary focus of this systematic review was on patients with severe emphysematous COPD. The term “emphysema” refers to pathologic changes of the lung, while the clinical diagnosis is referred to as COPD. However, inclusion criteria strictly based on the COPD diagnosis appeared to exclude historically pivotal RCTs that enrolled patients regardless of their COPD diagnosis. Given the substantial overlap between emphysema and COPD, our study does not require patients to have an explicit COPD diagnosis as long as their clinical characteristics align with COPD. For instance, studies with a mean or median forced expiratory volume in 1 s (FEV₁)/forced vital capacity less than 70% were included.

Treatments

We compared volume reduction procedures, including LVRS, EBV, IBV, EBC, TVA, SAB, and ELS. Both unilateral and bilateral surgeries were categorized within the surgery arm. Simultaneous cancer resection during LVRS was excluded as it deviates from the typical LVRS procedure. Bullectomy and lung transplantation were excluded due to their patient eligibility differing from that for LVRS. Treatments other than volume reduction procedures and bronchoscopic interventions were collectively considered as standard of care (SoC), which includes inhaled medications, smoking cessation, rehabilitation programs, and vaccination. Sham control was also classified as SoC since it does not provide substantial therapeutic benefits. Studies that offered rehabilitation for one arm were excluded as this study design might underestimate the treatment effect of volume reduction procedures.

Targeted nerve denervation, which modifies vagus nerve branches and relaxes the smooth muscles of the airways, was excluded from this study. Nitrogen cryospray and rheoplasty, bronchoscopic interventions for the chronic bronchitis phenotype of COPD (non-emphysematous), were also excluded from this study.

Outcomes

All primary and secondary outcomes were assessed for a mid-term follow-up period except for long-term survival (5-year mortality). The preferred timing for collecting outcome data is 6 months after the intervention; however, in a case where data at 6 months were missing, a substitute using the data with the longest observation between 3 and 6 months was allowed. The number of patients

experiencing an event was tabulated as cumulative at 6 months after the procedure.

Primary outcomes included pulmonary function (mean difference [MD] in FEV₁ change from baseline, in mL), quality of life (MD in St. George Respiratory Questionnaire [SGRQ] change from baseline, in points, SGRQ range 0[best]–100[worst]), functional exercise capacity (MD in 6 min walking distance [6MWD] change from baseline, in meters), and mortality (risk ratio [RR] for all-cause death over 6 months). A COPD-specific SGRQ was not utilized in our study.

Secondary outcomes included serious adverse events (one or more of SAE, RR), pneumothorax (one or more of RR), exacerbation (one or more of RR), and long-term mortality (RR for all-cause death over 5 years). Variations in the definition of exacerbation such as “acute exacerbation” were accepted.

For continuous variables, the Minimum Clinically Important Difference (MCID) was set according to prior studies as a 100-mL change in FEV₁ [18], a 30-m change in 6MWD [19], and a 4-point change in SGRQ [20]. For binary variables, the MCID was defined according to the GRADE handbook as an RR of less than 0.8 or greater than 1.25 [21].

Data Extraction

Two review authors (N.H. and S.Y.) extracted data regarding study characteristics, such as author name, publication year, age of patients, and sex ratio. Outcome data described in the “Outcomes” section and items for RoB and CINeMA were also transcribed.

Data were extracted from a supplementary file and the registered protocol as long as the main page of the original article. The authors performed numerical calculations as needed. For example, the number of death cases might be calculated from the number of death cases and mortality. A full analysis set was preferred for adverse event analysis. Normal distribution was supposed for continuous variables and standard deviation was estimated according to the Cochrane method [22]. When the two authors could not agree on the extracted data, the third review author (R.I.) mediated.

For a crossover trial, the data after the crossover were ignored to avoid duplicate use of the same patients [22].

Data Synthesis

A Bayesian NMA, grounded in a random effects model, serves as the backbone of our meta-analysis. We applied weakly informative prior distributions based on various comparisons and outcome types [23, 24] (S-Methods 1). Continuous variables underwent analysis using MD and a 95% credible interval (CrI). Binary variables related to

events, such as the incidence of deaths and adverse events (AEs), underwent analysis using the RR and a 95% CrI. All analyses engage JAGS (Just Another Gibbs Sampler, Ver. 4.3.1) for executing Markov Chain Monte Carlo (MCMC) simulations, leveraging the R packages ‘Rjags’ and ‘Gemtc’ on the R ver. 4.2.2.

We confirmed the convergence of MCMC through Gelman and Rubin’s MCMC Convergence Diagnostic Test. A multivariate potential scale reduction factor below 1.05 serves as the criterion for establishing MCMC convergence. ANOHE analysis in the Gemtc package was used to compare direct and indirect evidence.

Calculation of the surface under the cumulative ranking curve (SUCRA) in primary outcomes serves as a ranking indicator, and we computed rank probabilities for every treatment group.

Regression analysis using coefficients of determination with reduction of RV were conducted for all outcomes except mid-term and long-term mortality.

Subgroup Analysis

For the four primary outcomes, we conducted subgroup analysis using studies based on collateral ventilation (CV) and type of emphysema. CV accepted assessment by computed tomography and Chartis. Heterogeneous emphysema was considered when > 90% of patients in the trial had it.

Sensitivity Analysis

Sensitivity analyses through meta-regression were conducted for three variances potentially influencing network estimates in primary outcomes: (1) RoB, where trials with high RoB might overestimate efficacy; (2) Small-study effect, where trials with fewer participants (< 100) might overestimate efficacy; and (3) Publication year, available medications, and vaccinations for COPD have increased and the treatment effects of SoC might be changed. The treatment effect of the intervention might be changed as the operator becomes more proficient.

Quality Assessment

We evaluated the reliability of network meta-analysis results using the confidence in network meta-analysis (CINeMA) framework [25], assessing credibility across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Bias within studies was assessed using Tool for Assessing Risk of Bias in Randomized Trials (RoB) [26]. Each domain was rated as having no, some, or major concerns. These evaluations led to four confidence levels for each intervention effect; very low, low, moderate, or high. Judgments were independently made by

two authors (N.H. and S.Y.), with disagreements resolved through discussion or consultation with a third author (R.I.).

