Comparative outcomes of lung volume reduction surgery and lung transplantation: a systematic review and meta-analysis

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Background: Lung volume reduction (LVR) and lung transplantation (LTx) have been used in different populations of chronic obstructive pulmonary disease (COPD) patients. To date, comparative study of LVR and LTx has not been performed. We sought to address this gap by pooling the existing evidence in the literature.

Methods: An electronic search was performed to identify all prospective studies on LVR and LTx published since 2000. Baseline characteristics, perioperative variables, and clinical outcomes were extracted and pooled for meta-analysis.

Results: The analysis included 65 prospective studies comprising 3,671 patients [LTx: 15 studies (n=1,445), LVR: 50 studies (n=2,226)]. Mean age was 60 [95% confidence interval (CI): 58–62] years and comparable between the two groups. Females were 51% (95% CI: 30–71%) in the LTx group *vs.* 28% (95% CI: 21–36%) in LVR group (P=0.05). Baseline 6-minute walk test (6MWT) and pulmonary function tests were comparable except for the forced expiratory volume in 1 second (FEV1), which was lower in the LTx group [21.8% (95% CI: 16.8–26.7%) *vs.* 27.3% (95% CI: 25.5–29.2%), P=0.04]. Postoperatively, both groups experienced improved FEV1, however post-LTx FEV1 was significantly higher than post-LVR FEV1 [54.9% (95% CI: 41.4–68.4%) *vs.* 32.5% (95% CI: 30.1–34.8%), P<0.01]. 6MWT was also improved after both procedures [LTx: 212.9 (95% CI: 119.0–306.9) to 454.4 m (95% CI: 334.7–574.2), P<0.01; LVR: 286 (95% CI: 270.2–301.9) to 409.1 m (95% CI: 392.1–426.0), P<0.01], however, with no significant difference between the groups. Pooled survival over time showed no significant difference between the groups.

Conclusions: LTx results in better FEV1 but otherwise has comparable outcomes to LVR.

Keywords: Lung transplantation (LTx); lung volume reduction (LVR); National Emphysema Treatment Trial (NETT); endobronchial lung volume reduction; lung volume reduction surgery (LVRS)

Introduction

Chronic obstructive pulmonary disease (COPD)/emphysema is the final and irreversible common pathway of various pulmonary pathologies leading to loss of lung elastic recoil, obstructed and hyper-inflated lungs, and severely symptomatic patients (1). In the US, it has consistently been among the top five causes of death, translating to an economic burden of almost 50 billion USD per year (2,3).

Surgical treatment/palliative options for COPD can be considered when medical treatment has been maximally utilized. These include lung volume reduction (LVR) and lung transplantation (LTx) (4). LVR is based on the premise that advanced COPD manifests with structural changes such as loss of elastic recoil and hyperinflation. Resection of such diseased portions should therefore improve lung elastic recoil and chest wall mechanics since the remaining lung would occupy less space within the thorax (5,6). Single or bilateral LTx on the other hand is also indicated in cases of severe COPD refractory to medical management (4). Globally, the most common primary indication for LTx is COPD (7).

These procedures have been used in different populations of COPD patients. The National Emphysema Treatment Trial (NETT) (8) identified subsets (based on physiological lung parameters) of COPD patients who stand to gain the most or the least from LVR. With respect to LTx, indications and absolute contraindications are also clearly elucidated (4). It remains to be seen whether patients who could potentially qualify for either LVR or LTx, such as those with non-upper lobe predominant emphysema and poor baseline exercise capacity, may accrue different benefits from undergoing one procedure compared to the other. However, the magnitude and direction of such benefit, if present, is unknown.

In addition, non-invasive methods of LVR, collectively referred to as endobronchial LVR are increasingly being utilized. These include devices which functionally exclude diseased lung segments without the need for surgery (9) such as endobronchial valves and the newer endobronchial coils. Compared to LVR, they have thus far shown good palliation and functional improvement in COPD patients with some mortality and morbidity benefit as well. However, long term data comparing surgical LVR to endobronchial LVR are scarce (10).

NETT (8) randomized COPD patients into a medical management group and a surgical LVR group. It was able to classify patients based on how beneficial surgical LVR was compared to standard medical management. However, questions remain regarding the place of surgical LVR in the present-day management of advanced COPD as well as the use of its less invasive versions such as endobronchial LVR. To date, there has not been a large-scale comparative study evaluating LVR and LTx. This knowledge gap has been highlighted by NETT investigators as well (11). In addition, endobronchial LVR has not been comparatively studied against surgical LVR.

