

Lung transplantation in chronic obstructive pulmonary disease: patient selection and special considerations

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity. Lung transplantation is one of the few treatments available for end-stage COPD with the potential to improve survival and quality of life. The selection of candidates and timing of listing present challenges, as COPD tends to progress fairly slowly, and survival after lung transplantation remains limited. Though the natural course of COPD is difficult to predict, the use of assessments of functional status and multivariable indices such as the BODE index can help identify which patients with COPD are at increased risk for mortality, and hence which are more likely to benefit from lung transplantation. Patients with COPD can undergo either single or bilateral lung transplantation. Although many studies suggest better long-term survival with bilateral lung transplant, especially in younger patients, this continues to be debated, and definitive recommendations about this cannot be made. Patients may be more susceptible to particular complications of transplant for COPD, including native lung hyperinflation, and development of lung cancer.

Keywords: emphysema, pulmonary hypertension, mortality, prognosis, outcomes, alpha-1 antitrypsin deficiency

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death, and it remains the most common indication worldwide for lung transplantation, accounting for 38% of all lung transplants performed between 1995 and 2013.¹ However, it remains unclear which patients with COPD will benefit most from lung transplant and at what point in the course of the disease listing should occur. Compared to other diseases for which lung transplant is performed, COPD has a slower rate of progression and less short-term mortality. In the US, lungs are allocated for transplant using the lung allocation score (LAS), which gives priority to patients with higher short-term mortality, thus leading to longer waiting times for patients with COPD. The choice of single vs bilateral lung transplant (SLT vs BLT) has also been debated in the literature, and the results are conflicting. In this review, we will discuss the measures used to predict mortality in COPD, attempts to use those measures to identify patients who are most likely to benefit from lung transplant, and the optimal timing of listing, choice of procedure, and potential complications from transplantation in this group of patients.

Predicting mortality in patients with COPD: the challenges of identifying prognostic factors

The natural course of COPD is more protracted than that of other respiratory diseases for which transplants are performed.² For this reason, it is often difficult to determine when

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in the course of their disease patients with COPD should be listed for lung transplant. Survival after lung transplant remains limited due to chronic lung allograft dysfunction (CLAD),³ with a median survival between 5 and 6 years for all patients as well as for those undergoing transplant specifically for COPD.¹ This time may be shorter than the expected survival without transplant of many patients with COPD, even in the advanced stages. A patient who is listed too early for lung transplant could lose years of life if his/her survival without transplant would exceed the typical survival posttransplant. The longer natural history of COPD has the potential to lead to more deconditioning over time compared to other indications for lung transplant. Hence, waiting too long to transplant allows for progression of debility due to disease and physical deconditioning, which can lead to poor outcomes after transplant. For this reason, an accurate assessment of expected survival is critical to maximizing the benefit of lung transplantation (Table 1).

Earlier studies assessing mortality in COPD focused on single measurements, in particular the degree of airflow obstruction measured by the forced expiratory volume in 1 second (FEV₁). An early study by Traver et al showed FEV₁ post-bronchodilator as the most significant predictor of mortality in patients with COPD.⁴ Patients with an FEV₁ <30% of predicted were found to have survival rates of 65% and 30% at 2 and 5 years, respectively. Due to this and other observations, an FEV₁ <30% was considered to be a threshold at which to consider listing for lung transplant. Later studies,⁵ particularly those which included patients with more advanced COPD, have shown that FEV₁ can be a fairly weak predictor of mortality and other factors should be considered. A low FEV₁ is perhaps the most common

reason for referral to a lung transplant center, but in itself is insufficient to identify which COPD patients will benefit from lung transplant.

Highlighting the need to look beyond the FEV₁, Martinez et al identified several physiologic factors which were independent predictors of mortality in the medical therapy arm of the National Emphysema Treatment Trial (NETT), which included 609 patients with advanced emphysema.⁶ Independent predictors of mortality included older age, supplemental oxygen use, lower hemoglobin, higher residual volume, lower CO diffusing capacity, lower maximal exercise capacity, and lower lobe-predominant emphysema. Interestingly, FEV₁ did not have a significant association with mortality in the multivariate analysis, perhaps due to the fact that FEV₁ was severely reduced in most patients and therefore lost its discriminatory ability. This finding also applies to patients with COPD being evaluated for lung transplant since the majority will have a low FEV₁.