Results

Search Results and Summary of Included Studies

A total of 1525 records were screened, culminating in the inclusion of 25 RCTs from 31 records (Fig. 1). The total randomized participant count was 4283, with 2462 assigned to intervention groups and 1821 assigned to SoC groups. The interventions comprised 7 trials evaluating LVRS, 8 trials examining EBV, 4 trials investigating IBV and EBC, and 1 trial each for SAB, ELS, and TVA. The median age of participants was 64 years (IQR 63–65) and 58.9% were male (IQR 51.1–62.0%). Regarding the evaluation of CV, 9 trials assessed it explicitly, while 16 trials did not evaluate it. Regarding the types of emphysema included, 7 trials included both homogeneous and heterogeneous emphysema, whereas 12 trials focused exclusively on heterogeneous emphysema. Geographically, 9 trials were conducted in North America, 15 trials in Europe, and 1 trial in Asia. A network plot across 25 RCTs is presented in Fig. 2, with network plots for each outcome detailed in S-Fig. 1. The basic characteristics and resources are shown in Table 1, S-Tables 3, and 4.

Primary Outcomes

MCMC convergence was confirmed for all outcomes and all comparisons in the main analysis (S-Table 5). Mid-term mortality was assessed in 25 trials involving 4,207 patients (Fig. 3). In the SoC group, the pooled mortality rate was 2.1% (37 deaths out of 1,798 patients).

For changes in FEV₁ from baseline, data from 18 trials and 2,906 patients were analyzed. In the SoC group, the weighted average change in FEV₁ was – 10.3 mL.

The change in 6MWD from baseline was analyzed involving 17 trials and 2475 patients. In the SoC group, and the weighted average change in 6MWD was – 14.5 m.

The changes in SGRQ from baseline were assessed across 14 trials with 2498 patients. In the SoC group, and the weighted average change in SGRQ was + 0.9 points.

Across all primary outcomes except mid-term mortality, LVRS showed the highest probability of being ranked as the most effective treatment (S-Table 6).

Secondary Outcomes

In the analysis of exacerbations, data from 17 trials involving 3,317 patients were evaluated. The pooled incidence rate in the SoC group was 12.6% (174/1381 patients) (Fig. 4).

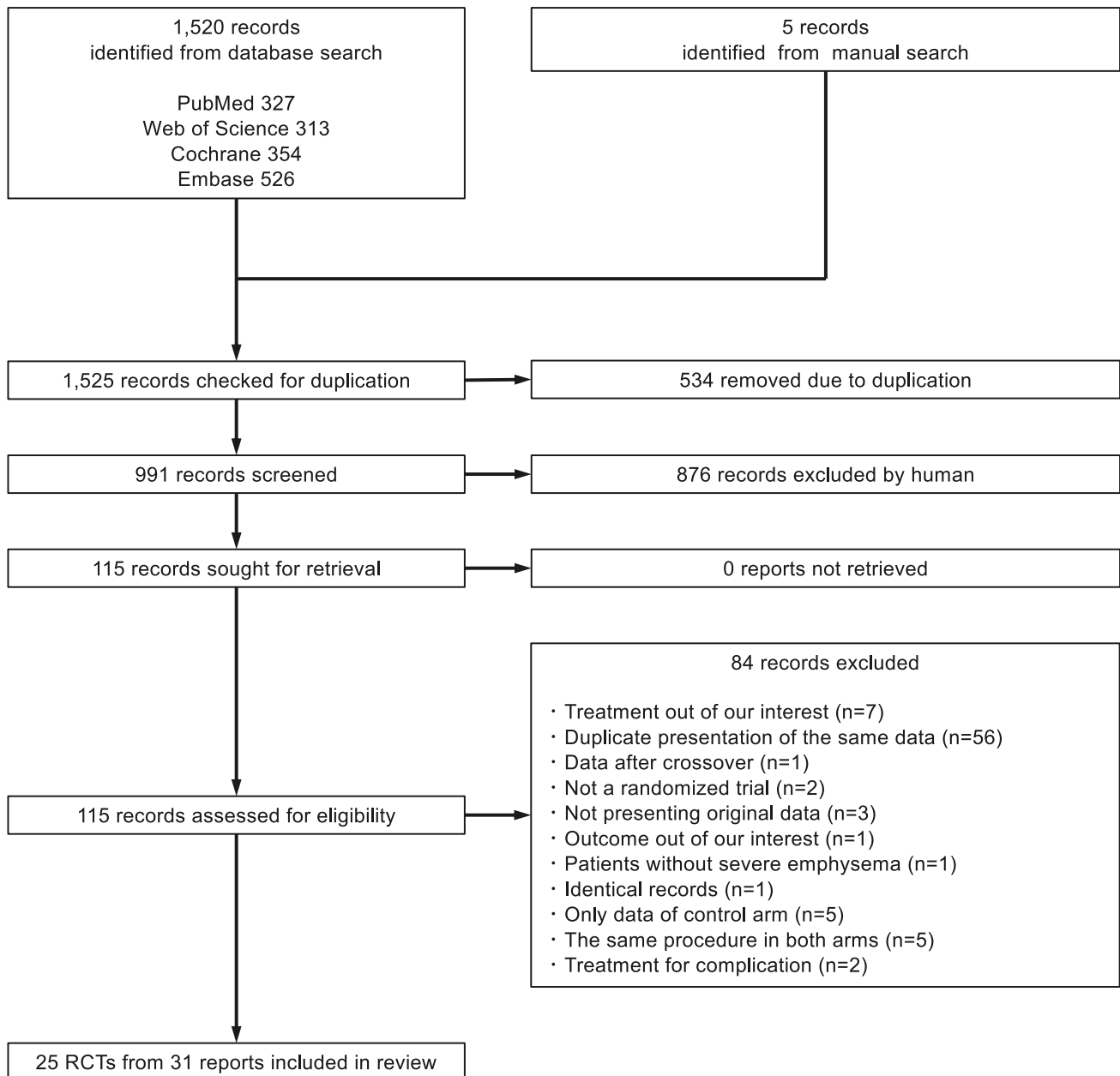


Fig. 1 Flowchart of study selection

For pneumothorax, 16 trials with 2068 patients were analyzed. The pooled incidence rate in the SoC group was 0.3% (2/791 patients).

