Systematic Review

Single versus double lung transplantation for fibrotic disease—systematic review

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Background: Lung transplantation has long been the accepted therapy for end-stage pulmonary fibrotic disease. Presently, there is an ongoing debate over whether single or bilateral transplantation is the most appropriate treatment for end-stage disease, with a paucity of high-quality evidence comparing the two approaches head-to-head.

Methods: This review was performed in accordance with PRISMA recommendations and guidance. Searches were performed on PubMed Central, Scopus and Medline from dates of database inception to September 2019. For the assessed papers, data was extracted from the reviewed text, tables and figures, by two independent authors. Estimated survival was analyzed using the Kaplan-Meier method for studies where time-to-event data was provided.

Results: Overall, 4,212 unique records were identified from the literature search. Following initial screening and the addition of reference list findings, 83 full-text articles were assessed for eligibility, of which 17 were included in the final analysis, with a total of 5,601 patients. Kaplan-Meier survival analysis illustrated improved survival in patients receiving bilateral lung transplantation (BLTx) than in those receiving unilateral transplantation for idiopathic pulmonary fibrosis at all time intervals, with aggregated survival for BLTx at 57%, 35.3% and 24% at 5-, 10- and 15-year follow-up, respectively. Survival rates for SLTx were 50%, 27.8% and 13.9%, respectively.

Conclusions: Whilst a number of studies present conflicting results with respect to short-term transplantation outcomes, BLTx confers improved long-term survival over SLTx, with large-scale registries supporting findings from single- and multi-center studies. Through an aggregation of published survival data, this meta-analysis identified improved survival in patients receiving BLTx versus SLTx at all time intervals.

Keywords: Lung transplantation; fibrotic disease; outcomes

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Introduction

Lung transplantation has long been an accepted therapy for end-stage pulmonary fibrotic disease given the poor long-term prognosis of patients managed with medical and conservative treatment (1). Presently, there is an ongoing debate over whether single (SLTx) or bilateral (BLTx) lung transplantation is the most appropriate treatment, with a paucity of high-quality evidence comparing the two approaches head-to-head (2). As such, practice is still largely specific to the institution or to the surgeon's preference. Historically, SLTx has been used under the rationale that it is a more limited operation and hence is more appropriate for high-risk candidates; however, as surgical techniques have improved, bilateral transplantation—particularly with its increasingly acceptable long-term

morbidity and mortality—has become predominant. Given the heterogeneity of interstitial lung diseases, particularly in terms of their etiology and pathophysiology, substantive subgroup analysis to date has been hindered outside of registry findings, with patient outcomes highly variable within the literature (3). The present systematic review will detail the mid- and late-term outcomes after SLTx *vs.* BLTx for pulmonary fibrotic disease and will provide an aggregation of the present data on survival outcomes.

Methods

Literature search

This review was performed in accordance with PRISMA recommendations and guidance (4,5). Electronic searches were performed on PubMed Central, Scopus and Medline from dates of database inception to September 2019, using the terms ("lung transplantation" OR "lung transplant") AND ("single" OR "unilateral" OR "bilateral" OR "double") AND ("pulmonary fibrosis" OR "idiopathic pulmonary fibrosis") as either keywords or MeSH headings. After removal of duplicate records, studies were screened according to their titles and abstracts, then reviewed according to the inclusion and exclusion criteria detailed below by two independent authors (AR Wilson-Smith, YS Kim). Conflicts were resolved by the senior researcher (AR Wilson-Smith). A PRISMA diagram of the search strategy is presented in *Figure S1*. Additional references for discussion were obtained by reference list searches, or via targeted database searches.

Inclusion and exclusion criteria

Studies were eligible for this review if they had at least ten patients in their cohorts and where transplantation (either SLTx or BLTx) was indicated primarily for idiopathic pulmonary fibrosis (IPF). Follow-up of a minimum of one year was also required. Non-English records, review articles, conference and paper abstracts, editorials, letters, case reports, series, and opinions were excluded. Studies were excluded from analysis if they failed to delineate between SLTx and BLTx outcomes, or if no mention was made of the outcome between the two approaches qualitatively.