Gas exchange has also been evaluated as a prognostic factor in COPD, but the association has been variable. A French study sought to evaluate hypoxemia as a predictor of mortality in COPD patients on home oxygen.⁷ Only patients with an arterial oxygen tension (PaO₂) <50 mmHg had significantly worse survival compared to the rest of the cohort of COPD patients on oxygen, which highlights the difficulty of using hypoxemia, except at the extreme end, to stratify patients with COPD. Hypercapnia may be a more robust predictor of mortality. Elevated arterial CO₂ tension (PaCO₂) levels have been shown to have a stronger association with mortality in COPD, though this too has been variable.^{8,9} A recent Swedish study by Ahmadi et al attempted to clarify the effect of hypercapnia on mortality in a national registry of COPD patients on long-term oxygen therapy.⁸ In keeping with prior studies which have shown either hypo-^{10,11} or hypercapnia¹² to be a risk factor for increased mortality, Ahmadi et al found that the association between PaCO₂ and mortality was U-shaped, with the lowest mortality at a PaCO₂ of about 49 mmHg.⁸ Increased mortality was seen at PaCO₂ levels <37.5 and >52.5 mmHg. The increased minute ventilation in COPD patients with hypocapnia may lead to respiratory muscle fatigue and failure, a finding that may reflect incapacity to adapt the breathing pattern to avoid fatigue. Furthermore, hypocapnia may foreshadow congestive heart failure or pulmonary embolism. The level of PaCO₂ has a significant impact on the selection of lung transplant candidates, as hypercapnia is often used to identify patients who have reached the point of needing a transplant, and it is used in the calculation of the LAS, with higher PaCO₂ leading to higher scores.

Table 1 Factors associated with mortality in COPD patients

Older age
Lower BMI
Increasing dyspnea
Need for supplemental oxygen
Lower maximal exercise capacity
Decreased 6MWD
Lower FEV ₁
Higher residual volume
Lower CO diffusion capacity
Hypoxemia/hyper- or hypocapnia
Lower hemoglobin
Predominantly lower-lobe emphysema
Pulmonary hypertension
BODE score

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index; BODE, BMI, obstruction, dyspnea, and exercise capacity; CO, carbon monoxide; FEV₁, forced expiratory volume in 1 second.

Subjective and objective assessments of dyspnea and functional capacity have been used to identify COPD patients with a higher risk of dying that may benefit from lung transplant. A Japanese cohort study followed 183 patients with COPD and evaluated dyspnea and FEV₁ as predictors of 5-year survival.¹³ The authors found that dyspnea, as measured on a five-point scale,¹⁴ was more closely associated with mortality than the American Thoracic Society (ATS) staging of COPD severity by FEV₁.¹⁵ More recently, Wilke et al¹⁶ found that a decreasing functional status by St George's Respiratory Questionnaire (SGRQ), COPD-specific version (SGRQ-C), which includes symptoms, activity level, and impact on life, was significantly associated with 2-year mortality. Although dyspnea and functional status are useful in predicting prognosis, they are subject to the patients' perceptions, which may vary in different populations.

A more objective measure of functional status is exercise capacity that can be assessed with cardiopulmonary exercise testing (CPET) or the 6-minute walk test (6MWT). Oga et al¹⁷ found that exercise capacity as measured by peak oxygen uptake (VO₂ max) during CPET was more strongly associated with 5-year mortality than FEV₁. A later study by Yoshimura et al confirmed the mortality risk conferred by a low VO₂ max, and identified increased hypoxemia, acidosis, and sympathetic activity during CPET as additional risk factors.¹⁸ CPET presents logistical difficulties as it requires specialized equipment, trained personnel, and expertise in interpreting studies. The simpler and readily available 6MWT also provides objective information about functional capacity, and though not as detailed as CPET, it has been shown to be useful in many cardiopulmonary diseases. Cote et al¹⁹ showed that CPET and the 6MWT had a modest correlation and, more importantly, both low VO₂ during CPET and decreased 6-minute walk distance (6MWD) were associated with mortality during the follow-up period, which averaged 5.5 years. Casanova et al also looked at 6MWD and pulse O₂ desaturation during the 6MWT, and both were more closely associated with mortality than FEV₁.²⁰ Interestingly, the 6MWT performed better in patients who had an FEV₁ <50% of predicted, thus showing its ability to distinguish patients with advanced obstruction at a higher risk of dying.

