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Patient-important outcomes in lung transplantation: a systematic review

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Abbreviations

6MWD	6-Minute Walk Distance
CLAD	Chronic lung allograft dysfunction
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
HADS	Hospital Anxiety and Depression Scale
IQR	Interquartile range
LTx	Lung transplantation
MRC	Medical Research Council
PIO	Patient important outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient reported outcome
PROM	Patient reported outcome measurement
SD	Standard deviation
SF-36	Short-form 36 health survey
SGRQ	Saint-Georges Respiratory Questionnaire
SPPB	Short physical performance battery

Abstract (224 wds)

Background

Patient-important outcomes (PIOs) have emerged in respiratory medicine, in order to place the patient at the center of research. Mortality is a debated PIO in lung transplantation (LTx). The use of PIO in this specific setting has never been studied. We aimed to systematically review the use of PIOs in LTx research.

Methods

MEDLINE, Cochrane Library and Embase databases were searched to include prospective studies published in 2019, involving adult LTx recipients. We excluded articles reporting non-prognostic studies, letters, reviews, commentaries, or case reports. PIOs considered were mortality, pain, physical function, pulmonary, gastrointestinal, neuropsychological, cardiac, sleep or sexual symptoms and quality of life. This systematic review was prospectively registered in the PROSPERO register (CRD42020163425).

Results

Among 1048 references retrieved, 51 were finally included in the analysis. In total, 26 (51%) studies investigated at least one PIO, as a primary outcome in 12 (23.5%) and secondary outcome in 21 (41.2%). In 15 (29.4%) studies, mortality was the most frequently reported PIO; 11 (21.5%) studies evaluated at least one PIO other than mortality, quality of life being this PIO in 6.

Conclusions

PIOs were described in half of prospective articles dealing with adult LTx recipients published in 2019. Outcomes other than mortality were insufficiently considered. A core outcome set of PIOs in LTx should be developed with patient input to guide future research in LTx.

Key Words: lung transplantation, patient important outcomes, systematic review

Word count: 2442 words

1. Introduction

Patient-important outcomes (PIOs) have gained attention in respiratory medicine and research, [1]. These outcomes are defined as “a characteristic or variable that reflect how a patient feels, functions or survives” [2,3]. The interest in PIOs has emerged for several years in various medical fields [3–6], including the transplantation field [7–9]. PIOs are to be distinguished from patient reported outcomes (PROs), which are used to capture the patient’s views about his or her health status; they should also be distinguished from patient reported outcomes measurements (PROMs) which are self-reported instruments, scales, or single item measures used to assess the PRO concept as perceived by the patient, obtained by directly asking the patient to self-report.

Lung transplantation (LTx) offers many patients end-stage lung disease improvements in survival and quality of life. An undisputable survival benefit of LTx has been demonstrated for interstitial lung disease [10,11], idiopathic pulmonary hypertension [12], and was true for cystic fibrosis patients [10,13] before the advent of new therapies [14]. In patients with chronic obstructive pulmonary disease (COPD), this survival benefit is more controversial [10] and depends on the underlying disease severity [15,16]. Furthermore, patients with chronic obstructive pulmonary disease seem to gain quality of life from LTx [17]. LTx carries its own symptomatic burden, whether from immunological complications or immunosuppression side effects, with increased risk of infection, cardiovascular disease or cancer. This set of complications might also impair participation in daily life activities.

Hence, PIOs are of particular interest in LTx. Moreover, LTx physicians and researchers are aware of the limited interest of assessing mortality in this field [18]. Therefore, we

wondered about the use of PIOs in LTx research. The main aim of this systematic review was to investigate whether recently published LTx research (2019) assessed PIOs.

2. Material and Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [19] for this systematic review. The protocol of this systematic review was prospectively registered at PROSPERO (CRD42020163425).

2.1. Search strategy and study selection

MEDLINE via PubMed, Cochrane Library and Embase databases were searched on January 27, 2020. The keywords included in the search strategy were “lung transplantation”, “heart-lung transplantation” (see Supplementary Material for details on search equations). Articles were eligible if they were written in French, English or Spanish; were published in 2019; had a prospective design; and involved adult LTx recipients.