Studies which aggregated etiologies in their survival analysis (e.g., IPF + cystic fibrosis + chronic obstructive pulmonary disease) were excluded from quantitative analysis, as were emergent surgeries. Duplicate studies were removed prior to the commencement of the literature screen and only the most up-to-date references from ongoing studies or registries were reviewed for statistical aggregation to minimize patient overlap. Studies were also excluded if they did not present baseline patient characteristics, or if the study was centered on pediatric patients (i.e., those <18 years).

Data extraction, statistical analysis and presentation

For the assessed papers, data was extracted from the reviewed text, tables and figures. Data was extracted independently by two independent authors (AR Wilson-Smith, YS Kim) into Microsoft Excel. Discrepancies were reviewed and discussed until a consensus was reached. Findings are presented in *Tables 1-3*. Estimated survival was analyzed using the Kaplan-Meier method in studies where time-to-event data was provided (6). Censoring was assumed to be constant, unless the particular curve had a long follow-up of only minimal patients—in which case, censoring was manually entered. Death events and censoring data were compiled for the entire patient cohort and overall survival curves were produced using R Studio (7).

Quality assessment of included studies

An appraisal schema based on the Canadian National Institute of Health Economics' (CNIHE) Quality Assessment Tool (i.e., the modified Delphi technique) for case series studies was employed to evaluate all included studies (*Figure S2*). Studies were categorized based on the following domains: clarity of study objective, adequate description of the study population, description of the intervention, adequate reporting of outcome measures, appropriate reporting of results/conclusions (quality findings are listed in *Table 1*, criteria are provided in *Figure S2*). Studies were considered to be of high quality if they addressed at least 15 of the 19 criteria outlined in the CNIHE tool. Moderate quality was defined as 13–15 of 19 and low quality below 13 of 19.

Results

Overall, 4,212 unique records were identified from the literature search (*Figures S1,S3*). Following initial screening and the addition of reference list findings, 83 full-text articles were assessed for their eligibility, of which 17 were included in the final analysis. Six studies were included

Table 1 Study characteristics and clinical outcomes

Study	Year	Institution	Country	Period	Type	Total patients	IPF patients	Stratify data by transplant indications	Stratify data by surgical type (SLTx *vs.* BLTx)	Stratify by transplant indication and surgery type	Study quality
Algar	2010	Lung Transplantation Unit, Hospital Universitario Reina Sofia, University of Cordoba, Cordoba, Spain	Spain	October 1993–December 2009	Single and bilateral	301	89	Yes	No	No	High
Burdett	2012	Freeman Hospital, Newcastle-upon-Tyne, United Kingdom	United Kingdom	1987–2010	Single	259	108	Yes	No	No	Moderate
Burton	2005	Hjertecentret, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark	Denmark	January 1992–December 2003	Single and bilateral	362	N/A	No	Yes	No	High
De Oliveira	2012	Division of Cardiothoracic Surgery, Department of Surgery, University of Wisconsin Hospital and Clinics, Madison, WI, USA	USA	January 1993–March 2009	Single and bilateral	111	79	Yes	Yes	Yes	High
De Perrot	2004	Toronto Lung Transplant Program, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada	Canada	1983–2003	Single and bilateral	501	97	Yes	Yes	No	High
Harringer	1999	Division of Thoracic and Cardiovascular Surgery, Hannover Medial School, 20623 Hannover, Germany	Germany	December 1987–September 1998	Single and bilateral	258	73	Yes	Yes	No	High
Mason	2007	Departments of Thoracic and Cardiovascular Surgery, Quantitative Health Sciences, and Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic, Cleveland, Ohio, USA	USA	February 1990–November 2005	Single and bilateral	469	82	Yes	Yes	Yes	High
Meyers	2000	Divisions of Cardiothoracic Surgery and Pulmonary and Critical Care Medicine, Washington University School Medicine, St Louis, Mo, USA	USA	July 1988–July 1998	Single and bilateral	433	45	Yes	Yes	Yes	High

Table 1 (*continued*)