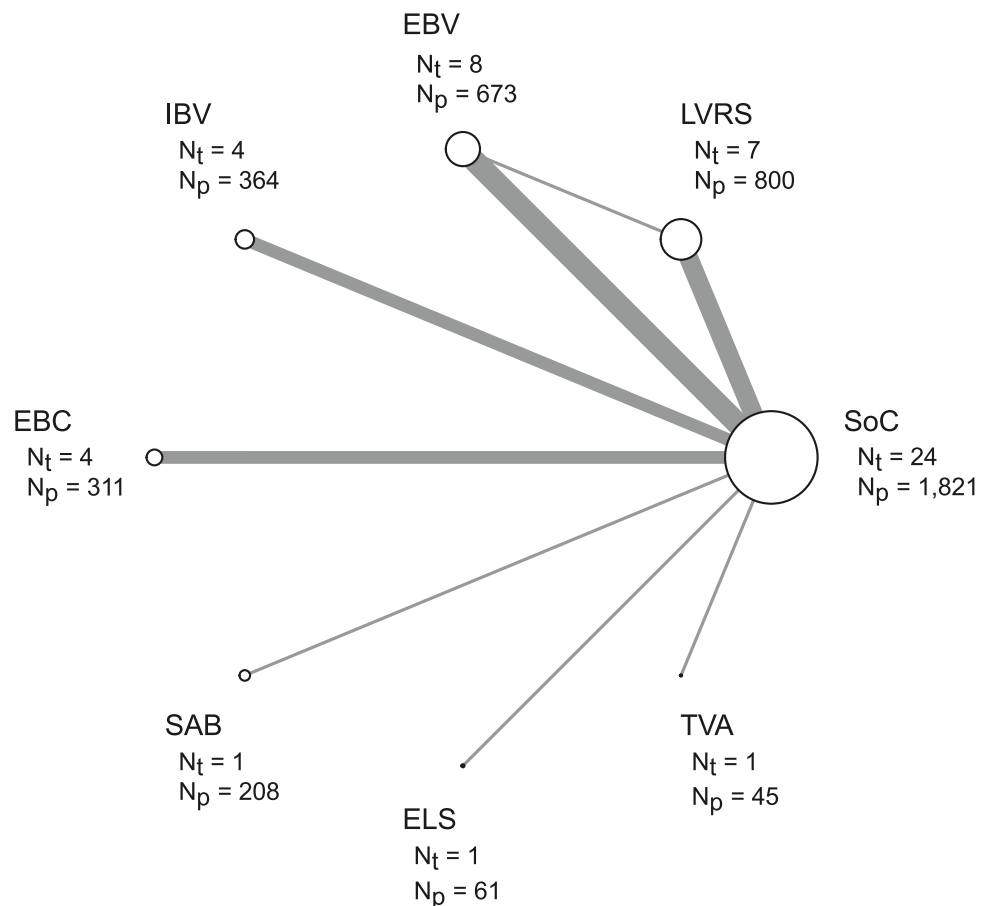
In the assessment of serious adverse events, data from 12 trials involving 1689 patients were analyzed. The pooled incidence rate in the SoC group was 8.6% (55/636 patients).

In the long-term mortality analysis, data from 3 trials involving 1,318 patients treated with LVRS were evaluated. The pooled incidence rate in the SoC group was 50.9% (336/660 patients).

Regression Analysis

The reduction in RV showed a correlation with the three efficacy outcomes (FEV₁, $R^2 = 0.587$; 6MWD, $R^2 = 0.614$; SGRQ, $R^2 = 0.666$) and the incidence of pneumothorax ($R^2 = 0.5480$) and serious adverse event ($R^2 = 0.6494$); however, it did not contribute to exacerbations ($R^2 = 0.0110$) (Fig. 5).

Fig. 2 Network plot across the trials. A total of 4207 patients from 25 studies were randomized. Solid lines indicate direct comparisons. The size of the nodes reflects the number of patients assigned to each group, and the thickness of the edges reflects the number of direct comparisons. N_t , number of trials, N_p , number of patients assigned to the intervention groups



Subgroup Analysis

The therapeutic effects of EBV and IBV varied depending on the presence of collateral ventilation and the type of emphysema in patients. In non-collateral ventilation and heterogeneous emphysema, IBV demonstrated nearly equivalent treatment efficacy compared to EBV (Table 2). Furthermore, in all subgroup analyses, the lower limit of the 95% credible interval for the mortality rate of LVRS was below 1.0.

Quality Assessment

The assessment of the six domains of CINeMA is presented in S-Tables 7–10 and S-Fig. 2. For all intervention-outcome combinations, the confidence rating was ‘Low,’ ‘Moderate,’ or ‘High’ (Figs. 3, 4, and S-Table 11).

Sensitivity Analysis

Regarding the impact of RoB, changes in FEV_1 were overestimated in IBV. For changes in 6MWD, EBC and IBV showed an overestimation. Changes in SGRQ were underestimated in EBC and overestimated in IBV (S-Table 12). Concerning the small-study effect, changes in 6MWD were

overestimated for EBC and EBV (S-Table 13). About the publication year, changes in FEV_1 were overestimated in EBV and IBV. Changes in 6MWD were also overestimated in IBV. For SGRQ changes, there was an underestimation in EBC and an overestimation in IBV (S-Table 14). Through the three sensitivity analyses, no covariates were identified that significantly affected the network estimates of mid-term mortality (S-Tables 12–14).