Pulmonary hypertension (PH), particularly of the precapillary type (mean pulmonary artery pressure [mPAP] ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg),²¹ is prevalent in patients with advanced COPD, and, when severe, can help identify patients at a higher risk for death. Several studies have shown an association between cor pulmonale or PH and mortality in

COPD patients.^{4,22,23} A retrospective review of data from 4,930 patients listed for lung transplant who had right heart catheterization found that 30% had precapillary PH, and an additional 17% of patients had postcapillary PH (mPAP ≥25 mmHg and pulmonary artery wedge pressure >15 mmHg).²³ Both groups of patients had increased mortality. Hurdman et al²⁴ identified from the ASPIRE registry 101 COPD patients with PH and noted that severe PH (mPAP >40 mmHg) was significantly associated with increased mortality at both 1 and 3 years. The 3-year mortality in COPD patients with severe PH was 67%, as opposed to 45% for those with less severe PH (mPAP 25–39 mmHg). These data suggest that patients with severe PH clearly have shorter expected survival and should be considered for transplant.

In light of the limitations of any one parameter to predict mortality in patients with COPD, multivariate approaches have become available. Perhaps the best known and most widely used remains the body mass index (BMI), obstruction, dyspnea, and exercise capacity (BODE) index, developed by Celli et al.²⁵ The BODE index combines BMI, FEV₁, the Modified Medical Research Council dyspnea scale, and 6MWD into a weighted 10-point score. Patients with COPD and a BODE score of 7–10 had a mortality of 80% at 52 months, whereas patients with the most severe airflow obstruction by ATS criteria (FEV₁ <35% of predicted)¹⁵ had a mortality of 55%. Considering that lung transplantation has an average survival of approximately 5–6 years, the BODE index would appear to better identify COPD patients that would benefit from this intervention. In addition, acute exacerbations of COPD, particularly those requiring hospitalizations, are also associated with mortality, and combining this information with the BODE index can add to its predictive value.²⁶

Outcomes after lung transplant: is there a survival benefit?

Predicting mortality is critical in determining which patients may potentially benefit from lung transplantation, but it is only the first step. Selection is further complicated by the fact that many of the factors which are related with mortality in patients with COPD can also be associated with poor outcomes after transplant. For example, physical deconditioning can lead to reduced 6MWD and predispose to worse outcomes after transplant. Low BMI, which is a component of the BODE index, has been associated with shorter survival after lung transplant.²⁷ The challenge is to identify those COPD patients with advanced disease that will recover after

lung transplant to achieve both a survival and quality-of-life benefit with this treatment.

The LAS was implemented in 2005 in response to a mandate that all organs be allocated in a manner which reduces wait times, and allocates according to medical urgency.²⁸ This system seeks to determine a survival benefit 1 year after lung transplant by calculating the difference between the 1-year survival on the wait list (ie, without a transplant) and 1-year survival after transplant.²⁹ In order to meet the expectation of reducing wait times and allocating organs to those in the most need, the wait list survival is weighted twice in the calculation of the score. The use of 1-year survival in the calculation of the LAS has a unique impact on patients with COPD. As previously described, the mortality in COPD is seen beyond 1 year, hence COPD patients will not receive priority given that the 1-year survival is better than that of other diseases such as pulmonary fibrosis. Additionally, the LAS does not take quality of life into account, and considering that the survival in lung transplant is relatively disappointing, improvement in quality of life is an important consideration when deciding who should be transplanted.³⁰ The equity, fairness, and utilitarianism of this system continue to be debated.

Although some investigations have shown that transplantation in COPD does not lead to a survival benefit,^{31–33} they studied populations with overall outcomes that are slightly worse than the current state. They do, however, highlight the need to identify the subsets of patients with COPD who stand to benefit most from transplant. Thabut et al used the United Network for Organ Sharing database and simulations to estimate the survival impact of lung transplant.³⁴ They found that 79% of patients with an FEV₁ < 16% of predicted will gain at least 1 year of survival after transplant, but only 11% of patients with an FEV₁ > 25% will do so. The systolic pulmonary artery pressure, FEV₁, BMI, 6MWD, need for continuous mechanical ventilation or supplemental O₂, and functional class (scored 1–4) affected the survival benefit.