We sought to bridge this gap in the literature by systematically pooling the existing evidence and performing quantitative meta-analysis. We aimed to answer the question of how LVR and LTx compared to each other in terms of survival as well as improvement in physiological lung parameters. In addition, in a subset analysis, we further compared outcomes between surgical and endobronchial LVR. To reduce noise in the data, these comparisons were made using only prospective studies conducted after the year 2000. NETT itself was not included in the analysis to avoid overlap and double entry of data from its participating institutions. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-63/rc).

Highlight box

Key findings
- LTx has better FEV1 compared to LVRS, but survival is comparable between the two.

What is known and what is new?
- Both LTx and LVRS are surgical options for end-stage COPD with distinct indications and populations. As highlighted by NETT investigators, there has been no comparison between the procedures for patients who may qualify for both.
- In the absence of head-to-head comparison due to inherent population differences, this manuscript pools existing studies to compare outcomes of the two procedures in an objective manner.

What is the implication, and what should change now?
- These findings highlight the need for direct comparison between the procedures for patients who may benefit from either. Further, it underscores the importance of considering both short- and long-term outcomes, when offering surgical options to patients with end-stage COPD.

Methods

Literature search strategy

An electronic database search was performed in January 2020 using MEDLINE (Ovid SP), Scopus, Cochrane Controlled Trials Register (CCTR), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). To achieve maximum sensitivity, the following terms were combined: "end AND stage AND lung OR respiratory AND insufficiency" OR "pulmonary AND emphysema OR heterogenous AND emphysema OR pulmonary AND disease" AND "lung AND transplantation OR lung AND volume AND reduction AND surgery OR lvr" included as either key words or MeSH terms. A manual search was also performed to ensure all relevant articles were included.

Eligibility criteria

Eligible articles were full-length, prospective studies published from January 2000 to December 2019 in the English literature that included adults undergoing LVR or LTx with an underlying diagnosis of homogenous or heterogenous emphysema. Both surgical and endoscopic techniques of LVR were eligible for inclusion. Studies that were retrospective, included patients not undergoing LVR or LTx, or included patients without emphysema were excluded. Case reports, abstracts, conference presentations, editorials, reviews, and expert opinions were also excluded. When institutions published more than one study including overlapping patient populations, only the most complete reports were included.

Data extraction and critical appraisal

All relevant study level data were extracted from the text, figures, and tables of all eligible articles (BEF, DCJ). Discrepancies between the reviewers were resolved by discussion and consensus. The Newcastle-Ottawa scale (NOS) and Cochrane Risk of Bias (ROB) assessment tool were used to assess the quality of studies and risk of bias. Further details are presented in the supplementary material (Tables S1-S3).

Statistical analysis

Variables were reported as the pooled mean with 95% confidence intervals (CI). For dichotomous variables, a meta-analysis of proportions with logit transformation was conducted. Continuous data were combined via meta-analysis with random-effects model. Heterogeneity was evaluated using I^2 test. Survival data from each study were collected and pooled to retrieve a weighted mean and 95% CI at specific time points. Such data were then graphically displayed to visualize survival over time. The main analysis was undertaken to compare patients undergoing LTx vs. lung volume reduction surgery (LVRS). Subgroup analysis was further undertaken for surgical vs. endobronchial techniques of LVR. Propensity matching was not done due to the limitations of the meta-analysis method. R software 3.5.0, meta package (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis. P values <0.05 were considered statistically significant.

Study characteristics

Eligible studies included all prospective studies on patients who underwent LVR or LTx for homogenous or heterogenous emphysema. After removal of duplicate articles, 1,925 of 2,155 articles were excluded after a detailed evaluation of the title and abstract. The remaining 230 articles underwent a full text evaluation, of which 65 articles met inclusion criteria with a collective 3,671 patients. This consisted of 15 LTx studies (n=1,445) and 50 LVR studies (n=2,226). A PRISMA flow diagram illustrating the search strategy is provided as Figure S1, while a detailed list of the studies included is provided as Table S1. A protocol was not prepared a priori, nor was this review registered.