Discussion

This study compared the efficacy and safety of mechanical lung volume reduction techniques in patients with severe emphysema. Aggregate data from 25 RCTs involving 4283 patients were included, identifying seven interventions beyond SoC and evaluating mid-term outcomes within 6 months. Among the seven interventions, EBC, EBV, and LVRS demonstrated efficacy compared to SoC. However, these interventions were also associated with several safety concerns, including an increased risk of mid-term mortality.

With a pooled mortality rate of 2.1% for SoC, LVRS shows an absolute risk increase in mid-term mortality of 5.2% (95% CrI 2.1–10.9%). In contrast, LVRS has shown no

Table 1 Characteristics of primary trials

Study name registration	Country ^a	Arm1	Arm2	Severity threshold (FEV ₁ %predicted)	Collateral ventilation	Homogeneous emphysema (%)	N Arm1	N Arm2	Men (%)	Age ^b	Baseline FEV ₁ ^b predicted, %	Baseline 6MWD ^b , m	Baseline SGRQ ^b , point	Time points for data extraction
Brompton [27]	UK	LVRs	SoC	Severe emphysema (FEV ₁ > 0.5L ^c)	Allowed	46	24	24	72.9	61	0.75 L ^c	N/A	N/A	6 months, 5 years ^d
Goldstein (2003) [28]	Canada	LVRs	SoC	< 40%	Allowed	0	28	27	60.0	65	32	380	N/A	6 months
NETT [6]	USA	LVRs	SoC	20–45%	Allowed	46	608	610	61.2	67	27	371	53.1	4 months, 5 years ^d
VOLREM [29]	Sweden	LVRs	SoC	< = 35%	Allowed	N/S	53	53	42.5	62	26	N/A	58.9	6 months
CLVRS [30]	Canada	LVRs	SoC	< = 40%	Allowed	N/S	32	30	66.1	64	24	330	N/A	3 months, 5 years ^d
Clarenbach (2015) [31]	Switzerland	LVRs	SoC	< 35%	Allowed	N/S	14	13	63.0	63	27	307	N/A	3 months
CELEB [13]	UK	EBV	LVRs	< 60%	No CV(Chartis)	0	47	41	52.3	65	31	N/A	N/A	6 months
NCT04537182	USA	EBV	SoC	15–45%	No CV(HRCT)	0	220	101	56.7	65	30	N/A	N/A	6 months
NCT00000606	Germany	EBV	SoC	15–45%	Allowed	N/S	111	60	71.9	60	29	347	57.0	6 months
NCT00129584	UK	EBV	SoC	< 50%	Mainly no CV (CT)	0	25	25	62.0	63	32	338	69.2	3 months
BeLieVeR-HiFi [33]	Netherlands	EBV	SoC	< 60%	No CV(Chartis)	53	34	34	32.4	59	30	375	59.2	6 months
STELVIO [34]	Germany	EBV	SoC	15–45%	No CV(Chartis)	100	43	50	38.7	64	29	318	61.3	6 months
IMPACT [35]	UK	EBV	SoC	15–45%	No CV(Chartis)	0	65	32	59.8	64	31	295	62.2	6 months
NCT02025205	USA	EBV	SoC	15–45%	No CV(Chartis)	0	128	62	46.8	64	27	308	54.5	6 months
TRANSFORM [36]	Belgium	IBV	SoC	< 45%	Allowed	0	37	36	58.9	61	34	342	60.5	3 months
NCT02022683	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
LIBERATE [37]	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
NCT01796392	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
Ninane (2012) [8]	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
NCT00880724	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
IBV valve trial [38]	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months
NCT00475007	USA	IBV	SoC	< = 45%	Allowed	0	142	135	57.0	65	30	311	55.9	6 months

Table 1 (continued)

Study name registration	Country ^a	Arm1	Arm2	Severity threshold (FEV ₁ % predicted)	Collateral ventilation	Homogeneous emphysema (%)	N Arm1	N Arm2	Men (%)	Age ^b	Baseline FEV ₁ ^b predicted, %	Baseline 6MWD ^b , m	Baseline SGRQ ^b , point	Time points for data extraction
EMPROVE [39]	USA	IBV	SoC	< =45%	No CV(HRCT)	0	113	59	53.5	67	30	305	56.3	6 months
NCT01812447														
REACH [40]	China	IBV	SoC	< =45%	No CV(HRCT)	0	72	35	99.1	63	28	330	56.9	6 months
NCT01989182														
RESET [9]	UK	EBC	SoC	<45%	Allowed	N/S	23	23	60.9	64	28	320	59.2	3 months
NCT01334307														
RENEW [41]	USA	EBC	SoC	< =45%	Allowed	77	158	157	47.6	64	26	307	58.8	6 months
NCT01608490														
REVOLENS [42]	France	EBC	SoC	<50%	Allowed	67	50	50	71.0	62	27	313	59.0	6 months
NCT01822795														
ELEVATE [43]	Netherlands	EBC	SoC	15–45%	Allowed	N/S	80	40	48.3	64	29	N/A	55.7	6 months
NCT03360396														
STEP-UP [10]	Germany	TVA	SoC	20–45%	Allowed	0	45	24	52.2	64	33	361	N/A	6 months
NCT01719263														
EASE [11]	UK	SAB	SoC	≤50% or FEV ₁ < 1L ^c	Allowed	100	208	107	51.1	64	23	300	57.1	6 months
NCT00391612														
ASPIRE [12]	USA	ELS	SoC	<50%	Allowed	0	61	34	58.9	65	29	306	55.3	6 months
NCT01449292														

^aCountry was collected as the affiliated institution of the corresponding author for the key reference in each trial

^bReported as mean or median

^cReported as FEV₁ (L)

^dUsed for the long-term mortality

Each trial was organized by treatment group in Arm1 and then sorted in ascending order of publication year. Only the key reference for each trial was cited. CV means interlobar collateral ventilation. N indicates the number of patients randomized in each trial

