Review Article

Outcomes after lung transplantation

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Abstract: With more than 50,000 procedures having been performed worldwide, lung transplantation (LT) has become the standard of care for patients with end-stage chronic respiratory failure. LT leads to dramatic improvements in both pulmonary function and health related quality of life. Survival after LTs has steadily improved, but still lags far behind that observed after other solid organ transplantations, as evidenced by a median survival rate that currently stands at 5.8 years. Because of these disappointing results, the ability of LT to expand survival has been questioned. However, the most recent studies, based on sophisticated statistical modeling suggest that LT confers a survival benefit to the vast majority of lung transplant recipients. Chronic lung allograft dysfunction (CLAD) that develops in about 50% of recipients 5 years after LT is a major impediment to lung transplant survival. A better understanding of the mechanisms underlying CLAD could allow for better post-transplant survival.

Keywords: Lung transplantation (LT); outcome; survival; quality of life

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Introduction

Although lung transplantation (LT) has become an invaluable approach for the treatment of end-stage respiratory disease, survival after the procedure is not yet as good as that after other solid-organ transplants (1). Because of this, patient survival has been the primary outcome measurement in most studies. Other indicators of outcomes like pulmonary function or quality of life have also been studied.

Survival

To date, the registry of the International Society for Heart and Lung Transplantation (ISHLT) has accrued data on more than 55,000 adult patients who received a LT in about 250 lung transplant centers from the early 90s (2). This registry provides invaluable information regarding lung transplant activity and outcome.

According to the 2016 report of this registry, adult patients who underwent primary LT between January 1990 and June 2014 had a median survival of 5.8 years, with unadjusted survival rates of 89% at 3 months, 80% at 1-year, 65% at 3 years, 54% at 5 years and 32% at 10 years (2). Post-transplant survival has improved over time with a median survival of 4.2 years in the 1990–1998 era compared to 6.1 years in the 1999–2008 era. It is remarkable that post-transplant survival continued to increase in spite of considerable change in patients' characteristics and severity at the time of transplant. In the US for instance, between 2002 and 2014, the proportion of patients aged more than 65 years old rose from 4.5% to 28.7%, the proportion of patients being in the ICU rose from 4.2% to 15.5%, the proportion of patients under mechanical ventilation doubled, and the proportion of patients under ECMO reached 2.2% (3,4). The same shift in patient case-mix has been observed in European countries with the development of organ allocation in high emergency (5,6). Despite

these improvements, survival outcomes for LT recipients remain inferior to those achieved after other solid-organ transplant procedures. For instance, the median survival after heart transplantation in the same registry is around 12 years (2).

A closer look at the LT survival curves shows that there is a large drop in early survival in the first months following LT followed by a slow attrition over time. Improvements in the management of patients in the early post-operative period led to a reduction in early mortality over the years. To this regard, some centers report on 1-year mortality well below 10% (7). However, the attrition rate after the first year, which is mainly attributable to chronic lung allograft dysfunction (CLAD) that develops in 50% of grafts at 5 years, remains largely unchanged (2).

One of the main determinants of LT outcome is the underlying disease, with a median survival of 8.9 years for cystic fibrosis (CF) patients, 6.7 years for chronic obstructive pulmonary disease (COPD) with alpha-1 antitrypsin deficiency (AATD), 5.6 years for COPD without AATD, 4.8 years for idiopathic interstitial pneumonia and 2.8 years for re-transplantation. These differences seem to be more related to differences in patients' characteristics at the time of LT than to the underlying disease by itself. For instance, patients with COPD are older, more frequently tobacco smokers and have more comorbidities than patients with CF.

Other prognostic factors are related either to the recipient (gender, age, 6 min walking distance, patient under mechanical ventilation, dialysis or hospitalized in ICU), the donor (diabetes, age, gas exchange at the time of harvest, cause of death), the donor/recipient interaction (number of HLA mismatches, CMV or gender mismatch), the surgical approach (single *vs.* bilateral) and the center volume (2,8). The role of other factors like size mismatch or graft ischemic time is more debated (9-11).

