Lung transplantation for COPD/pulmonary emphysema

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Shareable abstract (@ERSpublications)
Lung transplantation remains a treatment option for very selected patients with endstage COPD, including α-1 antitrypsin deficiency, and increases quality of life and survival although several complications may lead to morbidity and mortality https://bit.ly/3BlastJ

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Abstract

COPD and α-1 antitrypsin deficiency emphysema remain one of the major indications for lung transplantation. If all other treatment possibilities are exhausted or not possible (including rehabilitation, oxygen therapy, noninvasive ventilation, lung volume reduction), patients may qualify for lung transplantation. Strict selection criteria are implemented with a lot of relative and absolute contraindications. Because of an ongoing donor shortage, only a minority of endstage COPD patients will finally get transplanted. The procedure may involve a single or a double lung transplantation, dependent on the experience of the centre, the waiting list, the availability of donor lungs and the patient's risk–benefit ratio. In general, the life expectancy as well as the health-related quality of life after lung transplantation for COPD are usually increased, and may be somewhat better after double compared with single lung transplantation. Several specific complications can be encountered, such as the development of solid organ cancer and chronic lung allograft dysfunction, which develops in up to 50% of patients within 5 years of their transplant and has a major impact on long-term survival, because of the current inefficient treatment modalities.

Introduction

Lung transplantation (LTx) is an established option for patients with endstage lung diseases after other therapeutic measures have been exhausted. Due to the high rate of complications and limited availability of organs, careful selection of candidates is essential and contraindications should be taken into account. Maximisation of conservative therapy options should be performed before an evaluation for LTx is performed. The number of LTxs worldwide is approximately 4500 per year; in Eurotransplant (Austria, Belgium, Croatia, Hungary, Germany, Luxembourg, the Netherlands, Slovenia), 630 lungs were transplanted in 2021 [1]. Bilateral LTx is performed most frequently; however, unilateral LTx and combination transplant procedures can also be performed.

LTx is a life-changing procedure and patient selection in COPD requires careful consideration by patients and physicians. Thirty-six per cent of all lung transplants worldwide between 1990 and 2017 (n=56 332) were performed in patients with COPD and, historically, COPD is the most common clinical indication for LTx [2]. In addition, in 6% of all procedures during the same period, α-1 antitrypsin deficiency (α-1 AD) was the underlying disease leading to LTx.

Patient selection

As with any intervention, LTx aims to improve survival and quality of life. Given the limited availability of organs, improving survival is the priority for patient selection. Not all patients with endstage COPD are

candidates for LTx. No randomised controlled trials are available to answer the question of the benefits of LTx for COPD. Balancing both benefits and risks is essential for the patient to make an informed decision.

To improve a patient's prognosis and achieve a realistic survival benefit, the predicted survival probability of the underlying disease with LTx should be higher than without LTx. The International Society for Heart and Lung Transplantation (ISHLT) provides a regularly updated consensus document for patient selection, with the latest version published in 2021 [3]. According to this document, LTx should be considered for adults with chronic, endstage lung disease who meet all of the following criteria:

- high risk of death (>50%) within 2 years if LTx is not performed; poor waiting list survival;
- high likelihood (>80%) of 5-year post-transplant survival if adequate graft function; poor waiting list survival; good long-term prognosis after LTx.

Contraindications and risk factors for LTx

It is essential to assess medical comorbidities, psychosocial factors and potential for rehabilitation in the evaluation of transplant candidates. The ISHLT consensus document for patient selection lists several absolute contraindications for LTx [3]. A modified list of the contraindications for patients with COPD is displayed in table 1. Candidates with these conditions are considered too high risk to achieve a successful outcome after LTx. More importantly, these contraindications significantly increase the risk of an adverse outcome and would even make transplant most likely harmful for a recipient. LTx programmes should not transplant patients with these factors except under very exceptional or extenuating circumstances.

Relative contraindications were mentioned in the previous version of the ISHLT document [3]. In the 2021 version, a new approach was taken by identifying risk factors with high or substantially increased risk (table 1). Candidates with these conditions may be considered in centres with expertise specific to the condition. Currently, there is no data to support transplanting patients with these risk factors, or there is substantially increased risk based upon the currently available data. If more than one of these risk factors is present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes. Modifiable conditions should be optimised whenever possible.