EBC endobronchial coil, IBV endobronchial valve, ELS endoscopic lung sealant, IBV intrabronchial valve, LVRS lung volume reduction surgery, SAB stent for airway bypass, SoC standard of care, TVA thermal vapor ablation, FEV₁ forced expiratory volume in 1 s, 6MWD six-minute walk distance, SGRQ St. George's respiratory questionnaire, HRCT high-resolution computed tomography, N/A not available, N/S not specified

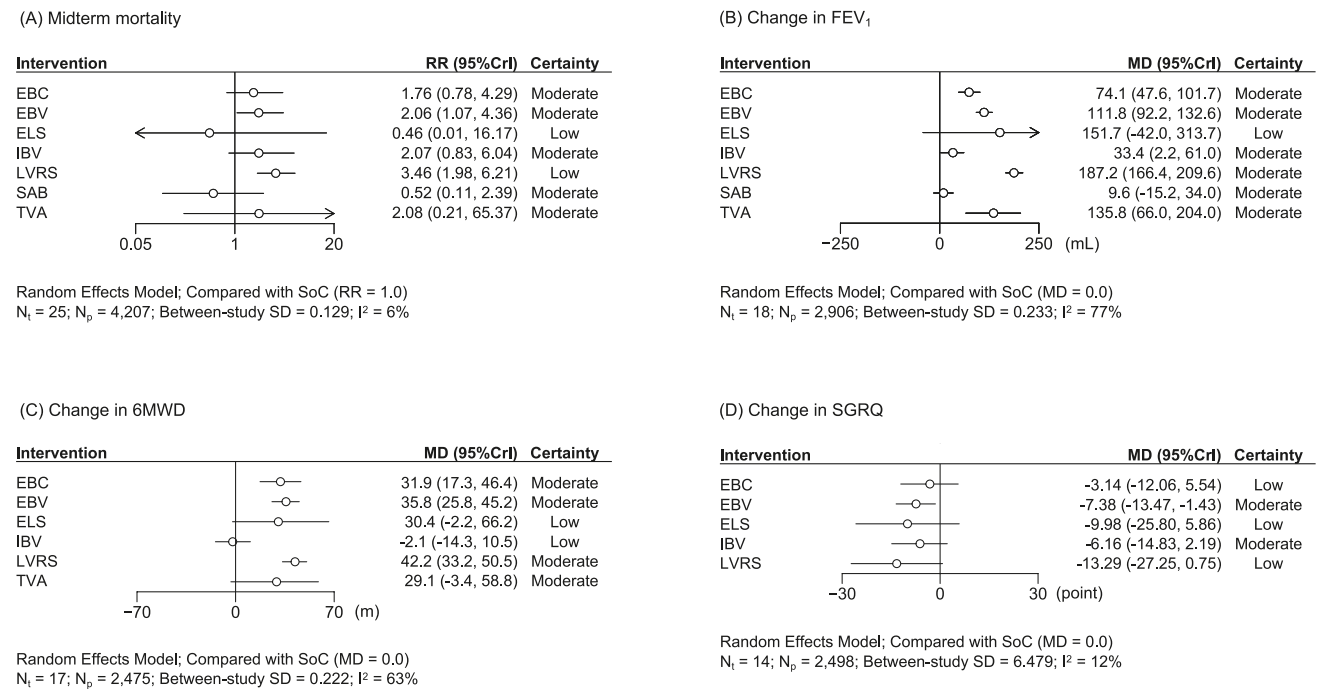


Fig. 3 Forest plots of primary outcomes. **A** Mid-term mortality. **B** Change in FEV₁. **C** Change in 6MWD. **D** Change in SGRQ. Effect size is based on the comparison to SoC. The certainty was assessed by CINeMA. Minimum Clinically Important Difference (MCID) was set as a 100-mL change in FEV₁, a 30-m change in 6MWD, and a 4-point change in SGRQ. For binary variables, the MCID was defined as an RR of less than 0.8 or greater than 1.25. The outcomes are listed in order of the number of trials included. *EBC* endobron-

chial coil, *EBV* endobronchial valve, *ELS* endoscopic lung sealant, *IBV* intrabronchial valve, *LVRS* lung volume reduction surgery, *SAB* stent for airway bypass, *SoC* standard of care, *TVA* thermal vapor ablation, *FEV₁* forced expiratory volume in 1 s, *6MWD* six-minute walk distance, *SGRQ* St. George’s respiratory questionnaire, *95%CrI* 95% credible interval, *N_t* number of trials, *N_p* number of patients analyzed in the primary studies, *SD* standard deviation, *MD* mean difference, *RR* risk ratio

significant difference compared to SoC in long-term mortality (Fig. 4D). The increased risk of mortality following LVRS, spanning from short to mid-term, is also supported by previous studies. The largest RCT for LVRS showed that the Kaplan–Meier curve crossed around 24-month post-operation [6]. Furthermore, a recent Cochrane review incorporating eight RCTs indicated that the mortality risk associated with LVRS compared to SoC varies depending on the timing of outcome collection, with odds ratios (ORs) changing over time (6.16 at 3 months, 4.36 at 6 months, 3.60 at 12 months, 1.00 at 24 months, and 0.76 at 3 years) [44]. NETT identified patients with a combination of % predicted FEV₁ under 20% and either homogeneous emphysema or a low-carbon monoxide diffusing capacity (<20%) as having a significantly higher mortality rate within 30-day post-operation, leading to their exclusion from the trial [45]. However, it would be unfair to disregard the accumulated evidence and technical progress of LVRS. In our subgroup analysis, when limited to heterogeneous emphysema, the lower limit of the 95% credible interval for the mortality rate of LVRS was below 1.0 (Table 2). The proportion of video-assisted thoracic surgery, which was only 30% in NETT [6], has increased significantly by the time of the CELEB trial [13].

Some institutions have further enhanced safety by employing robotic thoracic surgery or non-intubated awake video-assisted thoracoscopic surgery [5].

