Lung transplantation for COPD – evidence-based?

Samir Lahzami, John-David Aubert

Service de Pneumologie et Centre de Transplantation, CHUV et Université de Lausanne, Switzerland

Summary

Lung transplantation has now been performed for more than 30 years in patients with end-stage chronic obstructive pulmonary disease (COPD). This disease is the major indication for lung transplantation, involving more than one third of the procedures worldwide. Although lung transplantation in COPD patients has clearly shown a positive impact on lung function, exercise capacity and quality of life, the survival benefit remains difficult to ascertain. Several methodological difficulties, particularly the absence of classical randomised studies, make the analysis especially challenging. There is however indirect but convincing evidence that lung transplantation can, when appropriate selection criteria are applied, provide not only an active post-transplant lifestyle but also a survival benefit for patients with COPD.

Key words: COPD; lung transplantation; survival; BODE index

Evidence-based medical management of COPD

Chronic obstructive pulmonary disease (COPD) is a major health problem in developed countries and a growing concern in low income nations as well. Epidemiological data show that the prevalence of COPD is increasing worldwide and it is expected that the number of patients with severe disease and the overall morbidity and mortality will increase in the coming years [1]. The global management of COPD is now well defined through international initiatives, and there is a broad consensus on therapeutic measures that are useful in this condition [2]. Treatment of COPD includes both pharmacological and non-pharmacological measures, with a stepwise approach depending on the severity of the disease. Although morbidity can usually be effectively alleviated, only a few treatments have had a real impact on mortality. Among these, the most cost-effective measure by far is the eradication of the exogenous risk factors, among which active or passive inhalation of cigarette smoke accounts for more than 90% of all cases. Pivotal cohort studies have demonstrated without any doubt the influence of cigarette smoke on airflow limitation and the benefit from quitting smoking, whatever the extent of the disease [3, 4]. Another cornerstone of care in COPD, although limited to a small subset of patients with severe disease, is the administration of long term oxygen therapy [5, 6]. Along with smoking cessation, it is the only medical treatment with a definite survival benefit in COPD.

In the late 90s great hopes were placed in the antiinflammatory properties of inhaled steroids, but ten years later there is still ongoing debate as to the real impact of this therapeutic class on mortality in COPD [7, 8]. If medical treatments other than smoking cessation and oxygen therapy have failed to demonstrate a survival benefit, their utility in the daily management of COPD is well established and consists in symptomatic relief, a decreased rate of exacerbations and improved exercise tolerance. This category of treatment includes bronchodilators, pulmonary rehabilitation and chronic non-invasive home ventilation [2].

Abbreviations

COPD	Chronic obstructive pulmonary disease
ISHLT	International Society for Heart and Lung Transplantation
UNOS	United Network for Organ Sharing
NETT	National Emphysema Treatment Trial
BODE index	Body mass index – Obstruction – Dyspnoea – Exercise

Surgical treatment in COPD

Surgical options have also been evaluated for patients with advanced emphysema. The North American National Emphysema Treatment Trial group (NETT) has demonstrated, through a carefully randomised study, a significant survival advantage after lung volume reduction surgery for patients with severe emphysema with both upper-lobe predominance and low baseline exercise capacity [9]. In an extension study, the authors have recently shown that this benefit extends beyond three years [10]. It must be emphasized that the clinical characteristics of the patients who will benefit from this type of surgery are relatively narrow, and therefore, unfortunately, a majority of patients with severe COPD will never meet the stringent criteria established by the NETT study.

Lung transplantation

Lung transplantation in patients with emphysema was first reported in the 70s and has been more widely practised since the late 80s. In the last decade more than 6500 lung transplants have been performed in patients with COPD (excluding α1-antitrypsin deficiency), which represents some 37% of all indications [11]. According to data from the International Society for Heart and Lung Transplantation Registry (ISHLT), survival achieved in the last ten years is now 81.5% for the first year and 64% after three years [11]. Table 1 gives the survival rates for selected published series from national and international cohorts. In comparison to other indications, recipients with COPD have the best first-year survival but the poorest survival after 10 years, with only 20% of recipients alive. This attrition probably reflects the older age of patients with COPD compared to patients with other diseases (e.g. cystic fibrosis) and possibly the toll of comorbidities such as a damaged cardiovascular system in former smokers. Whereas heart-lung transplantation is nowadays no longer performed in COPD except for some specific cases, single lung transplantation remains an option provided that no chronic suppurative airway disease remains in the native lung. In very recent years single lung transplantation has been performed in about 45% of transplant recipients with COPD, whereas it was the operation of choice in the early 90s. Early post-transplant survival appears to be similar in single versus double lung transplantation. However, in the largest studied cohort (9883 patients), the median survival after single lung transplantation (4.6 years) was significantly shorter than after double lung transplanation (6.4 years) [12]. According to these data single lung transplantation is considered an option for older recipients aged 60 years or over or for patients with additional comorbidities, notably of the cardiovascular system, that increase the perioperative risk [13].