Risk factors in table 1 may have unfavourable implications for outcome after LTx. It may be acceptable for programmes to consider patients with these risk factors but multiple risk factors together may increase risk for adverse post LTx outcome.

A controversial upper age limit for lung transplant candidacy is being discussed. In the United States (US), patients >65 years of age now comprise more than 30% of the waiting list. Several studies have demonstrated a similar short term (1-year) survival in carefully selected older compared with younger recipients, but a considerably lower 5-year survival was noted in patients 65 years and older [4]. This fact may reflect the impact of comorbidities which should be thoroughly assessed in patients in the elderly age group.

Coronary artery disease is frequent in elderly lung transplant candidates even in the absence of cardiovascular risk factors. Single centre reports have been published and have shown successful revascularisation during LTx in patients with non-multivessel disease and do not report worse survival compared with those patients without coronary artery disease [5], although prolonged hospital stay was noted.

Malignancy with high risk of recurrence or associated death is an absolute contraindication for LTx but not all neoplastic diseases are equal and cancer progression or recurrence is not significantly affected uniformly by immunosuppression. Individual oncological judgement may be necessary in case of a disease-free interval of less than 2 years and statements from tumour boards are recommended to address this issue [6, 7].

Early post-transplant mortality is increased for obese recipients compared with normal or overweight candidates. Patients who are obese should be encouraged to lose weight to improve post-transplant survival. Low body mass index (BMI) has been associated with increased mortality to a lesser extend [8].

LTx candidates must demonstrate strict abstinence from use of all tobacco and nicotine products including nicotine replacement therapy prior to transplant. Serial urinary cotinine testing is standard of care in most centres before LTx in patients with smoking-associated lung disease. A short period of abstinence (lower than 6 months) and exposure to second-hand smoking was associated with a higher risk of relapse [9].

TABLE 1 Risk factors for poor post-transplant outcomes (reproduced and modified from Leard *et al.* [3])

Absolute contraindications	Risk factors with high or substantially increased risk	Risk factors
Malignancy with high risk of recurrence or death related to cancer	Age >70 years	Age 65–70 years
Glomerular filtration rate <40 mL·min^{-1}·1.73 m^{-2} unless being considered for multi-organ transplant	Severe coronary artery disease that requires coronary artery bypass grafting at transplant	Glomerular filtration rate 40–60 mL·min^{-1}·1.73 m^{-2}
Acute coronary syndrome or myocardial infarction within 30 days	Reduced left ventricular ejection fraction <40%	Mild to moderate coronary artery disease
Stroke within 30 days	Significant cerebrovascular disease	Severe coronary artery disease that can be treated *via* percutaneous coronary intervention prior to transplant
Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant	Severe oesophageal dysmotility	Patients with prior coronary artery bypass grafting
Acute liver failure	Untreatable haematologic disorders including bleeding diathesis, thrombophilia or severe bone marrow dysfunction	Reduced left ventricular ejection fraction 40–50%
Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery	Body mass index ⩾35 kg·m^{-2}	Peripheral vascular disease
Septic shock	Body mass index <16 kg·m^{-2}	Severe gastro-oesophageal reflux disease
Active extrapulmonary or disseminated infection	Limited functional status with poor potential for post-transplant rehabilitation	Oesophageal dysmotility
Active tuberculosis infection	Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems	Thrombocytopenia, leukopenia or anaemia with high likelihood of persistence after transplant
HIV infection with detectable viral load	Unreliable support system or caregiving plan	Osteoporosis
Limited functional status (*e.g.* non-ambulatory) with poor potential for post-transplant rehabilitation	Lack of understanding of disease and/or transplant despite teaching	Body mass index 30–34.9 kg·m^{-2}
Progressive cognitive impairment	Hepatitis B or C infection with detectable viral load and signs of liver fibrosis	Body mass index 16–17 kg·m^{-2}
Repeated episodes of non-adherence without evidence of improvement	Chest wall or spinal deformity expected to cause restriction after transplant	Frailty
Active substance use or dependence including current tobacco use, vaping, marijuana smoking or intravenous drug use	Extracorporeal life support	Hypoalbuminaemia
Other severe uncontrolled medical condition expected to limit survival after transplant	Redo transplant <1 year following initial lung transplant	Poorly controlled diabetes
	Redo transplant for restrictive chronic lung allograft dysfunction	Edible marijuana use
	Redo transplant for antibody mediated rejection	HIV infection with undetectable viral load
		Previous thoracic surgery
		Prior pleurodesis
		Mechanical ventilation
		Redo transplant >1 year for obstructive chronic lung allograft dysfunction