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Study	Year	Institution	Country	Period	Type	Total patients	IPF patients	Stratify data by transplant indications	Stratify data by surgical type (SLTx *vs.* BLTx)	Stratify by transplant indication and surgery type	Study quality
Rubin	2015	Pavilhão Pereira Filho, Santa Casa de Porto Alegre; and at the Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brasil	Brazil	January 2006–December 2012	Single	218	79	Yes	N/A	N/A	Moderate
Smith	2006	Departments of Surgery, Public Health Sciences, and Internal Medicine, University of Virginia, Charlottesville, Virginia, USA	USA	1995–2005	Single and bilateral	182	37	Yes	No	No	High
Thabut	2003	Service de Pneumologie et Re´animation Respiratoire, a Service de Chirurgie Thoracique et Vasculaire, b and Service d'Anatomopathologie, Ho^pital Beaujon, c Clichy, France	France	N/A	Single	28	28	Yes	N/A	N/A	High
Wei	2019	Transplant Center, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Jiangsu, China	China	January 2015–December 2017	Single and bilateral	109	109	Yes	Yes	Yes	High
Kreisel	2011	Division of Cardiothoracic Surgery, a Department of Surgery, and The Division of Pulmonary and Critical Care Medicine Department of Medicine, Washington University in St Louis, Mo, USA	USA	July 1988–January 2009	Single and bilateral	1,000	161	Yes	Yes	Yes	High
Schachna	2006	Johns Hopkins Hospital and the University of Pittsburgh Medical Center	USA	December 1989–June 2002	Single and bilateral	689	70	Yes	No	No	High
Neurohr	2010	Ludwig-Maximilians University, Munich, Germany	Germany	1997–2008	Single and bilateral	76	76	Yes	Yes	Yes	High
Keating	2009	Lung Transplant Service, Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia	Australia	1990–2008	Single and bilateral	585	90	Yes	Yes	Yes	High
Grossman	1989	Mount Sinai Hospital and the University of Toronto	Canada	November 1983–August 1989	Single	20	20	Yes	N/A	N/A	High

SLTx, single lung transplantation; BLTx, bilateral lung transplantation; N/A, not available.

Table 2 Single versus bilateral lung transplantation study characteristics

Study	De Oliveira *et al.*, 2012	Mason *et al.*, 2007	Meyers *et al.*, 2000	Wei *et al.*, 2018	Kreisel *et al.*, 2011	Rubin *et al.*, 2015	Thabut *et al.*, 2003	Neurohr *et al.*, 2010	Keating *et al.*, 2009	Grossman *et al.*, 1989
Total IPF patients	79	82	45	109	161	44	28	76	90	20
Males (%)										
Single	76.5	63.4	59	91.1	–	66	71.4	54.3	70	85
Double	70	–	54	96.7	–	–	–	60	–	–
Age (years)										
Single	56.8±7.2	52±11	48.8±9.1	62.6±7.8	–	57	49.3	53.74±1.15	52	48.4
Double	43.4±12.3	–	52.9±8.7	53.7±9.3	–	–	–	50.38±1.34	–	–
Transplant approach (n)										
Single	65	50	32	79	–	44	28	46	53	20
Double	14	32	13	30	–	–	–	30	37	–
1-year survival (mean) (%)										
Single	81.8	67	81	80.8	–	74	79.4	69.6	78	55
Double	73	81	77	66.7	–	–	–	79.5	68	–
3-year survival (mean) (%)							50			
Single	65.4	34	63	73.8	–	–		55.3	49	–
Double	60.2	55	54	63.3	–	–		74.2	50	–
5-year survival (mean) (%)										
Single	62.7	–	50	–	44.9	45	39	41.7	29	–
Double	53.5	–	38	–	58.9	–	–	66.8	50	–
10-year survival (mean) (%)										
Single	39	–	–	–	20.8	22	–	–	–	–
Double	42.8	–	–	–	36.7	–	–	–	–	–