Unlike the previous NMA [14] and Cochrane review [46] on BLVR, this study suggests an increased mid-term mortality risk for EBV compared to SoC (absolute risk increase of 2.2%, 95% CrI: 0.2% to 7.1%). This discrepancy would be due to the inclusion of a larger number of trials in this NMA compared to previous analyses. However, this finding requires cautious interpretation. The lower limit of the 95% prediction interval in our study falls below an RR of 1.0 (S-Table 10-a), and the pair-wise analysis does not indicate a significant risk increase (S-Fig. 2-a). Currently, available 10-year survival data of EBV are limited to small size; just 19 cases [47]. To accurately assess the contribution of EBV to mortality risk, the reporting of long-term data from each trial and the accumulation of survival data in actual clinical practice are required.

EBC and EBV show similar efficacy, but they differ in procedural applicability; EBV efficacy decreases in the presence of interlobar CV [32]. We re-emphasize the necessity of following the GOLD algorithm [4] for high-resolution computer tomography pattern recognition of emphysema

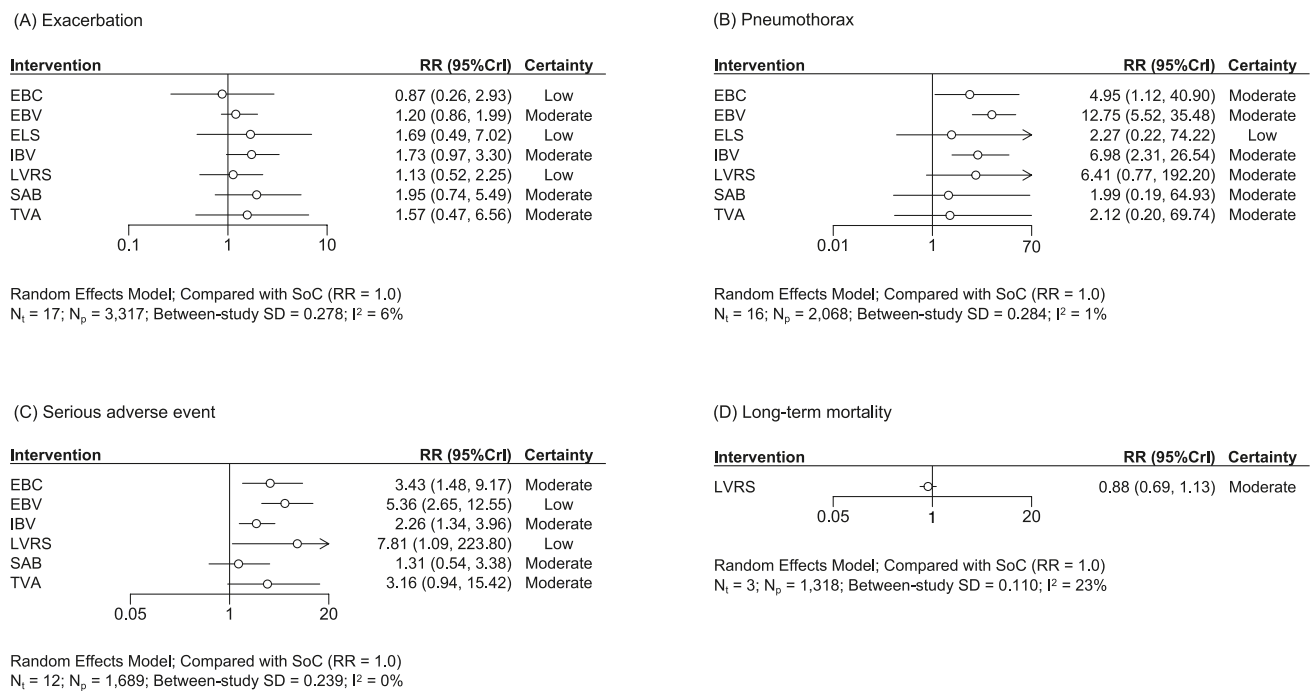


Fig. 4 Forest plots of secondary outcomes. **A** Exacerbation. **B** Pneumothorax. **C** Serious adverse event. **D** Long-term mortality. Effect size of each intervention is based on the comparison to SoC. The certainty was assessed by CINeMA. For binary variables, the Minimum Clinically Important Difference (MCID) was defined as an RR of less than 0.8 or greater than 1.25. The outcomes are listed in order of the number of trials included. *EBC* endobronchial coil, *EBV* endobron-

chial valve, *ELS* endoscopic lung sealant, *IBV* intrabronchial valve, *LVRS* lung volume reduction surgery, *SAB* stent for airway bypass, *SoC* standard of care, *TVA* thermal vapor ablation, *FEV₁* Forced expiratory volume in 1 s, *6MWD* six-minute walk distance, *SGRQ* St. George's respiratory questionnaire, 95%CrI 95% credible interval, N_t number of trials, N_p number of patients analyzed in the primary studies, *SD* standard deviation, *RR* risk ratio

distribution, determining the treatment target lobe, and conducting bronchoscopic block tests with Chartis and high-resolution computed tomography to confirm CV [48]. With the increasing significance of CV, the CELEB trial employed an advanced study design [13]. In this trial, Chartis was conducted prior to randomization and only CV-negative patients with heterogeneous emphysema were eligible, enabling a comparison between unilateral LVRS and EBV. The results showed no significant differences between the two groups in the percentage improvement of FEV₁ predicted or in the i-BODE score, nor in six-month postoperative mortality rates (LVRS: 2.9% vs. EBV: 2.2%). Although the composite outcome of the i-BODE score was not included in the current analysis, LVRS remains a potential treatment option for CV-negative cases. The increased risk of pneumothorax seen in EBC, EBV, and IBV is due to compensatory over-expansion of the other lung lobes with rapid volume reduction in the target lobe [49]. The severity of the pneumothorax can range from mild—self-limiting only with observation—to tension pneumothorax leading to death [33], thus requiring evaluation of risk factors for pneumothorax [49] before BLVR and careful follow-up after BLVR. The present study demonstrated a strong correlation between the magnitude of RV reduction and the incidence of pneumothorax.