Timing of referral

As for other diseases, referral of patients with COPD to a lung transplant centre should be considered in the presence of progressive disease, despite maximal medical therapy and without obvious contraindications. Nowadays, in most Western countries, patients with COPD have a median age of 55–60 years when referred.

The ISHLT consensus document recommends referral to a LTx centre for a COPD patient with a BODE (BMI, obstruction, dyspnoea, and exercise capacity) score of 5 or higher with additional factors present, suggestive of increased risk of mortality (frequent acute exacerbations, increase in BODE score >1 over the past 24 months, pulmonary artery to aorta diameter >1 on CT scan and a forced expiratory volume in 1 s (FEV_1) <25% predicted). Clinical deterioration should be documented despite maximal treatment

(including optimising medication, pulmonary rehabilitation, oxygen therapy, and, as appropriate, nocturnal noninvasive positive pressure ventilation). Poor quality of life that is unacceptable to the patient should be present. Simultaneous referral for both LTx and for endoscopic or surgical lung volume reduction (LVR) evaluation is appropriate [3]. The BODE score has not been validated among transplant candidates and differences in outcome in comparison to the derivation cohort reflect the marked differences in age, comorbidities and active smoking in the population of LTx candidates.

In our personal view, recurrent exacerbations, presence of respiratory failure (need for either long-term oxygen therapy (LTOT) and/or noninvasive ventilation (NIV)) and signs of pulmonary hypertension in patients at advanced COPD stages do necessitate referral.

Listing criteria

The ISHLT consensus document recommends admitting a COPD patient to the waiting list for LTx in the case of a BODE score of 7–10, and additional factors including a FEV_1 of <20% pred and presence of moderate to severe pulmonary hypertension [3]. The evidence for these recommendations is low.

Table 2 summarises selected features associated with survival derived from large cohorts of patients with COPD. Most of these cohorts include patients with COPD who are generally older and who have additional comorbidities, and are not representative of typical patients with COPD listed for LTx. Applying the recommended general selection criteria from the ISHLT document with an expected 2-year survival of 50% or lower, frequent exacerbations with hospitalisation, especially those with hypercapnia and the presence of resting hypoxaemia in stable conditions seems to be clinically applicable criteria.

Prognostic models were developed to determine a survival benefit of LTx in patients with COPD but survival is highly variable and prediction imprecise. Thabut *et al.* [28] have developed a model for prediction of a gain of 1 year or more by LTx in 8182 US-patients listed for LTx. Major determinants of a survival benefit identified in patients with COPD were an elevated systolic pulmonary artery pressure, FEV_1 <20%, low BMI, low exercise capacity and the need for continuous mechanical ventilation or oxygen [28].

α-1 antitrypsin deficiency

The ISHLT consensus document does not differentiate selection criteria between patients with COPD and those with α-1 AD. In general, patients with α-1 AD are younger and have fewer comorbidities in comparison to patients with non-α-1 AD COPD. Single centre and registry reports show similar or slightly better long-term survival of patients transplanted with α-1 AD in comparison to non-α-1 AD patients with COPD [4, 29–34]. The risk of early gastrointestinal complications seems to be higher in α-1 AD patients [29, 32]. Careful evaluation of liver disease is necessary in patients with severe α-1 AD [35] and recurrence of emphysema in LTx recipients with α-1 AD was reported [36, 37]. However, in these two case reports of recurrence of emphysema two and 11 years after LTx, both recipients resumed smoking.