Table 1

Survival after lung transplantation for COPD from different registries.

Registry (ref)	Period	N	1-year survival	3-year survival
ISHLT [11]	1994–2004	7113	81	64
ISHLT [11]	2003–2007	1712	85.8	69.1
UNOS/USA [31]	1997–2004	1209	86.6	66.0
Swiss registry [32]	1992–2002	79	80	75
Australia [33]	1989–2003	112	86	NA
St Louis [34]	1988–2000	220	88.8	76.5

ISHLT = International Society for Heart and Lung Transplantation
UNOS = United Network for Organ Sharing

Criteria for lung transplantation

Earlier criteria for lung transplantation in COPD were the presence of an FEV1 <25% of predicted value, a $PaCO_2$ ≥55 mm Hg (7.3 kPa), or the diagnosis of concomitant pulmonary hypertension with progressive clinical deterioration [14, 15]. These criteria have been used for many years as guidelines for the selection of COPD lung transplant candidates. In 2004, Celli and colleagues published, from a large multicentric cohort of COPD patients, a composite of four parameters showing a strong association with survival in COPD: Body-mass index (BMI), airflow Obstruction, Dyspnoea and Exercise capacity [16]. These parameters were used to design the BODE index, a validated scoring system which proved to be a better predictor of survival than the spirometric staging system developed by the American Thoracic Society [17]. The BODE index assigns a score for disease severity on a scale of 0 to 10, with the higher score indicating a more severe disease and predicting a poorer outcome for the next four years (table 2).

The BODE index was recently adopted by the ISHLT expert panel. The 2006 updated interna-

Table 2

Clinical parameters of the BODE index [16].

Parameters/points	0	1	2	3
BMI kg/m^2	>21	≤21		
FEV$_1$ % predicted	≥65	50–64	36–49	<35
MMRC dyspnea scale	0–1	2	3	4
6-minute walk test (m)	≥350	250–349	150–249	≤149

Table 3

Criteria for listing lung recipient candidates among COPD patients [18].

Patients with a BODE index of 7 to 10 or at least 1 of the following:
History of hospitalisation for exacerbation associated with acute hypercapnia (PCO$_2$ >50 mm Hg/6.7 kPa)
Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.
FEV$_1$ of <20% predicted and either DLCO of <20% predicted or homogeneous distribution of emphysema.

tional guidelines for the selection of lung transplant candidates [18] added a BODE ≥5 for referral to a transplant centre and a score ≥7 for patient listing. However, these guidelines have not yet been validated by retrospective or prospective cohort studies. The expert recommendations are given in table 3.

Published studies on the survival benefit after transplantation in COPD

Several groups have addressed the question of survival benefit after lung transplantation for COPD. All the studies to date have compared survival after transplantation to survival of patients on the waiting list (table 4). Whereas two papers found no survival benefit for COPD patients [19, 20], three have established some survival advantage at least for selected subgroups [21–23]. It should be noted that all the studies but one have included patients with α-1 antitrypsin deficiency, and that the time frame under study is rather large, dating back to the late 80s, a time when lung transplantation was still in its infancy. Accordingly, most studies reported a one-year survival significantly inferior to more recent data from national and international registries (table 1). Moreover, it is likely that patients were listed somewhat prematurely in the early years, increasing the disadvantage of transplantation compared to survival on the waiting list. The recently published analysis by Thabut and colleagues is by far the largest and most sophisticated study on the topic [22]. Founded on the UNOS registry, these authors have developed a model based on individual risk factors to predict survival with and without transplantation for patients with COPD. Among the

most discriminating parameters was the need for oxygen, the need for mechanical ventilation, the 6-minute walk distance, the presence of pulmonary hypertension and FEV$_1$. Here again the control group was the cohort of patients on the waiting list. According to their statistical analysis, Thabut et al. found a survival benefit in about 50% of recipients after lung transplantation. Importantly, this analysis was performed under the old allocation policy of the UNOS organisation based essentially on waiting time, whereas the new lung allocation score prioritises recipients according to disease severity in order to increase transplant benefit [24]. As the authors and their reviewers acknowledged, it would be premature to use their equations on a clinical basis until externally validated and tested with other lung allocation systems [25].