The regression analysis provides guidance for practice and future development of mechanical LVR. Hyperinflation and RV are the primary therapeutic targets of mechanical LVR and their reduction strongly correlated with three efficacy outcomes (Fig. 5A–C). The RV reduction in BLVR was smaller than in LVRS. In other words, what is required for BLVR is the development and implementation of techniques that achieve greater reductions in RV. However, it is important to note that this approach may be a double-edged sword, as it is expected to promote an increase in pneumothorax and serious adverse events (Fig. 5D).

Implementation for Clinical Practice and Future Research

This study has four strengths for clinical practice and future research. First, it is the inaugural NMA comparing LVRS and BLVR, offering support for clinical decision-making by highlighting both the significant efficacy and risks associated with LVRS. Our study highlights the importance of clinical decision-making based on the risk–benefit balance of each procedure and clarifying the objectives of these interventions. As demonstrated in Figs. 3B and C, changes in FEV₁ and 6MWD surpassed the MCID exclusively in LVRS. In

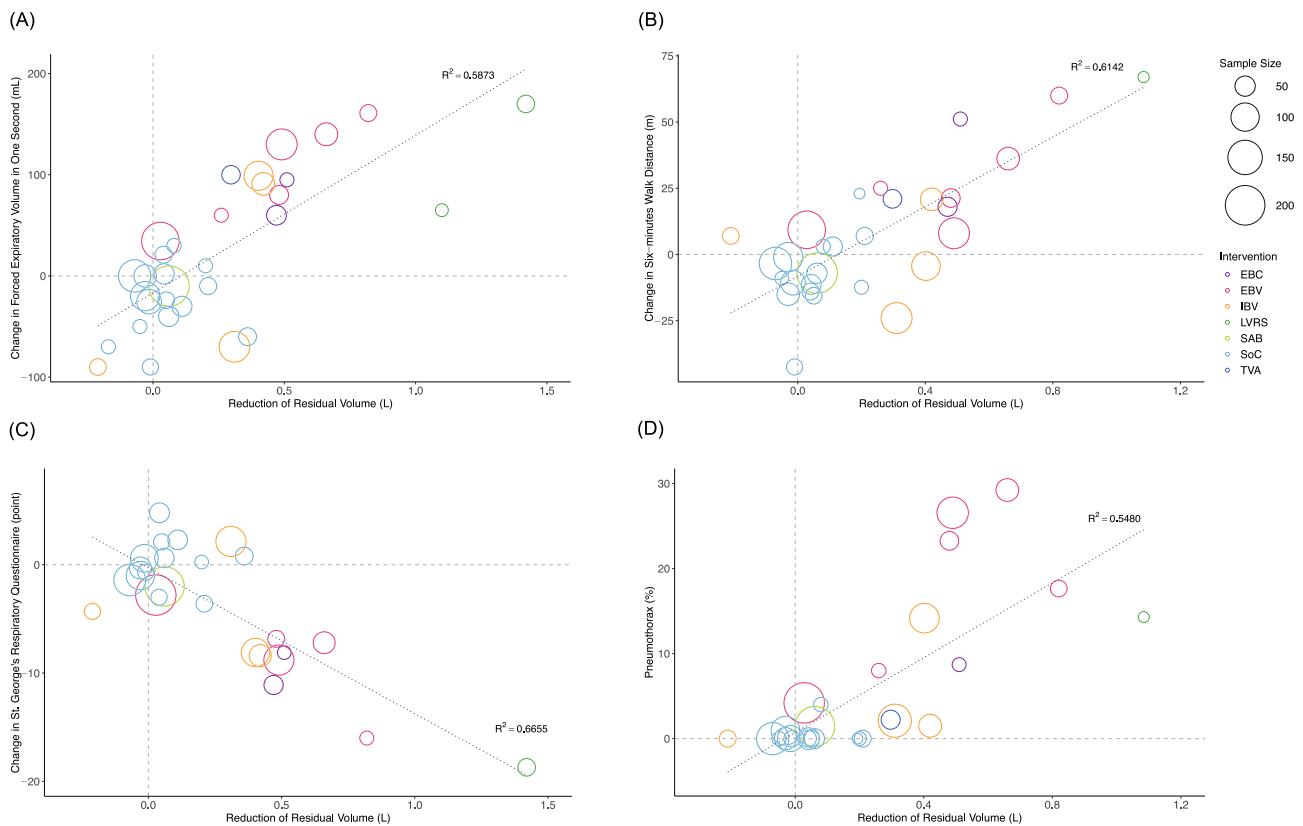


Fig. 5 Regression plots between reduction of residual volume and outcomes. Coefficient of determination were calculated from Pearson's correlation coefficients (dotted line). **A** Change in FEV_1 . A total of 1947 patients from 16 trials reported reduction of residual volume and change in FEV_1 from the baseline. **B** Change in 6MWD. A total of 1844 patients from 15 trials reported reduction of residual volume and change in 6MWD from the baseline. **C** Change in SGRQ. A total of 1848 patients from 13 trials reported reduction of residual

volume and change in SGRQ from the baseline. **D** Pneumothorax. A total of 1874 patients from 14 trials reported reduction of residual volume and prevalence of pneumothorax. *EBC* Endobronchial coil, *EBV* Endobronchial valve, *ELS* Endoscopic lung sealant, *IBV* Intra-bronchial valve, *LVRS* Lung volume reduction surgery, *SAB* Stent for airway bypass, *SoC* Standard of care, *TVA* Thermal vapor ablation, *FEV₁* Forced expiratory volume in 1 s, *6MWD* six-minute walk distance, *SGRQ* St. George's respiratory questionnaire

contrast, SGRQ did not exceed the MCID for any of the interventions (Fig. 3D). These findings support the rationale for reducing lung volume to improve respiratory function and functional exercise capacity. Second, the regression analysis provided guidance for the future development of BLVR techniques. Third, it includes the largest number of studies among NMAs and meta-analyses conducted on mechanical lung volume reduction techniques to date, minimizing publication bias through a comprehensive literature search that included conference proceedings. Fourth, the analysis employs Bayesian statistics, allowing for flexible interpretation and a broad coverage rate.