TABLE 2 Selected features associated with 2-year survival derived from patients with COPD

Feature	Frequency	2-year survival	Cohort's median age, years
BODE score >7	82/469 (17%) [10], 139/625(23%) [11]	75% [11], 70% [11]	64 [10], 66 [11]
Resting hypoxaemia (P_{O_2} ⩽55 mmHg)	81/175 LTx referrals (46%) [12]	50% (COPD) to 70% (α-1 AD) [13]	56 [12], 63–73 [13]
Hypoxaemia on exertion (S_{pO_2} <88%) without resting hypoxaemia	33/173 (19% in patient using oxygen) [14]	80% [15, 16]	56 [14], 68 [16]
Home noninvasive ventilation	147/402 LTx referrals(36%) [12]	65% [17, 18]	65 [17], 67 [18]
Exacerbation with hypercapnia	325/4343 (7%) [19, 20]	51% [21], 35% [22], 47% [23]	59 [21], 69 [22], 63 [23], 70 [19, 20]
⩾1 exacerbation with hospitalisation	105/304 (34%) [24]	70% [24]	69 [24]
FEV_1 <20%	69/1033 (7%) [25]	80% [25]	63 [25]
Mean pulmonary artery pressure ⩾35 mmHg	16/409 (4%) [26], 44/4305 (6%) [27]	70% [26], 58% [27]	54 [26], 59 [27]

BODE: body mass index, obstruction, dyspnoea and exercise capacity score; P_{O_2}: oxygen tension; S_{pO_2}: peripheral oxygen saturation; FEV_1: forced expiratory volume in 1 s; LTx: lung transplantation; α-1 AD: α-1 antitrypsin deficiency.

Given the rarity of recurrence and the potential role of smoking, α-1 replacement therapy is not the standard of care after LTx and there is also no reimbursement in several countries. All potential efforts should rather be made to prevent smoking resumption after LTx.

Evaluation and preparation

There is no standardised work-up of LTx candidates between centres. Usually basic diagnostics before presentation in the transplant centre are spirometry, arterial blood gases, laboratory tests evaluating blood count, kidney and liver function, echocardiography, abdominal ultrasound, chest computer tomography, dental examination, and gynaecological check-up (including mammography in females above 50 years) or prostate cancer screening. Invasive testing in suitable patients before listing usually includes human leukocyte antigen typing and an antibody screen, coronary angiography (in patients at risk who are >40 years old or smokers), right-heart catheterisation, vascular ultrasound (neck and venous, and arterial lower extremity), bone densitometry and colonoscopy above the age of 50.

Choice of surgical procedure

Single as well as double LTx can be performed in patients with endstage COPD, whereas in patients with α-1 AD, a double lung transplant may be the preferred option. In recent years, the global number of double lung transplants for classical COPD/emphysema has increased to >55% of procedures, whereas the number of double lung transplants far outweighs single LTx for patients with α-1 AD (69%) [38]. A lot of centres worldwide nowadays only perform double lung transplants for patients with COPD, including our own programmes in Leuven and Hannover. Although single lung transplant is much easier to perform and theoretically two recipients can be transplanted with one donor, there are also different disadvantages in the choice of this procedure. In fact, there may be problems with ventilating the patient at the intensive care unit, as most of the perfusion will go to the transplanted lung, in preference to the native lung, leading to ventilation/perfusion mismatch and hyperinflation of the native lung, which may prolong weaning. Infection of the native lung may be more difficult to treat and the risk of cancer in the native lung is increased to 7–10% during follow-up [39, 40], which carries a bad prognosis [40, 41]. In a recent study encompassing 72 single LTxs for COPD, there was no difference in 30-day survival in patients with or without early native lung complications, although the late survival was significantly worse in the patients who developed late native lung complications (5-year survival 50% *versus* 80%) [42].