Results

Baseline characteristics

Mean age was 60 (95% CI: 58–62) years and females comprised 32% (95% CI: 24–40%) of all patients with greater preponderance in LTx group [51% (95% CI: 30–71%) vs. 28% (95% CI: 21–36%), P=0.05]. Heterogenous alpha-1 antitrypsin deficiency was less common in the LTx group [69% (95% CI: 42–87%) vs. 96% (95% CI: 94–97%), P<0.01] however more patients in this group were on home oxygen therapy prior to surgery [95% (95% CI: 77–99%) vs. 63% (95% CI: 41–80%), P=0.01]. Further information is provided in *Table 1*.

Preoperative lung parameters

Overall forced expiratory volume in 1 second (FEV1) (%

Table 1 Baseline and preoperative characteristics of patients in lung transplant and lung volume reduction groups

Variable	Lung transplant				Lung volume reduction				Overall				
	Pooled value, mean [95% CI]	No. of patients (N or n/N)	No. of studies	I² (%)	Pooled value, mean [95% CI]	No. of patients (N or n/N)	No. of studies	I² (%)	Pooled value, mean [95% CI]	No. of patients (N or n/N)	No. of studies	I² (%)	P value
Age (years)	52 [47, 56]	444	10	52*	63 [62, 65]	1,825	40	0	60 [58, 62]	2,269	50	43*	<0.01
BMI (kg/m²)	20.6 [17.7, 23.5]	213	3	0	22.9 [22.0, 23.8]	817	18	0	22.7 [21.8, 23.6]	1,030	21	0	0.14
Female (%)	51 [30, 71]	240/415	9	51*	28 [21, 36]	680/1,759	41	68*	32 [24, 40]	920/2,174	50	71*	0.05
Heterogenous A1AT (%)	69 [42, 87]	365/529	6	84*	96 [94, 97]	1,180/1,195	31	13	95 [91, 97]	1,545/1,724	37	73*	<0.01
Home oxygen requirement (%)	95 [77, 99]	429/450	3	93	63 [41, 80]	422/877	22	95*	69 [49, 84]	851/1,327	25	97*	0.01
Smoking (pack years)	27 [0, 56]	188	1	–	48 [39, 58]	873	15	0	46 [37, 55]	1,061	16	0	0.17
6MWT (m)	212.9 [119.0, 306.9]	249	3	0	286.1 [269.4, 302.9]	1,886	38	0	283.9 [267.4, 300.4]	2,135	41	0	0.13
FEV1	0.65 [0.29, 1.02]	488	2	0	0.70 [0.65, 0.74]	1,975	41	0	0.69 [0.65, 0.74]	2,463	43	0	0.83
FEV1 (% pred)	21.8 [16.8, 26.7]	756	6	0	27.3 [25.5, 29.2]	1,892	40	0	26.7 [25.0, 28.4]	2,648	46	0*	0.04
DLCO (% pred)	36.0 [4.6, 67.4]	31	1	–	32.8 [29.0, 36.6]	1,164	21	0	32.9 [29.2, 36.6]	1,195	22	0	0.84
FEV1/FVC	32.0 [5.7, 58.3]	5	1	–	34.0 [29.6, 38.4]	467	12	0	34.0 [29.6, 38.3]	472	13	0	0.88
RV (% pred)	310.0 [12.0, 608.0]	5	1	–	231.3 [204.9, 257.7]	1,382	32	84*	231.8 [205.5, 258.2]	1,387	33	83	0.61
TLC (% pred)	135.0 [56.1, 213.9]	29	1	–	134.5 [131.6, 137.4]	1,078	28	0	134.5 [131.6, 137.4]	1,107	29	0	0.99

*, significant heterogeneity present (P<0.05). CI, confidence interval; BMI, body mass index; A1AT, alpha-1 antitrypsin; 6MWT, 6-minute walk test; FEV, forced expiratory volume; DLCO, diffusion capacity of carbon monoxide; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

Table 2 Comparison of post-operative variables between lung transplant and lung volume reduction groups

Variable	Lung transplant				Lung volume reduction				Overall				
	Pooled value, mean [95% CI]	No. of patients	No. of studies	I² (%)	Pooled value, mean [95% CI]	No. of patients	No. of studies	I² (%)	Pooled value, mean [95% CI]	No. of patients	No. of studies	I² (%)	P value
BMI (kg/m²)	24.1 [19.7, 28.5]	89	3	0	24.69 [23.6, 25.77]	119	3	0	24.65 [23.6, 25.71]	208	6	0	0.8
6MWT (m)	454.4 [334.7, 574.2]	61	2	0	408.3 [391.2, 425.5]	1,392	27	0	409.2 [392.3, 426.2]	1,453	29	0	0.45
FEV1 (% pred)	54.9 [41.4, 68.4]	122	5	25	32.5 [30.1, 34.8]	697	17	0	36.8 [32.8, 40.9]	790	22	45*	<0.01