Among two senior respiratory disease physicians (GW and JM) and a methodologist (NG), two authors independently double screened all titles and abstracts to identify articles meeting eligibility criteria and requiring full-text reading. Disagreements were resolved by discussion and consensus or with a third author (one of the respiratory physicians or the methodologist) in case of persistent disagreement.

We excluded articles reporting non-prognostic studies (e.g., studies assessing a diagnostic strategy or performance, a pathophysiological hypothesis) as well as letters, abstracts, commentaries, reviews and case reports considered “other study types”. Letters and abstracts were excluded as some studies’ outcomes were likely to be missing and not reported in such small formats.

2.2. Data extraction

The data extraction form was designed from previous literature review and discussion among co-authors. The following data were independently extracted from the selected articles and collected via the REDCap data-capture tool [20]: general data (journal and its 2019 impact factor [21]), geographical origin of the first author, mono- or multicentric study); methods (aim of the study, interventional design, type of intervention tested, randomization; inclusion restricted to some ages, type of underlying disease or type of transplantation), length of the recruitment period, number of included participants, main demographical characteristics, median length of follow-up, number and characteristics of the outcomes, type of PIO.

Outcomes were classified as “PIOs” or “not PIOs” based on published literature on PIOs in other medical fields [1–3,22] and by consensus between authors. A methodologist (NG) and two respiratory physicians trained in LTx (GW and JM) *a priori* identified outcomes considered PIOs among the following: mortality, pain, pulmonary symptoms (i.e., dyspnea, tracheostomy, cough), gastrointestinal symptoms (i.e., diarrhea, gastroparesis, gastroesophageal reflux, constipation), physical function (i.e., fatigue, walking function, return to work), neuropsychological symptoms (i.e., anxiety, depression, psychological symptoms), cardiac symptoms, sleep symptoms, sexual symptoms, quality of life, or other symptoms. Graft failure, defined as death or re-transplantation, was considered as a PIO, while chronic lung allograft dysfunction [23] (CLAD) was not, but classified as a functional measure rather than a clinical symptom.

2.3. *Statistical analysis*

Continuous variables are described with mean (standard deviation [SD]) or median [interquartile range (IQR)] according to distribution. Categorical variables are described with frequency (percentage). Statistical analysis was performed with R 3.2.0 (2015 The R Foundation for Statistical Computing).

3. Results

3.1. Selection of articles

The search retrieved 1048 articles. After excluding duplicates, triplicates and 711 references based on the title or abstract, 148 full articles were selected. Finally, 51 articles were included in the analysis (Figure 1). The included references are detailed in the Supplementary material Table A.1.

3.2. Characteristics of the 51 included articles

Main characteristics of articles are summarized in Table 1. Briefly, articles originated from 33 different journals, with 7 published in a journal with a 2019 impact factor above 6. The first author originated from Europe for 26/51 (51.0%) articles, North America for 16 (31.4%), Oceania for 5 (9.8%), and Asia for 4 (7.8%). Twelve (23.5%) studies were multicentric.

Among the 51 included studies, 20 (39.2%) were interventional, including 12 (60%) randomized controlled trials. The median number of included patients was 46 [IQR 24-115]. For 19 studies, the median of the mean age was 51.0 [46.3-55.8] years, and for 5, the median of the median age was 55.0 [53.0-57.0] years. The median of length follow-up was reported in 17 studies and was less than 1 month for 2 (11.8%), 1 month to 1 year for 6 (35.3%) and more than 1 year for 9 (52.9%).

3.3. PIOs in the included articles

The 51 studies evaluated a median of 3 [IQR 2–8.5] outcomes; 9 (17.6%) reported only a single outcome. In total, 26 studies (51%) assessed at least one PIO, 12 as a primary outcome and 21 as a secondary outcome (Table 2). Seven (13.7%) studies assessed at least 2 PIOs.