Table 3 Reported mortality and morbidity

Study	Mortality		Additional factors	Comments
	SLTx	BLTx		
Algar	–	–	–	BLTx conferred higher observed perioperative and 1-year mortality rates compared to SLTx
Burton	n=228. 30-day perioperative mortality (7.9%) and 90-day perioperative mortality (9.7%)	n=112. 30-day perioperative mortality (3.6%) and 90-day perioperative mortality (10.8%)	–	This was not stratified by indication
De Oliveira	9.40%	7.70%	Length of hospital stay (days): SLTx, 15 (IQR, 10–25); BLTx, 24 (IQR, 16–48) Readmission <30 days: SLTx, 21 (25.9%); BLTx, 8 (26.7%) Length of ICU stay: SLTx, 4 (IQR, 3–9); BLTx, 8 (IQR, 6–24)	P values: mortality difference, 0.46; length of hospital stay, <0.01; readmission, 0.94; length of ICU stay <0.01
Mason	30-day perioperative mortality (6%)	30-day perioperative mortality (6%)	–	–
Meyers	In-hospital mortality 9.4% of 32 SLTx patients	In hospital mortality of 7.7% of 13 BLTx patients	Length of hospital stay (days): SLTx, 21 [13–32]; BLTx, 23 [15–39] Intensive care unit stay (days): SLTx, 5 [3–10]; BLTx, 6 [4–12] Mechanical ventilation (days): SLTx, 3 [2–9]; BLTx, 4 [3–18]	P values: difference in hospital mortality is not significant; length of hospital stay was 0.4; length of ICU stay 0.7; mechanical ventilation 0.5
Wei	–	–	Post-operative ICU days (mean ± SD): SLTx, 5.8±6.3; BLTx, 4.6±2.8 P value for: post-op length of stay was 0.014; post-op ICU stay 0.551 Post-operative length of stay in days (mean ± SD): 49.8±33.0; 33.1±25.2	30-day mortality was higher in BLTx but not statistically significant based on the Mantel Haenzel log rank test (P=0.131) The difference in the number of complications including primary graft dysfunction, pulmonary bacterial infection, anastomotic complications, heart failure, arrhythmia, acute kidney injury and malignant tumour was not significant between SLTx *vs.* BLTx
Neurohr	–	–	–	Increased 90-day mortality in SLTx without difference reaching statistical significance (P=0.06)

SLTx, single lung transplantation; BLTx, bilateral lung transplantation; IQR, interquartile range; ICU, intensive care unit; SD, standard deviation.

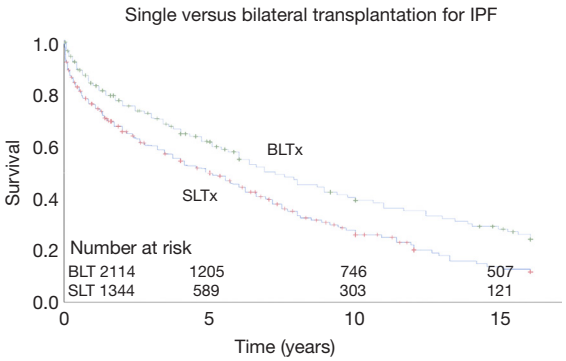

Figure 1 Kaplan-Meier survival analysis for single versus bilateral lung transplantation in IPF. IPF, idiopathic pulmonary fibrosis; BLTx, bilateral lung transplantation; SLTx, single lung transplantation.

in the quantitative synthesis (8-13). The search of 4,212 records yielded 17 studies which met inclusion criteria, with a total of 5,601 patients. The majority of studies (90%) were found to be of high quality according to the CNIHE tool, with the remainder as moderate quality. The majority of studies included in the final analysis were from European or United States centers, with the remainder being drawn from Asian, Canadian or Central American centers.

Survival—SLTx *vs.* BLTx

All curves digitized and aggregated in this study were unadjusted. Aggregated survival for SLTx at 5-, 10- and 15-year time intervals was 50%, 27.8% and 13.9%, respectively. Survival for BLTx was 57%, 35.3% and 24%, respectively (*Figure 1*).

Morbidity—SLTx *vs.* BLTx

Reported morbidity findings are detailed in *Table 3*. Three studies outlined morbidity data quantitatively (8,10,11). Length of hospital stay was statistically significant in two studies in favor of SLTx. Length of ICU stay was only significant in one study in favor of SLTx. All other reported complication rates were not statistically significant between the two surgical modalities.