Although most of these factors are not alterable, the surgical approach is. The choice between single and bilateral LT has been debated for a long time. Although the vast majority of patients with suppurative lung diseases (including CF) receive a bilateral LT (BLT), the choice of procedure remains a matter a debate for patients with COPD and IPF. Unadjusted survival rates are in favor of BLT with a median survival of 7.3 years compared to 4.6 years for single LT (SLT) recipients according to the ISHLT registry (12). However, SLT is in general proposed to older and more frail patients and analyses adjusted for patients characteristics showed conflicting results (13-15). In the absence of randomized controlled trial it is difficult to draw definitive conclusions, and the evidence comes mainly from the analysis of large registries. In COPD patients, Thabut *et al.* found a better survival after BLT especially in patients aged more than 60 years old (14). Schaffer *et al.*, using more recent data but closely related methods, did not find a statistically significant difference between both surgical approaches in this indication (15). In IPF patients, although Thabut *et al.* failed to detect any difference in survival between both procedures (13), Schaffer *et al.* found better adjusted survival after BLT (15). These differences may be explained in part by differences in the characteristics of patients between the two studies, the study by Schaffer *et al.* including patients receiving a LT after LAS implementation.

It must be kept in mind that most of the evidence about post-transplant survival comes from large registries that lump together the outcomes of transplantations performed many years ago in centers that no longer exist with those performed in the recent years in high volume centers.

Survival benefit

Given the disappointing long-term survival of patients after LT, its ability to extend survival has been questioned (16,17). In the absence of randomized trials, appraisal of the survival benefit of LT is complex and relies on statistical modeling (18). These approaches have to deal with the following issues: patients referred to a LT center form a very selected subgroup of patients with the disease of interest, and patients who ultimately receive a LT form a selected subgroup of patients who are put on a waiting list, that may not be reflected by the characteristics of patients measured at the time of registration (18). Methods taking into account the evolution of patients' characteristics after registration have recently been developed and provide more sensible estimates of the survival benefit of LT (18,19). Besides these technical issues, the reader must keep in mind that the results of these studies are valid for a given organ allocation system and may not apply for transplantations performed in the same indication, but in another country and may not be valid 10 years from now, because of the evolution of both pre- and post-transplant survival. In the case of CF for instance, the spontaneous life expectancy improved from 31 to 37 years over the past decade and new drugs able to dramatically change the expected survival have been developed recently (20).

About 20 studies have been published that aimed to

assess the survival benefit of LT in different indications (14,16,17,19,21-34). These studies are summarized in *Table 1*. The survival benefit of LT is best documented in patients with IPF and CF whereas it is still debated in COPD and a lack of data precludes definitive conclusion in pulmonary arterial hypertension (PAH). In the case of COPD, a few prognostic factors have shown association with post-transplant outcome and could be used as markers to refine patient's selection.

Quality of life

One of the main clinical aims of LT is to improve quality of life, and may be the only expected clinical benefit of LT in some indications like COPD where the survival benefit is still unclear. Quality of life encompasses many subdomains like financial status, social support, physical environment and health (36). Many studies have been published in the recent years that focused on health-related quality of life (HRQoL) before and after LT. However, the interpretation of these studies is not trivial. First, there are plenty of instruments available to measure HRQoL. Some of these instruments are generic (36-item Short Form Survey—SF-36 for instance) whereas others are disease-specific (SGRQ). In some cases, health utility measures are used that can be combined with survival to derive quality adjusted life survival. In a recent systematic review focusing on the estimation of HRQoL after LT, Seiler *et al*. retrieved 39 studies that used 13 different HRQoL instruments (37). Although all these instruments have advantages and limitations, they do not explore the same domains and are thus likely not to provide the same estimation of the benefit of LT. Second, a major limitation of these studies is related to the fact that patients must be well enough to fill out the questionnaires. In other words, in these studies, the data are not missing at random. For instance, in a study published 10 years ago, the authors report on the HRQoL of patients before and after LT using the SGRQ (38). In this study, patients who died after LT were excluded. This study does not allow to conclude on the improvement in HRQoL provided by LT, but only on the improvement of HRQoL in patients doing well after LT. Several methods have been used to account for these missing not at random data, like imputing the worst possible HRQoL to those who died post-transplant or combining survival and HRQoL (39).

All the studies focusing on HRQoL after LT found dramatic improvements in HRQoL regardless of the indication for LT and whether HRQL is measured by generic, respiratory-specific HRQL instruments, or by utility measures (36,37). *Table 2* reports the benefit of LT on quality of life measured by both generic and specific tools.

The most popular generic HRQoL instrument is the SF-36. The SF-36 features physical and mental summary scores (PCS and MCS), and a 4-point change in the SF-36 is considered clinically significant (MCID). In a multicenter randomized controlled trial about CMV prophylaxis, SF-36 was measured before transplantation and every 3 months up to 1 year after LT (41). The authors observed a 10.9 points improvement in PCS score, almost reaching the norms of the US population. Concomitant with increased PCS scores, they also found increase in the subdomains that contribute to PCS: physical function, role-physical, and general health. In contrast, the MCS did not change from baseline level, remaining well below the US population norm throughout the first post-operative year. Further evaluation of the MCS domains showed that mental health and vitality domain scores did not improve, whereas increases were observed in social function and role-emotional domains. In a recent prospective study involving 326 patients that contributed to HRQoL measurements both before and after LT, a 17.7 improvement in the SF-36 physical component score was observed (39). Again, the improvement in the mental component score was more modest (7.8 points). Other studies using the SF-36 or other HRQoL instruments have reported mostly the same results. Similar results were found in studies performed after the introduction of the LAS score in the US (40).