3.3.1. Mortality

Mortality was assessed in 15/51 (29.4%) studies, representing 57.7% studies assessing at least one PIO. Mortality was assessed as a primary outcome (n=4) and/or secondary outcome (n=13). The time point for mortality assessment was reported in 15 studies and corresponded to 30 days for 2 (13.3%), 6 months for 2 (13.3%), 1 year for 7 (46.7%), 5 years for 4 (26.7%) and another time point for 3 (20%). In four (26.7%) studies, mortality was assessed at more than one time point (two studies assessed mortality at two time points and two assessed mortality at three time points).

3.3.2. Other PIOs

Eleven of 26 (42.3%) studies assessed at least one PIO other than mortality, as a primary outcome (n=8) and/or secondary outcome (n=8). These PIOs were physical function (n=7), quality of life (n=6), pain (n=2), pulmonary symptoms (n=1), or neuropsychological symptoms (n=4) (Table 2).

3.3.3. Quality of life outcomes

In the six studies assessing quality of life as a PIO, time of assessment was 30 days in one study, 3 months in two studies, 6 months in two studies, 1 year in one study and another time point in two studies. In one additional study, the assessment time point was not reported. Quality of life was assessed more than once in three studies. The scales used to assess quality of life are detailed in Table 3. A generic tool was used in three studies (Short-form 36 health survey, n=2; EUROQOL EQ-5D, n=1), and a respiratory-specific instrument in two studies (St. George's Respiratory Questionnaire, n=2; Chronic Respiratory

Questionnaire, n=2; Leicester Cough Questionnaire, n=1). No study used a tool specifically designed for LTx recipients [24].

3.4. Non-PIO primary outcomes

When a PIO was not studied as a primary outcome (n=14/26 studies), the primary outcome was the occurrence of CLAD (n=4); primary graft dysfunction (n=2); infection episodes (n=3); a physiological outcome, such as forced expiratory volume in 1 sec (n=3); a biological measure (n=1); and digestive complications after LTx (n=1).

4. Discussion

This systematic review of 51 prospective studies published in 2019 in the field of LTx revealed 1) at least one PIO assessed in half of the included studies (n=26; 51%); 2) mortality as the PIO the most frequently PIO assessed, in one third of all articles (n=15; 29.4%) dealing with LTx; and 3) quality of life rarely assessed (n=6), with other PIOs assessed encompassing physical, pulmonary or neuropsychological symptoms or pain.

To date, our systematic review is the only one to investigate the use of PIOs in LTx-related research. Therefore, we used the definition of PIOs derived from other research areas, whether respiratory research [3,5] or not [2,6]. Obviously, mortality is a key PIO, even more so when dealing with a life-saving treatment such as LTx. Increasing the life years is clearly an objective, but assessing the effects of LTx on health-related quality of life or physical functioning is likely important for both LTx professionals [18] and patients. Nevertheless, in a Delphi survey in kidney transplantation, mortality was not considered important for kidney transplant recipients and their caregivers or for healthcare professionals [25].

In this systematic review, we classified outcomes as “PIOs” or “non-PIOs”. We tried to follow the spirit of the PIO definition by focusing on how the patient feels, functions or survives [2,3]. However, our interpretation of the original definition might be imperfect. For instance, we classified “graft failure” as a PIO. Indeed, for LTx recipients, graft loss might be of crucial importance because it implies either a re-do LTx, with its own morbidity and mortality [26], or death. Conversely, we did not include some outcomes in the PIO set (e.g., length of hospital stay, renal dysfunction or occurrence of cancer).

Unlike in other research fields [4,27], LTx research lacks a core outcome set for PIO. As an example, the Core Outcome Measures in Effectiveness Trials Initiative [28] does not identify any study aiming at defining a core outcome set specifically designed for LTx, whereas such effort has already been made for end-stage, or chronic, kidney disease, kidney transplantation, chronic liver diseases and liver transplantation; or in other fields of respiratory diseases, such as lung cancer, asthma, COPD, interstitial lung diseases, or cystic fibrosis. This systematic review is a call for developing a core outcome set in the field. A core outcome set is a consensus-based standardized set of outcomes that should be reported, as a minimum, in all clinical trials in a specific area of health [29]. The patient's perspective is a prerequisite for including PIOs in a core outcome set definition in LTx. The Delphi methodology is an adequate and validated methodology [22,25,27] to elaborate such a core outcome set reflecting patients', caregivers' and health professionals' perspectives and priorities for improving the relevance and reliability of LTx studies.