*, significant heterogeneity present (P<0.05). CI, confidence interval; BMI, body mass index; 6MWT, 6-minute walk test; FEV, forced expiratory volume.

pred) was 26.7% (95% CI: 25.0–28.4%) and less in the transplant group [LTx: 21.8% (95% CI: 16.8–26.7%) vs. LVR: 27.3% (95% CI: 25.5–29.2%), P=0.04]. The 6-minute walk test (6MWT) was comparable between the groups [LTx: 212.9 (95% CI: 119.0–306.9) vs. LVR: 286.1 m (95% CI: 269.4–302.9), P=0.13]. Further details are given in *Table 1*.

Postoperative lung parameters

The postoperative FEV1 (% pred) was significantly greater in the LTx group [LTx: 54.9% (95% CI: 41.4–68.4%) vs. LVR: 32.5% (95% CI: 30.1–34.8%), P<0.01]. The postoperative mean 6MWT distance was however comparable between the groups [LTx: 454.4 (95% CI: 334.7–574.2) vs. LVR: 409.1 m (95% CI: 392.1–426.0), P=0.45] (*Table 2*).

Significant improvements were seen in postoperative FEV1 (% pred) in both the LTx group [Preop: 21.8% (95% CI: 16.8–26.7%) vs. Postop: 54.9% (95% CI: 41.4–68.4%), P<0.01] and LVR group [Preop: 27.3% (95% CI: 25.5–29.2%) vs. Postop: 32.5% (95% CI: 30.1–34.8%), P=0.01] (*Figure 1A*). Similarly, significant within-group improvements in 6MWT (m) were seen in the LTx [Preop: 212.9 (95% CI: 119.0–306.9) vs. Postop: 454.4 m (95% CI: 334.7–574.2), P<0.01] and LVR groups [Preop: 286 (95% CI: 270.2–301.9) vs. Postop: 409.1 m (95% CI: 392.1–426.0), P<0.01] (*Figure 1B*). Further details are in Table S4.

Pooled survival analysis

Survival at 6 months, 1 year, 5 years, and 8 years was 96% (95% CI: 95–97%), 93% (95% CI: 92–95%), 62% (95% CI: 57–67%), and 19% (95% CI: 5–53%) in the LVR group. In the LTx group, it was 93% (95% CI: 82–98%), 88% (95% CI: 80–93%), 60% (95% CI: 60–68%), and 41% (95% CI: 33–49%) respectively. Pooled survival over time (*Figure 2A*) showed no significant difference between the groups.