Limitations

This study presents a number of limitations: Firstly, the degree of adherence to the SoC recommended by GOLD across the studies was uncertain, and the efficacy of SoC could shift over time due to various factors, including

vaccine compliance and the use of additional inhaled corticosteroids or biologics (S-Table 14). Secondly, due to the nature of the interventions, it was impossible to implement double-blinding in all trials. Although some trials attempted to reduce the risk of bias by introducing sham controls and center-based effect assessments, concerns remain regarding the effect assessments in many studies. Thirdly, in 5 of the 25 trials, α 1-antitrypsin deficiency was documented in the exclusion criteria. The limited number of patients with α 1-antitrypsin deficiency—just only 7 patients from the STELVIO trial [34]—provides that caution should be exercised in generalizing efficacy for emphysema in these patients. Fourthly, the exclusion of comparisons within the same intervention leaves the relative efficacy within the same technique unclear, including how unilateral versus bilateral LVRS, the number of coils/valves placed, or the operator's skill level might influence outcomes. In particular, we were unable to distinguish between different surgical techniques for LVRS. This is because, while NETT [6], CLVRS [30],

Table 2 Subgroup analysis

	Mid-term mortality RR, median (95%CrI)	Change in FEV ₁ mL, median (95%CrI)	Change in 6MWD m, median (95%CrI)	Change in SGRQ point, median (95%CrI)
Non-collateral ventilation				
No. of patients (No. of trials)	11,170 patients (9 trials)	991 patients (8 trials)	983 patients (8 trials)	990 patients (7 trials)
EBV vs. SoC	2.08 (0.99, 4.82)	114.4 (91.6, 137.1)	37.5 (26.89, 47.7)	- 6.78 (- 8.96, - 4.67)
IBV vs. SoC	1.08 (0.30, 4.43)	104.5 (67.7, 138.4)	15.6 (- 1.0, 33.5)	- 12.24 (- 16.15, - 8.33)
LVRS vs. SoC	2.87 (0.07, 112.96) ^a	N/A	N/A	N/A
<i>I</i> ²	30%	69%	71%	44%
Heterogeneous emphysema				
No. of patients (No. of trials)	1483 patients (12 trials)	1204 patients (9 trials)	1200 patients (9 trials)	1172 patients (7 trials)
EBV vs. SoC	3.72 (1.43, 12.30)	107.9 (85.7, 133.4)	32.0 (19.9, 44.1)	- 6.01 (- 12.89, 0.66)
ELS vs. SoC	0.49 (0.02, 17.39)	124.3 (- 177.6, 323.4)	32.6 (- 4.4, 66.3)	- 9.97 (- 23.02, 3.09)
IBV vs. SoC	2.09 (0.83, 6.00)	34.2 (5.6, 58.4)	- 2.4 (- 15.8, 10.2)	- 5.88 (- 13.08, 0.73)
LVRS vs. SoC	3.12 (0.43, 32.27)	N/A	N/A	N/A
TVA vs. SoC	2.04 (0.22, 50.20)	129.3 (61.3, 200.4)	29.2 (- 1.0, 63.5)	N/A
<i>I</i> ²	12%	88%	68%	23%
Non-collateral ventilation and heterogeneous emphysema				
No. of patients (No. of trials)	1009 patients (7 trials)	830 patients (6 trials)	823 patients (6 trials)	849 patients (5 trials)
EBV vs. SoC	3.99 (1.47, 14.22)	109.8 (86.8, 131.6)	31.9 (18.9, 44.2)	- 5.54 (- 8.14, - 3.01)
IBV vs. SoC	1.08 (0.32, 4.27)	104.1 (71.2, 139.8)	15.5 (- 3.1, 31.7)	- 12.23 (- 16.06, - 8.37)
LVRS vs. SoC	5.55 (0.14, 248.64) ^a	N/A	N/A	N/A
<i>I</i> ²	20%	77%	67%	25%

EBC endobronchial coil, *EBV* endobronchial valve, *ELS* endoscopic lung sealant, *IBV* intrabronchial valve, *LVRS* lung volume reduction surgery, *SAB* stent for airway bypass, *SoC* standard of care, *TVA* thermal vapor ablation, *FEV₁* forced expiratory volume in 1 s, *6MWD* six-minute walk distance, *SGRQ* St. George's respiratory questionnaire, *N/A* not available, *RR* risk ratio, *95%CrI* 95% credible interval

^aNetwork estimate based on indirect comparison

and CELEB [13] reported the proportions of median sternotomy and video-assisted thoracic surgery performed, not all trials reported outcomes stratified by surgical technique. Finally, some network estimates revealed overestimated therapeutic effects for certain combinations of interventions and outcomes. Interpretations of these estimates should require careful consideration (S-Table 12–14).

Conclusion

For patients with advanced emphysema, performing LVRS, EBV, and EBC has therapeutic benefits in lung function and functional exercise capacity. LVRS demonstrates the highest efficacies but is associated with an increase in mid-term mortality. Among BLVR procedures, EBV and EBC exhibit notable therapeutic effects; however, both carry an elevated risk of pneumothorax, with EBV also showing a concerning increase in mortality. For accurate assessment, outcomes stratified by surgical technique and long-term survival data from BLVR trials is needed.

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Author Contributions N.H. takes responsibility for the paper as a whole. S.Y. and N.H. conceived the study. N.H. provided statistical advice. S.Y., R.I., and T.N. analyzed the data. S.Y. drafted the manuscript, and all authors contributed substantially to its revision. The content is solely the responsibility of the authors.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest S. Yamamoto has received overseas scholarships from the Japan Society for Promotion of Science. This organization has no role in conducting this research. The other authors declare no financial/nonfinancial relationships.

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