We focused on PIOs, not just PROs or PROMs. Indeed, some outcomes might be important for the patient but assessed by the investigators. Mortality is a good example of a PIO which obviously cannot be a PRO. Conversely, PROs might be far from important to the patient: for example, "adherence to medications", among the top four PROs reported in kidney transplant research [30], may not seem important for a transplant recipient, although associated with allograft and patient survival or the occurrence of chronic allograft dysfunction in LTx [31].

In a systematic review of all kinds of solid organ transplantation [32], Brett et al. identified the use of 317 quality metrics for measuring healthcare quality in 76 articles. These metrics

could be condensed into 140; among those, 114 domains of quality metrics could be studied. Patient-centered domains accounted for nine quality metrics, with four being PROs, four patient-reported experience measures, and one patient-centered but measured by a healthcare provider. In kidney transplantation, a systematic review of 397 randomized trials [30] identified “mortality”, “graft survival”, “infection” and “malignancy” as the top four reported outcomes. In this systematic review, PROs were reported in 15% of trials [30]. Unfortunately, the authors did not identify those that were actually PIOs. A review of PROs in face-transplant recipients is ongoing (CRD42020137164). The inventory of PIOs for other organs is still missing. **Moreover, the study of PROMs, the measurement tools used to evaluate PROs, should be a subsequent step of this systematic review.**

The implication of patients in defining PIOs is critical. In a Delphi survey involving kidney transplant recipients, their caregivers and healthcare professionals [25], 11 outcome domains were rated higher by patients and caregivers than healthcare professionals. Thus, the patients’ viewpoint must be taken into account to define PIOs as a preliminary step in developing a relevant core outcome set for kidney transplantation research. This step is mandatory in LTx research, **and is presently ongoing, with the help of expert-patients, LTx recipients and their relatives.**

We acknowledge a few limitations in our systematic review. First, we focused on articles published up to the end of 2019. The aim of the research was to make an inventory of recent transplantation research and was therefore deliberately focused on one-year period of time. This period was restricted for reasons of feasibility. However, our results are not likely biased for research published in other years. Such a change is unlikely in this short timeline,

furthermore because our review is the only one to date to point out this caveat in PIOs in LTx research. Second, we used our own definition of PIOs. Obviously, this classification stems from healthcare workers and researchers and not patients, which renders their “PIO” qualification questionable. Patients’ viewpoints must be taken into account, in a Delphi survey for instance. We found it necessary to perform this review of the current literature as a first step, before establishing a core outcome set. Nevertheless, our classification derives from other research fields [1,5,2,6,3]; LTx recipients may be compared fairly with surveyed patients of other fields. This systematic review followed PRISMA guidelines but the risk of bias tool was not assessed. The ambition of this research was not to carry out a meta-analysis, but to take a comprehensive inventory, as a first step, in order to support the development of a core-outcome set.

5. Conclusion

This systematic review showed that in LTx studies, PIOs were assessed in more than half of prospective studies in adult LTx recipients, however, outcomes other than mortality were only included considered in 21.5% of the studies included. Defining a core outcome set that includes PIOs is critical in LTx research. The participation of patients, **their families** and their caregivers will be essential to develop such an outcome set.

Investigators of the Bichat Lung Transplant Group

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Author contributions

GW, NG and JM designed the project and collected data; NG performed the analysis; GW, NG and JM drafted the manuscript. AR, AT-D, VB, CG, PM, PhM, YC, HM and SG participated in the data analysis, commented on the manuscript and contributed to the final manuscript.

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Figure

Figure 1. Study flow diagram. The search retrieved 1048 articles. Among those, 183 were duplicates, and three were triplicates. After exclusion of 709 references on title or abstract, 150 full articles were selected. Finally, 51 articles were included in the analysis.