Subgroup analysis: surgical vs. endobronchial LVR

The subgroups were comparable in all baseline characteristics (Table S5). The mean operation time [116 (95% CI: 58–173) vs. 47 min (95% CI: 28–67), P=0.03] and hospital stay [9 (95% CI: 7–12) vs. 2 (95% CI: 1–4) days, P<0.01] were longer in the surgical subgroup compared to the endobronchial subgroup. Post-LVR, the rates of significant bleeding [Surgical: 2% (95% CI: 1–4%) vs. Endobronchial: 1% (95% CI: 0–3%), P=0.16]
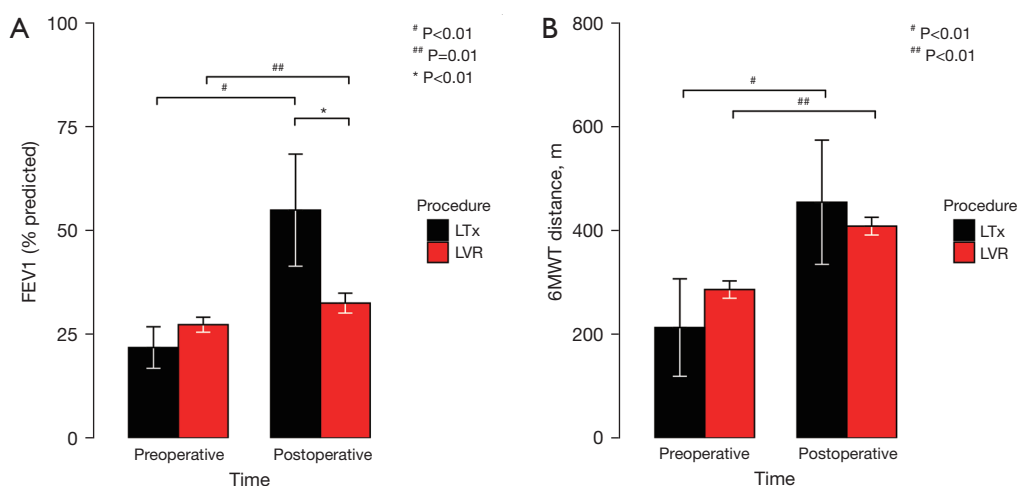
Figure 1 Preoperative *vs.* postoperative comparison of (A) FEV1 (% pred) and (B) 6MWT distance between and within LVR & LTx groups. Bars represent mean & error bars represent 95% confidence intervals. FEV, forced expiratory volume; LTx, lung transplant; LVR, lung volume reduction; 6MWT, 6-minute walk test.
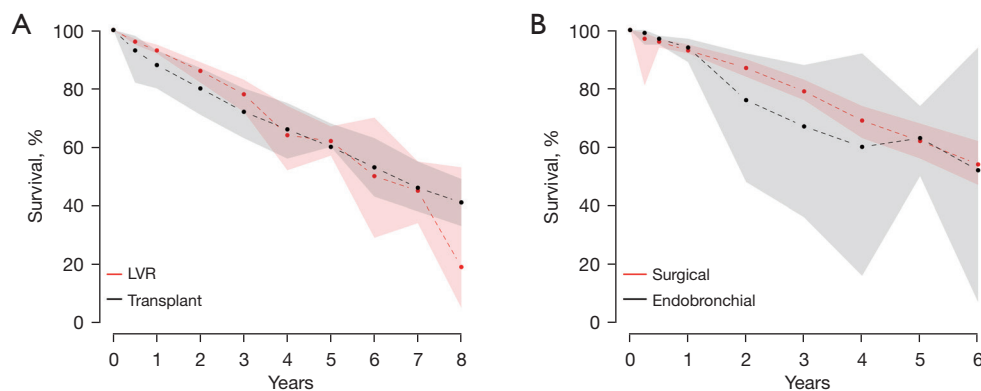

Figure 2 Pooled survival over time after (A) LVR *vs.* lung transplantation and (B) surgical *vs.* endobronchial lung volume reduction. Central dashed line represents pooled means while shaded region represents 95% confidence intervals. LVR, lung volume reduction.

and pneumothorax [Surgical: 3% (95% CI: 1–9%) *vs.* Endobronchial: 4% (95% CI: 2–10%), P=0.62] were also comparable between the subgroups (Table S6).

At 3 months post-procedure, the 6MWT was greater in the endobronchial subgroup compared to the surgical subgroup, however, trends reversed after this time. Similarly, FEV1 peaked in the endobronchial subgroup at 3 months post-LVR followed by a decline while it peaked in the surgical subgroup at 6 months followed by a decline at one year. Figure S2 compares the trends in physiologic lung parameters between both subgroups. Survival was comparable between the subgroups as shown in *Figure 2B*.

Discussion

NETT (8) was undertaken to compare maximal medical treatment with surgical LVR. One benefit of this extensive study was the clarity it provided in the indications for LVR and the subset of patients who were most likely to benefit from it. These were patients who had predominantly upper-lobe emphysema with poor preoperative exercise capacity (8). Patients with an FEV1 (% pred) ≤20% with either a diffusion capacity of carbon monoxide (DLCO) ≤20% or homogenous emphysema were the least likely to benefit from LVR (12) and such patients could potentially benefit from LTx (13). Generally, alongside other criteria,

a patient with a FEV1 (% pred) ≤45% qualifies for LVR. In contrast, for LTx, FEV1 (% pred) criteria for consideration is ≤25 (13,14). The group of patients with FEV1 (% pred) between 20–30 could potentially qualify for either procedure depending on various patient and procedural factors (11,14). Although these procedures are generally used in COPD populations with distinct indications for each, there may exist a potential overlap in indications in the FEV1 (% pred) range alluded to previously, where select patients may stand to benefit from either procedure. The LVR and LTx groups only overlap partially as seen from the 95% CI of baseline FEV1 (% pred) in each.

Despite the benefits seen in advanced COPD from LVR (as described by NETT), it has not gained much traction as a treatment for end-stage COPD (11). The reasons for this could be the high cost, restrictive eligibility criteria, less surgeon experience, and unclear idea of benefits reported by NETT (11,15). However, recent trends in the US indicate increasing utilization of LVR with regional variation in uptake. This increase is being seen simultaneously with lower morbidity and mortality (16).