The ISHLT registry data show that double lung recipients have a significantly better long term survival than single lung recipients [11]. However, this advantage seems to disappear for patients aged 60 or over [12]. Hence the procedure of choice for this category of recipients is still debated.

Table 4

Published studies on the survival benefit after lung transplantation for COPD.

Ref	Patients included	Period analysed	α1-AT deficiency excluded	Follow-up (years)	1 year survival %	Main result
[20]	843	1992–1994	yes	2	82	No benefit
[23]	395	1990–1996	no	2	67	Benefit after 260 d
[21]	122	1984–1999	no	1	73	Benefit after 1 year
[19]	86	1990–2003	no	4	74	No benefit
[22]	5873	1987–2004	no	5 (median)	86.6*	Benefit in ~50%

* According to the UNOS registry 1997–2004 from which the data were collected
α1-AT = alpha 1-antitrypsin

Methodological problems in assessing the survival benefit of lung transplantation

Organ transplantation cannot be evaluated in the same way as other conventional therapy. For obvious ethical reasons it will never be possible to conduct a true randomised study involving potential lung recipient candidates. Hence, according to the established rules of evidence-based medicine, lung transplantation will never receive the "A" label granted only after rigorously designed randomised and blinded studies. Another methodological problem lies in the definition of the true medical decision in the process of organ transplantation: the major medical procedure is to list or not to list a patient for transplantation. The subsequent decision to transplant a patient on the waiting list will depend on the local allocation rules and potential contraindications either for the donor or the recipient. The time on the waiting list will therefore depend on the specific organ allocation rules, which differ from country to country. In some organisations (e.g. UNOS for the USA) disease severity is now a criterion for allocation, whereas in other countries (e.g. Switzerland) this is not the case and the waiting time is the main determinant except for some specific high urgency criteria. In other words, the survival benefit of listing should be distinguished from the benefit of transplantation [25]. Moreover, it is likely that patients on the waiting list do not receive the same type of care as patients not considered for or denied lung transplantation. For all these reasons, comparisons of survival for patients after lung transplantation and those on the waiting list are potentially biased, as are comparisons of programmes with different allocation systems.

A methodologically correct evaluation would be, as applied by the investigators of the NETT study for lung volume reduction [9], to randomise eligible patients for lung transplantation to either a waiting list or to best standard care, and compare mortality in the two groups including deaths on the waiting list. As such a study will probably never be performed, another approach could be to compare actual survival after lung transplantation with the predicted survival determined by markers of disease severity such as the BODE index [16]. This latter approach would be largely free of the bias mentioned above. However, the discriminative power of such survival equations should be robust, and caution is needed when extending them to populations from other geographical areas or other time periods.

Beyond survival benefit

While demonstrating a survival advantage remains a challenge in lung recipients with COPD, these patients clearly benefit from enhanced lung function, better exercise tolerance [26, 27] and, most importantly, a better quality of life [28]. These benefits are especially crucial for lung transplant candidates with COPD. It is of interest to note that the benefit in quality of life seems to persist even when there is some decrease in lung function, as found in the bronchiolitis obliterans syndrome [29]. With a mean age of 56 years at transplant (11), many of these patients would readily exchange years of life crippled with severe disease for the same or even a smaller number of years with a better quality of life [25]. However, the dramatic shortage of organs available for transplantation faces the transplant team with an ethical dilemma in weighing patients' needs and equity in the allocation of scarce resources: transplanting patients with no predictable survival advantage after the procedure may well jeopardise the survival of others on the waiting list who would definitively survive longer if transplanted. The new Lung Allocation Score system, introduced in May 2005 in the USA, was established to address this question by estimating the respective transplant benefit of all listed patients [24, 30]. How this new system will alter disease distribution in lung transplantation programmes and the selection criteria for candidates with COPD in this country warrants prospective long term studies.

Conclusion

Lung transplantation is a therapeutic option in carefully selected patients with COPD, provided they fulfil established inclusion and exclusion criteria. When these criteria are met, there is strong evidence that a majority of these recipients will derive a survival advantage from the procedure, together with an improvement in lung function, exercise capacity and quality of life. Better predictors of mortality in COPD are likely to help transplant teams worldwide to select candidates and refine the listing criteria. These tools will be crucial in achieving a fair allocation of what remains a limited resource.