In order to further help identify which COPD patients could benefit from lung transplant, Lahzami et al calculated the BODE index score before transplant on 54 lung transplants performed for COPD.³⁵ The authors found that most patients transplanted outlived their predicted survival by the BODE score and noted that a survival benefit 4 years after transplant was only evident in patients with BODE ≥ 7 . The finding of survival benefits being limited to patients in the highest BODE quartile (≥ 7) was confirmed in an analysis by Cerón Navarro et al on 107 patients transplanted at a single Spanish center.³⁶

Other studies have addressed the specific questions of outcomes after transplantation for COPD, including mortality

as well as incidence of complications such as primary graft dysfunction (PGD), acute rejection, and chronic rejection or bronchiolitis obliterans syndrome. Tanash et al reviewed a cohort of patients transplanted in two centers in Sweden.³⁷ Patients transplanted for COPD had a median survival of 9 years. Though the authors did not set out to make this claim, based on the BODE index, FEV₁, and 6MWD, the observed median survival would most likely exceed that expected of this population without transplant. Interestingly, patients with alpha-1 antitrypsin deficiency (A1ATD) had better survival compared to those with smoking-related emphysema without A1ATD. Improved outcomes in patients with A1ATD as compared to patients with emphysema from other causes are also seen in the International Society for Heart and Lung Transplant (ISHLT) registry.¹ Zeriuoh et al³⁸ sought to study the consecutive outcomes of 88 patients undergoing lung transplant for COPD, excluding patients with A1ATD. They noted a 6-year survival of 57%, which is comparable to described registry outcomes.¹ Interestingly, they observed significantly less PGD, which could be explained in part by a trend toward less use of cardiopulmonary bypass in patients with emphysema as opposed to patients with other indications for lung transplant (63% vs 75%).

Recent studies have also identified factors which could have a negative effect on outcomes of lung transplant for COPD. In an analysis of outcomes from 108 recipients undergoing lung transplant for emphysema (including A1ATD), Inci et al found that age ≥ 60 years at the time of transplant was associated with reduced 1- and 5-year survival (91% vs 79% and 84% vs 54%, respectively).³⁹ In addition, patients 60 years or older accounted for more cases of early CLAD than younger subjects. Advanced age has been shown to negatively affect long-term outcomes in patients with other diseases,⁴⁰ and in COPD, where the survival benefit is often seen later after transplant, this is particularly noteworthy.

PH, as described above, is associated with increased mortality from COPD. It is however, also associated with increased complications of lung transplant such as bleeding and PGD.^{41,42} Singh et al addressed the question of whether PH is associated with 1-year mortality after lung transplant in patients with COPD, idiopathic pulmonary fibrosis, and cystic fibrosis.⁴³ Although patients with COPD had a lower incidence of PH, the relative risk of mortality at 1 year after transplant was increased significantly in COPD, but not for the other diseases. The difference could be due to the fact that PH is found in the patients with advanced COPD who may have additional comorbidities and more physical deconditioning which are known to lead to poor outcomes after transplant.

Older patients are now being transplanted for COPD and other indications. The previously held age cutoff of 65 years is not recognized by many transplant centers, which instead choose to base decisions on “physiologic” age. From 1985 to present, the median age of transplant recipients has increased from 45 to 55 years, and since 2006, approximately 10% of patients transplanted are over the age of 65 years.⁴⁴ This frequency continues to increase every year. However, transplanting older patients means more recipients will have comorbidities with the potential to complicate outcomes. Coronary artery disease (CAD) and osteoporosis are particularly common in older transplant candidates due to a combination of risk factors including age, history of smoking, chronic steroid use, and vitamin D deficiency. While CAD can lead to cardiovascular mortality, several studies have shown that revascularization of coronary disease prior to or concurrent with lung transplant surgery can lead to outcomes comparable to patients without CAD,^{45,46} suggesting that CAD amenable to revascularization is not a contraindication to lung transplant. The prevalence of osteoporosis or osteopenia has been shown to be as high as 86% in end-stage lung disease patients being evaluated for lung transplant,⁴⁷ and fragility fractures are common in these patients.⁴⁸ Patients with COPD, particularly those with chronic glucocorticoid use, are particularly at risk. As with CAD, osteoporosis is a potentially manageable comorbidity. Importantly, one or a few comorbidities can be treated with good outcomes, but the cumulative effect of many can lead to shortened survival or impaired quality of life after transplant.