The same results have been found in studies using respiratory-specific HRQoL. One of the most popular disease-specific HRQoL tool is the St. George's Respiratory Questionnaire (SGRQ) that provides a summary score and a score for 3 sub-domains: impact, symptoms and activity. In a prospective cohort study involving 326 patients in whom HRQoL has been measured pre and post transplantation using various questionnaires, average improvements in SGRQ was 47 points, which is more than 10 times the MCID for this tool (39). These changes greatly exceed those seen with other treatments for advances lung disease. For instance, in recent studies on bronchoscopic lung volume reduction (BLVR) in COPD patients, the mean improvements in total SGRQ was 13.4 points (42) to be compared to 49.9 points improvements in patients receiving a LT in the study by Singer *et al.* (39).

Table 1 Studies assessing the survival benefit of lung transplantation

First author (reference)	Publication year	Diseases	Study type	Cohort period	Main conclusion
Hosenpud (17)	1998	Adult CF, COPD, ILD	UNOS Registry, US	1992–1994	LT improves survival in patients with CF and ILD, no benefit for patients with COPD
Geertsma (31)	1998	Adult CF, COPD, ILD, PAH	Single center, Netherlands	1990–1996	LT improves survival for the whole cohort of patients. Disease specific analysis limited by the small sample size
Aurora (34)	1999	Pediatric CF	Single center, UK	1988–1998	LT improves survival in children with CF
Liou (28)	2001	Pediatric and adult CF	UNOS registry, US	1992–1997	LT improves survival for patients with CF and a predicted 5-year survival <5 years. Most patients with CF have unclear or even negative survival effect
De Meester (32)	2001	Adult CF, COPD, ILD, PAH	Eurotransplant registry	1990–1996	LT improves survival in all indications except Eisenmenger syndrome
Charman (33)	2002	Adult CF, COPD, ILD, PAH	Single center, UK	1984–1999	LT improves survival in all indications except Eisenmenger syndrome
Thabut (22)	2003	ILD	Single center, France	1988–2001	LT improves survival for patients with ILD
Liou (27)	2005	Pediatric and adult CF	UNOS registry, US	1988–2002	LT improves survival in adult patients with CF, a 5-year predicted survival <50% and no Burkholderia cepacia or arthropathy. No benefit in pediatric CF
Stavem (25)	2006	COPD	Single center, Norway	1990–2003	LT does not improve survival in patients with COPD
Liou (16)	2007	Pediatric CF	UNOS registry, US	1998–2004	LT improves survival for <1% of pediatric CF patients
Thabut (35)	2008	COPD	UNOS registry, US	1987–2004	LT improves survival by at least 1-year for 45% of COPD patients undergoing BLT and for 22% undergoing SLT
Titman (21)	2009	Adult CF, COPD, ILD, PAH	National registry, UK	1995–2006	LT improves survival in all patients
Hofer (30)	2009	Pediatric and adult CF	Single center, Switzerland	1992–2007	LT improves survival in children and adult patients with CF
Lahzami (29)	2010	COPD	2 centers, Switzerland	1993–2007	LT improves survival for patients with COPD and a BODE >7
Tanash (24)	2011	AATD related emphysema	National registry, Sweden	1990–2010	LT improves survival in AATD patients with emphysema
Russo (26)	2011	All patients >12 years old	UNOS, US	2005–2009	LT improves survival in patients with a LAS >40
Thabut (23)	2013	Adult CF	UNOS, US	2005–2009	LT improves survival in adult CF patients
Vock (19)	2017	Adult CF, COPD, ILD, PAH	UNOS, US	2005–2011	Almost ¾ of patients achieve a 2-year survival benefit

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; AATD, alpha-1 antitrypsin deficiency; LT, lung transplantation; BLT, bilateral lung transplantation; SLT, single lung transplantation.