Tables

Table 1. Main characteristics of studies of lung transplantation (LTx) recipients with no patient-important outcomes (PIOs) and with PIOs included in the analysis.

	All studies n= 51	Studies with no PIOs n=25	Studies with at least one PIO n=26
Journals, n	33	16	22
Journals with impact factor > 6	7	5	2
Geographical origin, n (%)			
North America	16 (31.4)	4 (16.0)	12 (46.2)
Asia	4 (7.8)	2 (8.0)	2 (7.7)
Europe	26 (51.0)	16 (64.0)	10 (38.5)
Oceania	5 (9.8)	3 (12.0)	2 (7.7)
Observational studies, n (%)	31 (60.8)	18 (72.0)	13 (50.0)
Comparative study, n (%)	20 (39.2)	14 (56.0)	6 (23.1)
Interventional studies, n (%)	20 (39.2)	7 (28.0)	13 (50.0)
Randomized controlled trials	12 (23.5)	5 (20.0)	7 (26.9)
Single center, n (%)	39 (76.5)	20 (80.0)	19 (73.1)
Multicenter, n (%)	12 (23.5)	5 (20.0)	7 (26.9)
Exclusion criteria, n (%)			
Age	28 (54.9)	11 (44.0)	17 (65.4)
Underlying disease	4 (7.8)	1 (4.0)	3 (11.5)
Type of lung transplantation	11 (21.6)	5 (20.0)	6 (23.1)
Infectious agent	7 (13.7)	2 (8.0)	5 (19.2)
Length of recruitment, months, median (IQR)	31.5 [14.5-48.5]	30.0 [12-46.5]	33.0 [17-59.5]
Included participants, median (IQR)	46 [24-115]	38 [18-105]	48 [28-116]

PIO: Patient important outcome; IQR: interquartile range

Table 2. Primary and secondary outcomes of studies assessing at least one PIO (n=26 articles).

PIO as a primary outcome (n=12)	
Mortality	4
Pain	1
Quality of life	2
Physical function	4
Neuropsychological symptoms	1
PIO as a secondary outcome (n=21)	
Mortality	13
Pain	1
Physical function	3
Quality of life	4
Pulmonary symptoms	1
Neuropsychological symptoms	3

PIO: Patient important outcome

Table 3. Details of PIOs other than mortality in articles published in 2019 (n=11).

Title	Author, Journal	Primary outcome and time of assessment	Instrument of the primary outcome	Secondary outcomes, and time of assessment	Instruments of the secondary outcomes	Number of included patients
Influence of Sleep-Disordered Breathing on Quality of Life and Exercise Capacity in Lung Transplant Recipients	Kruse et al. <i>Adv Exp Med Biol</i>	Quality of life/ not detailed	SF-36	Physical function/ not detailed	6MWD Cardiopulmonary exercise testing	53
Impairments in Postural Control and Retest Reliability of Dynamic Posturographic Measures After Lung Transplantation	Ebenbichler et al. <i>Am J Phys Med Rehabil</i>	Physical function/ 2 months after pulmonary rehabilitation	Sensory Organisation Test	Physical function / 2 months after pulmonary rehabilitation	Motor Control Test Limits of Stability Test 6MWD	50
Discharge frailty following lung transplantation	Courtwright et al. <i>Clin Transplant</i>	Physical function / at discharge	SPPB	Physical function / at discharge	SPPB	111
The Efficacy of Outpatient Pulmonary Rehabilitation After Bilateral Lung Transplantation	Candemir et al. <i>J Cardiopulm Rehabil Prev</i>	Physical function/ after pulmonary rehabilitation	Incremental and endurance shuttle walk, handgrip	Respiratory function/ after pulmonary rehabilitation Neuropsychological function/ after pulmonary rehabilitation Quality of life / after pulmonary rehabilitation	Dyspnea MRC score HADS SGRQ CRQ	23
Health-related quality of life and stress-related post-transplant trajectories of lung transplant recipients: A three-year follow-up of the Swiss Transplant Cohort Study	Barbara B et al. <i>Swiss Med Wkly</i>	Quality of life/ 3 years after LTx	EuroQuol (EQ-5D)	Psychological distress/ 3 years after LTx	The Symptom Checklist	27
A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation	Gottlieb et al. <i>Am J T</i>	Not a PIO		Quality of life / 1 year after transplantation	SF-36	130
Improvements in functional and	Andrianopoulos et	Not a PIO		Neuropsychological	HADS	24