Referral and listing for lung transplant

In 2014, ISHLT released new guidelines for selection of lung transplant candidates.⁴⁹ Referral to a transplant center was recommended for COPD patients who demonstrate progressive disease despite maximal therapy, are hypercapnic (>50 mmHg) or hypoxemic (<60 mmHg), or have an FEV₁ <25% of predicted. The BODE index is suggested as a threshold for referral (a score of 5–6) and listing (a score of ≥7). The presence of severe PH is also recommended as a criterion for listing, given its association with mortality. Exacerbations are associated with mortality in COPD, particularly in patients who have more than three hospitalizations for this reason in 1 year. Accordingly, ISHLT guidelines recommend listing for patients with three or more exacerbations requiring hospitalizations or just one exacerbation when associated with hypercapnic respiratory failure.

Although patients meeting the above criteria are thought to derive a survival benefit from transplant, they are in most cases likely to receive a low priority on the list. Although PaCO₂ and pulmonary artery pressures are used in determining the LAS, other factors such as frequency of exacerbations, FEV₁, and degree of dyspnea are not included. In many US centers that routinely perform transplants on higher risk patients, this could result in long waiting times for patients with COPD. As the time from listing to transplant is being evaluated as a quality metric by third-party payers, this may impact how centers choose to time the listing for transplant.

A1ATD and transplant

Patients who have A1ATD are likely to have a different phenotype of emphysema from most patients with typical emphysema from smoking. They tend to present with advanced disease at a younger age, and hence may reach the point of requiring transplant sooner than patients with emphysema from other etiologies. This may be an advantage if they are transplanted at a younger age with fewer comorbidities and less physical deconditioning. Patients with A1ATD made up 6% of those patients transplanted between 1995 and 2012, as compared to 33% with COPD not associated with A1ATD.¹ The recommendations for selecting patients for listing with A1ATD are not different from those for patients with other forms of COPD. In fact, the BODE index demonstrates a similar ability to predict mortality in patients with A1ATD as it does with patients with COPD who are alpha-1 replete.⁵⁰ The management of patients with A1ATD after transplant is no different from that of other patients with emphysema. Banga et al compared 45 patients with A1ATD undergoing lung transplantation with 231 A1AT-replete patients with emphysema.⁵¹ They found no difference in overall rate of FEV₁ decline after transplant or in frequency or severity of episodes of acute cellular rejection. Although there are biologic mechanisms proposed by which A1AT could modify pathways leading to development of CLAD,⁵² there is no definitive evidence to support the use of augmentation in patients who have been transplanted, and the debate about the utility of this costly therapy continues.

Management of patients undergoing evaluation and listing for transplant

Waiting times for lung transplant are likely longer for patients with COPD. This brings up the question of how best to maintain patients' fitness for transplant and how to potentially delay the need for lung transplant and increase overall survival. Pulmonary rehabilitation is known to improve

exercise capacity and quality of life and reduce exacerbations. It has been shown to also be of benefit to patients awaiting lung transplant.^{53,54} A Toronto, Canada group demonstrated that patients undergoing pulmonary rehabilitation before transplant maintained their 6MWD and that a higher 6MWD led to a shorter hospitalization after transplant.⁵⁴ Therefore, patients with COPD who are listed for lung transplant should remain in pulmonary rehabilitation to preserve their physical conditioning and optimize their posttransplant potential for recovery.

Unfortunately, alternatives to lung transplant for any end-stage lung disease, including COPD, are rare. Lung volume reduction (LVR), either surgical (LVRS) or endoscopic, offers the possibility of improved quality of life by increasing exercise capacity and decreasing dyspnea. In a large randomized trial, patients with poor exercise capacity and predominantly upper-lobe emphysema had improvements in exercise capacity as well as survival.⁵⁵ The effect of LVRS on outcomes after subsequent lung transplant is a source of debate. Nathan et al demonstrated that patients undergoing LVRS prior to lung transplant had no difference in the need for reoperation, hospital length of stay, or survival after transplant.⁵⁶ A more contemporary study found that patients undergoing prior LVRS had significantly worse posttransplant survival than those undergoing transplant alone.⁵⁷ These conflicting findings make it difficult to offer LVRS to patients who are expected to require lung transplant eventually.