Table 2 Benefit of lung transplantation on quality of life measured by both generic and specific tools, according to the underlying disease (these measures are made during the first year following lung transplantation)

Type	Tool	Underlying disease	Value, mean (range)	First author (reference)
Generic	SF12-PCS (MCID =5)	COPD	15.9 (11.5–20.3)	Singer (40)
		PAH	7.9 (1.0–14.7)	
		CF	23.8 (19.5–28.1)	
		IPF	13.8 (11.9–15.8)	
	SF12-MCS (MCID =5)	COPD	2.7 (–0.9–6.4)	
		PAH	0.1 (–5.5–5.7)	
		CF	10.3 (6.4–14.1)	
		IPF	4.8 (3.1–6.6)	
	EQ5D (MCID =0.06)	COPD	0.15 (0.08–0.21)	
		PAH	0.07 (–0.05–0.19)	
		CF	0.30 (0.22–0.39)	
		IPF	0.16 (0.13–0.19)	
	SF-36 PCS (MCID =4)	COPD	18.3 (16.4–20.1)	
		PAH	18.0 (14.6–21.3)	
		CF	19.6 (17.5–21.8)	
		IPF	15.4 (13.6–17.1)	
	SF-36 MCS (MCID =4)	COPD	8.4 (6.4–10.4)	
		PAH	7.7 (4.0–11.3)	
		CF	9.1 (6.7–11.5)	
		IPF	4.4 (2.5–6.3)	
Specific	SGRQ (MCID =4)	COPD	47.7 (44.3–51.0)	Singer (39)
		PAH	36.3 (30.3–42.3)	
		CF	46.0 (42.0–49.9)	
		IPF	38.5 (35.4–41.7)	
Utility	QALYs	COPD	2.33 (2.03–2.63)	Singer (39)
		PAH	2.53 (2.02–3.04)	
		CF	2.87 (2.53–3.20)	
		IPF	2.17 (1.90–2.44)	

This table does not intend to summarize all the data available, but is a selection of a few recent studies reporting quality of life benefit according to the underlying disease. QALYs, quality adjusted life years; SGRQ, St. George's Respiratory Questionnaire.

In another study, an improvement of 33 points was found, with similar improvements in the 3 domain scores (43). This improvement persisted even when the worst possible values were imputed to patients who died after LT. These improvements were similar to those found after other solid organ transplantations (44).

Most studies focused on the first years following LT and very few studies reported on QoL of patients surviving more than 3 years after LT. As such, the trajectory of QoL beyond 3 years post-transplant remains uncertain. A few

factors have been associated with post-transplant QoL. CLAD developing in about 50% of patients at 5 years appears to be the strongest determinant of physical health status (45). The other predictors of HRQoL after LT were immunosuppressants side-effects, indication for LT, older age at the time of transplant, a single-lung transplant, and recurrent infections (37).

Pulmonary function tests

The pulmonary function of transplant recipients results from pre-transplant factors (underlying disease in the case of SLT), operative factors (pleural or diaphragmatic injury) and post-transplant complications (bronchial strictures). In the first weeks after LT, pulmonary function is hampered by various factors including pain and early graft dysfunction, and the peak in pulmonary function is in general observed between 3 to 12 months following LT. The average function declines thereafter because of CLAD that develops in 50% of patients at 5 years. Surgical approach (SLT *vs.* BLT) and underlying disease in case of SLT are the two main factors associated with post-transplant pulmonary function.

Patients who receive a BLT typically achieve normal pulmonary function tests (FEV_1, FVC, TLC) as well a gas exchange whatever the indication for LT (46). Lower PFTs are achieved following SLT and depend on the indication. Almost normal FEV_1 can be expected in patients with PAH, whereas IPF patients have typically FEV_1 between 60 and 80 percent of predicted value and COPD patients achieve typically FEV_1 in the 50–60% range (47). Blood gases are typically normal. Small sample size studies performed many years ago have shown that considerable exercise limitations persisted after either single or bilateral LT despite pulmonary function restoration, with VO_2 around 50% of predicted values (48). Similar results were found in a study including 153 patients in recent years (49,50). Interestingly, BLT did not result in better exercise tolerance than SLT (49,50). The skeletal muscle appears to be the cause of exercise limitation in most and may, in part, reflect persistence of a pre-transplant skeletal muscle injury (46).

Other outcomes have been reported like employment status. For instance, in the ISHLT registry, at 5 years post-transplant, about 40% of patients are not working, 30% are retired and a little less than 20% are working part or full-time. However, these figures are likely to vary from country to country and pose the same issues of missing values at that already mentioned for HRQoL.

In conclusion, LT allows for major improvements in lung function and exercise tolerance that translates into dramatic improvement in HRQoL that far exceeds the effects of other treatments of end-stage lung diseases. Although recent studies suggest that LT improves survival in most cases, post-transplantation survival remains hampered by the frequent development of CLAD. A better understanding of the mechanisms implicated in CLAD development could allow to match the outcomes after other solid organ transplantations.

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Footnote

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