References

1 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370:765–73.

2 Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176:532–55.

3 Doll R, Peto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. Br J Cancer. 2005;92:426–9.

4 Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233–9.

5 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party: Lancet. 1981;1:681–6.

6 O'Reilly P, Bailey W. Long-term continuous oxygen treatment in chronic obstructive pulmonary disease: proper use, benefits and unresolved issues. Curr Opin Pulm Med. 2007;13:120–4.

7 Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.

8 Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. Eur Respir J. 2008;31:927–33.

9 Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348:2059–73.

10 Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, Decamp MM, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006; 82:431–43.

11 Trulock EP, Christie JD, Edwards LB, Boucek MM, Aurora P, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report – 2007. J Heart Lung Transplant. 2007;26:782–95.

12 Thabut G, Christie JD, Ravaud P, Castier Y, Brugiere O, Fournier M, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet. 2008;371:744–51.

13 Lawrence EC. Lung transplantation for COPD: one lung, two lungs, or none? Lancet. 2008;371:702–3.

14 International guidelines for the selection of lung transplant candidates. The American Society for Transplant Physicians [ASTP]/American Thoracic Society[ATS]/European Respiratory Society[ERS]/International Society for Heart and Lung Transplantation[ISHLT]: Am J Respir Crit Care Med. 1998; 158:335–9.

15 Trulock EP, III: Lung Transplantation for COPD. Chest. 1998;113:269S–276S.

16 Celli BR, Cote CG, Marin JM, Casanova C, Montes de OM, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.

17 Martinez FJ, Han MK, Andrei AC, Wise R, Murray S, Curtis JL, et al. Longitudinal Change in the BODE Index Predicts Mortality in Severe Emphysema. Am J Respir Crit Care Med. 2008.

18 Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, et al. International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update – A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:745–55.

19 Stavem K, Bjortuft O, Borgan O, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. J Heart Lung Transplant. 2006;25:75–84.

20 Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet. 1998;351:24–7.

21 Charman SC, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. J Heart Lung Transplant. 2002;21:226–32.

22 Thabut G, Ravaud P, Christie JD, Castier Y, Fournier M, Mal H, et al. Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177:1156–63.

23 De Meester J, Smits JM, Persijn GG, Haverich A. Listing for lung transplantation: life expectancy and transplant effect, stratified by type of end-stage lung disease, the Eurotransplant experience. J Heart Lung Transplant. 2001;20:518–24.

24 Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al. Development of the new lung allocation system in the United States. Am J Transplant. 2006;6:1212–27.

25 Murray S, Kawut S. Defining transplantation and listing benefit in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177:1054–5.

26 Garrity ER, Moore J, Mulligan MS, Shearon TH, Zucker MJ, Murray S. Heart and lung transplantation in the United States, 1996-2005. Am J Transplant. 2007;7:1390–403.

27 Cai J. Double- and single-lung transplantation: an analysis of twenty years of OPTN/UNOS registry data. Clin Transpl. 2007;1–8.

28 TenVergert EM, Vermeulen KM, Geertsma A, van Enckevort PJ, de Boer WJ, van der BW, Koeter GH. Quality of life before and after lung transplantation in patients with emphysema versus other indications. Psychol Rep. 2001;89:707–17.

29 Gerbase MW, Spiliopoulos A, Rochat T, Archinard M, Nicod LP. Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. Chest. 2005;128:1371–8.

30 Kozower BD, Meyers BF, Smith MA, De Oliveira NC, Cassivi SD, Guthrie TJ, et al. The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. J Thorac Cardiovasc Surg. 2008;135:166–71.

31 Cai J. Thoracic transplantation in the United States: an analysis of UNOS Registry data. Clin Transpl. 2006;41–56.

32 Speich R, Nicod LP, Aubert JD, Spiliopoulos A, Wellinger J, Robert JH, et al. Ten years of lung transplantation in Switzerland: results of the Swiss Lung Transplant Registry. Swiss Med Wkly. 2004;134:18–23.

33 Gunes A, Aboyoun CL, Morton JM, Plit M, Malouf MA, Glanville AR. Lung transplantation for chronic obstructive pulmonary disease at St Vincent's Hospital. Intern Med J. 2006;36:5–11.

34 Cassivi SD, Meyers BF, Battafarano RJ, Guthrie TJ, Trulock EP, Lynch JP, et al. Thirteen-year experience in lung transplantation for emphysema. Ann Thorac Surg. 2002;74:1663–9.