The question whether single or double lung transplant for patients with COPD is the best option remains open and may give rise to several other considerations, as recently suggested by Hull *et al* [43]. In their paper, they report the outcome of a retrospective analysis (using the United Network for Organ Sharing (UNOS) database) of waiting list and post-transplant survival in patients with COPD: 4.87% of the patients died while waiting and another 4.75% were removed from the waiting list because of clinical deterioration. However, in patients who were listed as unrestrictive, meaning either single or double lung (whatever comes first) *versus* restricted (double lung only), the waiting list mortality was significantly lower (4.0 *versus* 5.9%, p <0.001). Also, the median survival was better in unrestricted patients (6.09 *versus* 4.39 years, p=0.002). However, the median post-transplant survival was better after double than after single LTx (6.6 *versus* 5.3 years). They conclude that, despite better long-term survival after double LTx with inherent related increased waiting list mortality, the current lung allocation score (LAS), which does not prioritise patients with COPD, may drive continued use of single LTx [43]. Depending on local organ availability and balancing individual patient risk–benefit ratio, unilateral LTx may therefore still be considered as the preferred option in some centres.

Outcome

According to the latest ISHLT registry report, the overall 1-year survival after LTx (transplants between January 2000 and June 2017) has increased to 85%, varying between 84% for idiopathic pulmonary fibrosis (IPF) and 90% for cystic fibrosis (CF), with COPD in between at 87%. In the latest era (2012–2017), the overall 1-year survival was 83%, and 86% after single lung and double LTx, respectively [44]. The overall 5-year survival (conditional on survival to 1 year) was 71% in the 2008–2013 era (>15 000 procedures), with a significantly better survival after double *versus* single LTx (74% and 61%, respectively). The 5-year survival after transplantation for COPD was 70.4%, compared with 79% for CF and 67% for IPF [43]. The median survival in patients with COPD with α-1 AD was 7.9 years compared with 6.2 years in the patients without α-1 AD [38].

In a paper by Crawford *et al*. [45], using transplant data from the UNOS, the authors looked at the lung transplant survival rates in 3554 patients with COPD, 38% (1358) single lung transplants and 62% (2196) double lung transplants. At 1 year after transplant, the survival was 88% for both procedures; however, 5-year survival was significantly lower after single lung compared with double lung transplant (51% *versus*

59%, p<0.01). After adjustment for underlying risk factors, the hazard ratio for 5-year mortality was significantly reduced after double LTx (hazard ratio 0.88 (95% CI 0.78–0.99), p=0.04) [45].

In another recent paper, Benvenuto *et al*. [46] compared survival after right single lung or double LTx with left single LTx in patients with COPD, using the UNOS database. Adjusted 5-year survival was 58% for double lung transplant recipients, 57% for right single lung and 51% for left single lung. They concluded that, in light of the ongoing donor lung shortage, preferential allocation to right single lung in patients with COPD should be considered, at least when patients are registered for a single LTx [46].

Riley *et al.* [47] specifically investigated the survival after LTx for α-1 AD. They identified 1556 such patients from the UNOS database. The patients who received a double lung transplant had a significantly better 5-year survival compared with single lung recipients (62% *versus* 47%). The median survival was 7.7 *versus* 4.4 years, respectively after double and single lung transplant. They concluded that the median survival after transplantation for α-1 AD is comparable to other diseases, but patients with α-1 AD have increased post lung transplant mortality due to infections and liver disease [47].

LTx for COPD may result in a survival benefit of at least 2 years in 39% of patients, with patients having a higher LAS (more severe patients) achieving the longest benefit [48]. In a recent study, Timofte *et al*. [49] compared the survival benefit of LTx in patients with COPD with medical management and pulmonary rehabilitation. They included 1337 patients with COPD from the UNOS database and 596 patients assigned to receive pulmonary rehabilitation and medical management in the National Emphysema Treatment Trial (NETT). UNOS patients with a 6-min walk distance (6MWD) <300 m or FEV_1 <20% pred had a better mean survival than NETT patients (5 years *versus* 3.4 years, respectively, p <0.0001), whereas the mean survival was comparable when the UNOS patients had a 6MWD >300 m or >20% pred FEV_1 (5.4 *versus* 4.9 years) [49].

Health-related quality of life (HRQOL) is reported to improve significantly, especially within the first 3 months after LTx for all indications and remains stable up to 3 years [50].