Patients in this analysis were similar at baseline except for a few key differences. The pooled preoperative mean FEV1 (% pred) was less in the LTx group (21.8%) compared to the LVR group (27.3%) and more LTx (95% *vs.* 63%) patients were on home oxygen therapy. It could therefore be surmised that patients undergoing LTx were more advanced in their pulmonary pathology than those undergoing LVR. This would not be out of place given the different criteria for each procedure. However, since meta-analysis methods do not allow for propensity-matching the populations, the populations can be expected to have key differences at baseline and findings should be contextualized within this limitation.

We found statistically comparable survival between both groups at all assessed time points; however, a greater degree of functional improvement [FEV1 (% pred)] was seen in LTx patients. When taken in the context of the advanced baseline pathology in LTx patients, the comparable survival may hint at a possibly greater survival benefit with LTx as LVRS patients with less advanced baseline pathology show similar long-term survival. In comparison, a single center study of 144 patients by Weinstein *et al.* reported greater overall and subgroup [FEV1 (% pred) 20–30] survival in LVR patients compared to LTx patients (14).

Postoperatively, we found that only FEV1 (% pred) was significantly better in the LTx group compared to LVR group (54.9% *vs.* 32.5%). However, FEV1 (% pred) and

6MWT improved within both surgical groups. This is in agreement with the review by Mora (1) and the study by Weinstein *et al.* (14) who showed greater functional improvement in their subgroup [FEV1 (% pred) 20–30] of patients undergoing LTx who survived more than one year after the surgery.

Our analysis also indicated that surgical LVR had a longer operation time (116 *vs.* 47 min) and hospital stay (9 *vs.* 2 days) compared to endobronchial LVR, however the rates of complications, such as bleeding and pneumothorax were comparable. Survival was also comparable between both subgroups. Of note, general trends indicated that lung function and dyspnea improved quickly after endobronchial LVR; however, improvement in the surgical LVR subgroup occurred later and was greater in magnitude and/or more sustained. One reason for the delayed benefit in the surgical subgroup could be the longer recovery time compared to endobronchial LVR procedures where quicker recovery may lead to earlier improvements post-procedure. It should however be noted that in most endobronchial studies, long term follow-up data was lacking.

Since a history of LVR does not disqualify from future LTx (17-19), it could be argued that in patients opting for initial LVR as "bridge to LTx", especially younger patients, it might be more practical to undergo a single procedure (LTx) which provides greater functional improvement with similar long-term survival. While LTx has been associated with more complications than LVR (4), we were not able to analyze this due to the limited data in the included studies. Thus, this suggestion should be viewed in the context of the lifetime management of emphysema and the greater complexity associated with LTx with risk/benefit assessment individualized to each patient.

The financial aspect of these procedures should also be considered. A single center study reported the total cost of LTx to be $381,732 at a mean follow-up of 2.4±2.5 years compared to $140,637 at a mean follow-up of 5.0±3.1 years for LVR (14). The additional cost of immunosuppression as well as the longer and more frequent follow-up associated with LTx may be behind its higher cost. Nevertheless, both procedures are expensive endeavors, and cost more than medical management (13). Therefore, cost-effectiveness analysis should be part of the patient selection process for these procedures to maximize benefit.

Limitations

Major limitations of this meta-analysis are due to the

inherent inconsistency of reporting patterns that are observed when working with pooled data. Additionally, this meta-analysis was not based on studies with direct comparison between LVR and LTx; which is why we attempted to systematically pool the available evidence on patients undergoing each procedure as the next best way to compare outcomes. While we do report short-term and long-term survival, we were not able to assess changes in physiological lung parameters over time between LTx and LVR. We also did not assess quality of life improvement after both procedures. This may be a major factor in the decision to choose one surgery over the other. Further granularity in the data such as location/extent of emphysema and its impact on choice of procedure, complication rates, and differences in outcomes after single *vs.* double LTx were also lacking.

Conclusions

LTx and LVR are management options in end-stage COPD for highly selective patients. While LTx led to greater improvement in FEV1 (% pred), survival was comparable between both groups. Surgical LVR and endobronchial LVR were also similar in terms of survival, however, surgical LVR led to late and more sustained functional benefits with longer duration of hospital stay.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-63/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-63/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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