Discussion

SLTx *vs.* BLTx: head-to-head studies

Out of the seven studies that present survival rates of BLTx *vs.* SLTx specifically for IPF patients, three of these studies establish improved survival in patients receiving SLTx. De Oliveira *et al.* demonstrate in 79 patients that survival is better in SLTx up to 5 years. The 1-, 3-, 5-year survival rates of SLTx *vs.* BLTx were 81.8% *vs.* 73%, 65.4% *vs.* 60.2%, 62.7% *vs.* 53.5% (P=0.68), respectively (8). The 10-year survival rate was 39% *vs.* 42.8%, respectively. Meyers *et al.* demonstrate survival rates of SLTx *vs.* BLTx being 81% *vs.* 77%, 63% *vs.* 54% and 50% *vs.* 38% for the 1-, 3- and 5-year endpoints (P=0.42) (10). These rates were established in 32 SLTx and 13 sequential BLTx; no difference in in-hospital mortality between SLTx (9.40%) and BLTx (7.70%) was noted.

The most recent single center study by Wei *et al.* (11) demonstrated survival rates in a cohort of 109 patients of 80.8% *vs.* 66.7% and 73.8% *vs.* 63.3% for SLTx *vs.* BLTx, at 1- and 2-year survival, respectively (P=0.13). When the survival rates of SLTx *vs.* BLTx in IPF patients are further stratified by age <60 and age >60, SLTx had significantly greater survival in the over-60 age-group (P=0.008).

The other studies align with the findings of the UNOS Registry and ISHLT registry, which outline that BLTx has improved survival for IPF patients over SLTx (14-22). In their cohort of 469 patients, 82 of which had IPF, Mason *et al.* found that patients receiving BLTx had better risk-unadjusted survival than those receiving SLTx, with 1-year survival at 81% and 67%, and 5-year survival at 55% and 34%, respectively. BLTx survival rates were similar to those for non-IPF indications (9). Following matched analysis, the benefit of BLTx over SLTx was not maintained, with perioperative mortality and short-term postoperative mortality both at 6% (10).

Neurohr *et al.* found a significant survival benefit of BLTx over SLTx in their cohort of 76 patients at 1-year and in overall survival (P=0.026) (13). Although SLTx had a higher percentage of acute rejection (35.6%) compared to BLTx (29.6%), this was not statistically significant; however, there was a significantly higher number of deaths in SLTx compared to BLTx as a result of the development of bronchiolitis obliterans. Kreisel *et al.* demonstrate a higher survival rate in BLTx for the 5- and 10-year mark (23). Interestingly, Kreisel extracted data from 1988 to 2009, including the data used in the Meyers *et al.* (10) study from the same institution (1988–1998); however, it appears that the data from the extended 10-year follow-up reversed the survival benefit that SLTx had over BLTx found by Meyers *et al.* (10) One reason for this finding may be improved surgical technique of BLTx within the last ten

years, or alternatively, BLTx may in fact have improved long-term survival benefits after the initial convalescence period. Keating *et al.* (12) demonstrated a survival rate pattern similar to that of De Oliveira *et al.* (8) up to the 3-year mark, the survival rate was higher for SLTx compared to BLTx; however, at the 5-year mark, BLTx conferred a higher survival rate of 50% compared to SLTx at 29%.

Six studies outlined findings for IPF patients undergoing transplantation but did not stratify for surgical approach with quantitative analysis. For instance, Algar *et al.* found that survival did not differ between SLTx and BLTx at long-term follow-up, noting that whilst BLTx conferred increased mortality in the short-term, the long-term survival benefit offset the initial mortality (24). A number of studies compared SLTx and BLTx, but did not differentiate for etiology. de Perrot *et al.* (15) found in their cohort of 501 patients, long-term survival was higher in patients receiving BLTx *vs.* patients receiving SLTx (P=0.07); when separately analyzing for etiology (i.e., cystic fibrosis, chronic obstructive pulmonary disease, IPF, etc.) this effect disappeared; however, no data were presented in-text.