Although lung function improves significantly after LTx, this is not always reflected in a good performance index. Indeed, the 6MWD, which is used to calculate the BODE index before LTx, is not systematically measured after LTx. There are in fact no studies available comparing pre- and post-transplant 6MWD [50]. When evaluating peak V'_{O_2} after LTx, this is mostly reduced to 40–60% of predicted values, independent of the pulmonary function and may be comparable after single as well as after double LTx. Although this seems a restriction, in most of the patients the peak V'_{O_2} at least doubles compared with pre-transplant settings [51].

Post-transplant follow-up and complications

Strict monitoring and close follow-up is mandatory in all transplanted patients. In a typical post-transplant setting, patients are asked to monitor their medication intake, and to measure their temperature daily and, whenever they have a problem, to perform home spirometry and contact the transplant centre when FEV_1 declines by 10% or more. Regular outpatient visits are planned according to the post-transplant time from once a week to three times a year. During these visits, blood is drawn (for routine tests and trough levels of immunosuppressive medication), a chest radiograph and spirometry (full pulmonary function including volumes and diffusion capacity at least yearly) are performed. In some centres, a chest CT is scheduled at least every year and whenever a problem arises (for instance, FEV_1 decline, new opacities on chest radiograph *etc.*). Surveillance bronchoscopy with bronchoalveolar lavage and transbronchial biopsies may be performed during the first 2 years and whenever a drop in FEV_1 occurs.

The frequency distribution of complications after LTx for COPD was significantly different from all other underlying diseases, such as pulmonary fibrosis, pulmonary arterial hypertension, CF and non-CF bronchiectasis. In fact, in our own experience, causes of death in transplanted patients with COPD were in decreasing frequency: chronic lung allograft dysfunction (CLAD), infections, (viral, bacterial and fungal), malignancies (primary lung cancer, post-transplant lymphoproliferative disorder/lymphoma, urogenital, gastrointestinal tract skin cancer), postoperative complications, some unknown causes and cardiovascular events [52].

CLAD remains one of the most important complications, leading to extensive morbidity, loss in HRQOL, mortality and high costs after LTx. There is no clear evidence that the development of CLAD differs between COPD and the other lung transplant indications [43]. CLAD is characterised by a progressive and permanent loss of FEV_1 of at least 20% compared with the best post-transplant FEV_1, in the absence of another cause and after at least 6 weeks of azithromycin treatment [53]. It affects up to 40–60% of patients

within 5 years of their transplant [44]. Different CLAD phenotypes have been identified, with their own characteristics for diagnosis, and a different survival after diagnosis (from 1–2 years to 3–5 years, according to the phenotype) [53, 54]. CLAD remains difficult to treat [55] and the ultimate treatment option may be a redo transplantation in highly selected patients, especially with the obstructive CLAD phenotype [52, 54].

Conclusions

Lung transplantation for endstage COPD/α-1 AD remains a valuable option in selected patients, who are willing to go through the transplant trajectory and able to follow a pulmonary rehabilitation programme. According to the LAS, the waiting time for patients with COPD may be longer, so early referral is certainly indicated. LTx is the final treatment option, after all other possibilities, including adequate drug therapy, rehabilitation, volume reduction (surgical or endoscopic) have been explored. Surgical or endoscopic volume reduction is no contraindication for LTx, but may be a bridging procedure to allow the patients to better rehabilitate.

The outcome of LTx for COPD is certainly acceptable and provides a better HRQOL and longer survival in most patients. The procedure, whether single or double lung, depends on the centre's experience, the waiting list, donor availability and the risk–benefit ratio for the patient.

Complications are rather the rule than the exception, and patients need to be informed about these possible threats before undergoing the transplant procedure, as specific treatments are sometimes very difficult or even lacking, leading to permanent loss in FEV_1, HRQOL, increased morbidity and finally death.

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Previous articles in this series: No. 1: Montes de Oca M, Laucho-Contreras ME. Smoking cessation and vaccination. *Eur Respir Rev* 2023; 32: 220187. No. 2: Volpato E, Farver-Vestergaard I, Brighton LJ, *et al.* Nonpharmacological management of psychological distress in people with COPD. *Eur Respir Rev* 2023; 32: 220170. No. 3: Owens RL, Derom E, Ambrosino N. Supplemental oxygen and noninvasive ventilation. *Eur Respir Rev* 2023; 32: 220159.

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