cognitive status following short-term pulmonary rehabilitation in COPD lung	al. <i>ERJ Open Res</i>			function/ after a pulmonary rehabilitation program Quality of life/ after a pulmonary rehabilitation program	CRQ	
Dornase alfa during lower respiratory tract infection post-lung transplantation: a randomized controlled trial	Tarrant et al. <i>Transplant International</i>	Not a PIO		Quality of life / 1 month, 3 months	Leicester Cough Questionnaire SGRQ	32
Frailty trajectories in adult lung transplantation: A cohort study	Venado et al. <i>J Heart Lung Transplant.</i>	Physical function/ 6 months after LTx	Short physical performance battery			
Home-Based Computerized Cognitive Training for Postoperative Cognitive Dysfunction After Lung Transplantation in Elderly Population: a Randomized Controlled Trial	Song et al. <i>J of Nerv and Ment Dis</i>	Neuropsychological function	Digit-Span Tests Verbal Fluency test Trail Making test Digit Symbol test Word recognition test			
Chronic pain after bilateral thoracotomy in lung transplant patients	Petersen et al. <i>Scand J Pain</i> 2019	Pain / 6 to 12 months after LTx	Neuropathic Pain Symptom Inventory Pain catastrophic scale	Allodynia Hyperphenomena		

6MWD: 6-Minute Walk Distance; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; LTx: Lung Transplantation; MRC: Medical Research Council; PIO: patient-important outcome; SF-36: Short-form 36 health survey ; SGRQ: Saint-Georges Respiratory Questionnaire; SPPB: Short physical performance battery.

Identification

Records identified (n=1048)
EMBASE = 618
COCHRANE = 211
MEDLINE = 219

Screening

Duplicates (n=183)
Triplicates (n=3)

Records screened
(n=859)

Records excluded based on title and abstract (n=711)

Not study type of interest, n=333
Not pulmonary transplanted subjects, n=189
Published prior to 2019, n=129
Not adult subjects, n=26
Not a prognostic study, n=22
Not English, French, Spanish language, n=12

Eligibility

Full text articles
assessed for eligibility
(n=148)

Full text articles excluded (n=97)

Not prospective studies, n= 26
Not study type of interest, n=57
Not pulmonary transplanted subjects, n=13
Not a prognostic study, n=1

Included

Full text articles
included in the analysis
(n=51)

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Pain	1
Physical function	3
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Pulmonary symptoms	1
Neuropsychological symptoms	3

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Improvements in functional and cognitive status following short-term pulmonary rehabilitation in COPD lung	Andrianopoulos et al. <i>ERJ Open Res</i>	Not a PIO		Neuropsychological function/ after a pulmonary rehabilitation program Quality of life/ after a pulmonary rehabilitation program	HADS CRQ	24
Dornase alfa during lower respiratory tract infection post-lung transplantation: a randomized controlled trial	Tarrant et al. <i>Transplant International</i>	Not a PIO		Quality of life / 1 month, 3 months	Leicester Cough Questionnaire SGRQ	32
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Home-Based Computerized Cognitive Training for Postoperative Cognitive	Song et al. <i>J of Nerv and Ment Dis</i>	Neuropsychological function	Digit-Span Tests Verbal Fluency test Trail Making test			

Dysfunction After Lung Transplantation in Elderly Population: a Randomized Controlled Trial			Digit Symbol test Word recognition test			
Chronic pain after bilateral thoracotomy in lung transplant patients	Petersen et al. <i>Scand J Pain</i> 2019	Pain / 6 to 12 months after LTx	Neuropathic Pain Symptom Inventory Pain catastrophic scale	Allodynia Hyperphenomena		

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