Database analysis of IPF patient outcomes

Villavicencio *et al.* (25) presents the most recent data comparing survival outcomes of SLTx *vs.* BLTx in IPF recipients. This study includes 9,191 lung transplant recipients with IPF from 1987 to 2015. They have demonstrated that BLTx has improved survival outcomes in IPF patients compared to SLTx across all lung allocation scores and additionally when adjusted for age, excepting those exceeding 70 years (P<0.001). The International Society for Heart and Lung Transplantation Registry (ISHLT) have collated the survival outcomes of SLTx *vs.* BLTx in IPF patients and presented their data on transplant recipients with IPF from January 1990 to June 2016. Kaplan-Meier curves were produced from 1,043 SLTx patients with IPF and 1,936 BLTx patients with IPF. BLTx was shown to have improved survival outcomes compared to SLTx at each year from the 1st year to the 16th year (P<0.0001).

Limitations

To the authors' knowledge, this is the most recent and thorough systematic review of the literature comparing SLTx to BLTx in the context of IPF and the only review to incorporate an aggregation of survival data across single- and multi-center studies and registries.

However, are several limitations with respect to the present review. The number of single- and multi-center studies analyzing the survival outcomes of IPF patients with clear stratification of which patients received SLTx and BLTx was low, with only 17 studies meeting the final inclusion criteria. The majority of these studies provided survival outcomes of IPF recipients compared to other transplant recipients of varying indications, and/or survival outcomes comparing SLTx *vs.* BLTx in all transplant recipients. Only six studies—with one potentially replicated dataset—were able to stratify survival outcomes by SLTx *vs.* BLTx specifically for IPF patients.

The limited number of studies with survival outcomes and stratification between surgical approaches prevented meaningful quantitative analysis of the single- and multi-center studies, requiring an aggregation of the findings from large registries. It is likely that there is a degree of patient overlap, as patients within the registries would have been drawn from these single- and multi-center studies; however, using the methods of Sampson *et al.* who present techniques for identifying cohort overlap, this was mitigated as far as possible (26). Although registry studies are extremely useful (i.e., they benefit from large numbers that allow for sound statistical analysis), it is of note that they include and collate data from a wide array of centers, with surgeons of variable expertise, using different surgical protocols and incomplete patient data. Hence, in centers which have always preferred one technique over another become highly proficient in that technique; it would not be surprising to note outcomes that go against the findings from registry data.

The primary constraint of this review is that the single- and multi-center studies identified have often yielded conflicting results, with largely uninterpretable or sparsely reported data (from a meta-analytical perspective) supporting their recommendations; often, no differentiation is made between the indications for transplantation (e.g., cystic fibrosis, IPF, etc.) or which patients are receiving what type of intervention (i.e., SLTx or BLTx). Further, very limited morbidity data were reported, with only three studies comparing SLTx and BLTx for IPF providing quantitative results (*Table 3*). Often, authors would make comments in their discussions noting that one technique was more favorable in terms of survival or complications, but with no analysis to substantiate the claims.

In order to carry out definitive analysis, it is critical that patients with different pathologies are not grouped and

vice versa for transplantation technique, as the level of heterogeneity strongly calls into question the validity of the findings. It is imperative that for future analysis of survival outcomes, clinicians and researchers provide datasets which have been stratified appropriately for etiology as well as for surgical approach.

Conclusions

Whilst a number of studies present conflicting results with respect to short-term transplantation outcomes, the consensus is that BLTx confers improved long-term survival over that of SLTx, with large-scale registries supporting the findings from single- and multi-center studies. Through an aggregation of the present survival data, this meta-analysis identified improved survival in patients receiving BLTx versus those receiving SLTx at all time intervals.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

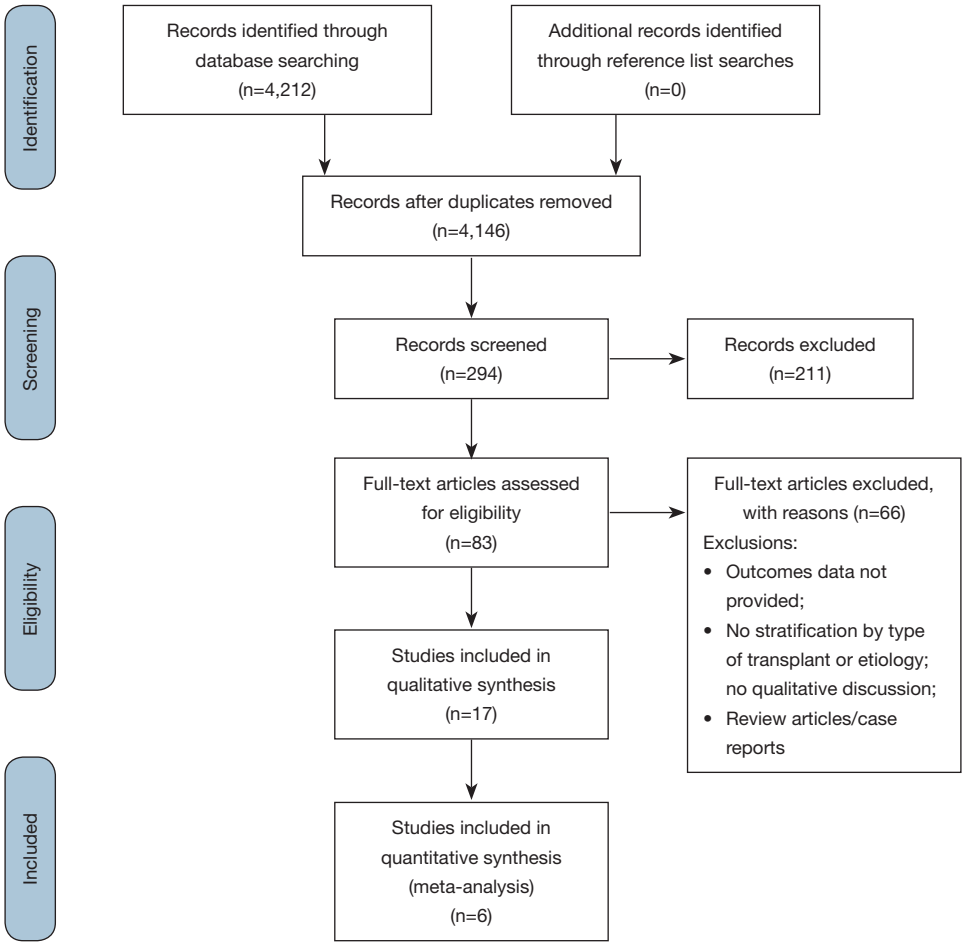

Figure S1 PRISMA flow chart detailing the literature search process for mid- to late-term outcomes of single *vs*. bilateral lung transplantation in the setting of pulmonary fibrosis.

Criteria No.	Criterion definition
1	Is the hypothesis/aim/objective of the study stated in the abstract, introduction, or methods section?
2	Are the characteristics of the patients included in the study clearly described?
3	Were the cases collected in more than one center?
4	Are the eligibility criteria (inclusion and exclusion criteria) explicit and appropriate?
5	Were patients recruited consecutively?
6	Did patients enter the study at a similar point in the disease?
7	Did the authors describe the intervention?
8	In addition to intervention, did the patients receive any co-interventions?
9	Was loss to follow-up reported?
10	Are outcomes (primary, secondary) clearly defined in the introduction or methodology section?
11	Did the authors use accurate (standard, valid, reliable) objective methods to measure the outcomes?
12	Were outcomes assessed before and after intervention?
13	Was the length of follow-up clearly described/reported?
14	Were the statistical tests used to assess the primary outcomes appropriate?
15	Does the study provide estimates of the random variability in the data for the primary outcomes (e.g., standard error, standard deviation, confidence intervals)?
16	Was the analysis of outcomes based on intention to treat?
17	Are adverse events that may be a consequence of the intervention reported?
18	Are the conclusions of the study supported by results?
19	Is there a competing interest statement about the type and source of support received for the study or about the relationship of the author(s) or other contributors with the manufacturer of the technology?

Figure S2 Quality appraisal criteria.

Database	Search terms	Results
PubMed Central	(“lung transplantation” OR “lung transplant”) AND (“single” OR “unilateral” OR “bilateral” OR “double”) AND (“pulmonary fibrosis” OR “idiopathic pulmonary fibrosis”)	556

Figure S3 Search strategy supplementary.