A multicenter European trial has shown that endoscopic LVR can improve SGRQ results and 6MWD in selected patients with emphysema,⁵⁸ suggesting it may offer a less invasive therapy with a reduced number of complications. A single-center German study has shown that patients undergoing endoscopic LVR prior to transplant do not experience worse outcomes after transplant.⁵⁹ Endoscopic LVR is still not approved in the US, but is currently being evaluated in randomized controlled trials (LIBERATE: NCT01796392, RENEW: NCT01608490).

Lung transplantation of critically ill patients is becoming more common. This includes patients who are bridged with either mechanical ventilation or extracorporeal life support (ECLS). Often, patients with COPD who progress to that point have accumulated too much disease burden and are no longer considered candidates. Singer et al used the Organ Procurement and Transplantation Network registry to compare 424 patients transplanted while on mechanical ventilation to propensity-matched patients not receiving this support.⁶⁰ Although early mortality was higher in patients transplanted while on mechanical ventilation, those

who survived 6 months had similar long-term outcomes. Patients with COPD and other obstructive lung diseases transplanted while on mechanical ventilation had no difference in survival at any time point when compared to propensity-matched, non-ventilated controls. These results suggest that selected patients with COPD who require mechanical ventilation for bridging can be transplanted successfully.

The use of ECLS to avoid some of the complications of mechanical ventilation such as propagation of lung injury and deconditioning due to sedation or neuromuscular blockade is becoming more frequent.⁶¹ Although studies of bridging to lung transplant with extracorporeal support do not generally include many patients with COPD,^{62,63} there is a growing body of evidence supporting the use of ambulatory ECLS to allow patients to undergo rehabilitation while awaiting transplant. Perhaps due to longer expected waiting times and increased accumulation of comorbidities in patients, ECLS is rarely used in patients with COPD, though it remains an option in selected patients.

Procedure choice: single vs bilateral

The choice of SLT or BLT as the optimal procedure for patients with COPD continues to be unclear. Unlike some other indications for transplant such as PH or cystic fibrosis, in COPD, either bilateral or single lung transplantation is a viable option. The main advantages of SLT are resource utilization and access to organs, since one donor can supply two recipients. Therefore, the waiting time for a single lung may be shorter than that for a pair. On the other hand, BLT offers more effective lung tissue and hence more reserve in the event of complications such as acute rejection, pneumonia, or the development of chronic rejection.

In patients with COPD, early studies suggested a benefit of BLT, particularly in younger recipients. Meyer et al performed survival analysis on 2,260 patients receiving a transplant for COPD in the ISHLT/UNOS database. They found that patients ≤ 60 years had a survival benefit with BLT as opposed to SLT, and that benefit increases further out from transplant.⁶⁴ However, in patients over 60 years, this benefit was not seen, as mortality after BLT increased in that population. Selection bias may confound this study, as SLT is often offered to patients who have comorbidities. Thabut et al later analyzed a larger cohort from the same dataset using propensity-based matching in an attempt to control for indication bias. They found that the mortality in patients receiving BLT was lower than for SLT.⁶⁵ More recently, the question of procedure choice and survival was readdressed by Schaffer et al using patients in the UNOS

database who were transplanted in the post-LAS period.⁶⁶ The authors found no survival difference at 5 years for BLT or SLT in patients with COPD, but noted that, if they had extended their analysis to 10 years, they would likely have seen a survival benefit in patients undergoing a BLT.

Patients with COPD receive less priority under the current LAS, therefore patients who are transplanted likely represent a population with more advanced disease, as opposed to before the implementation of the LAS. Patients with more severe disease may be less likely to tolerate a BLT, therefore mitigating the survival benefit seen in earlier studies. In an effort to address the question of whether it is beneficial to accept an offer for a single lung, as opposed to waiting for a pair Wang et al used a sequential stratification method. Whereas accepting a single lung offer conferred a survival for pulmonary fibrosis patients waiting on the list, it did not do so for patients with COPD.⁶⁷ In summary, it is reasonable to consider BLT in younger patients, who are more likely to tolerate that procedure and might expect a longer survival but utilize SLT in older patients who may not tolerate a longer operation or the longer wait times or BLT.

Pitfalls of lung transplantation for COPD

Patients with COPD due to smoking and other factors are at increased risk for developing bronchogenic carcinoma. The immune system plays a role in suppressing tumor development, and the use of immunosuppressive therapy for prevention of allograft rejection is associated with an increased risk of malignancy.⁶⁸ Since lung transplant recipients are more heavily immunosuppressed, their higher cancer risk is well described in the literature.⁶⁹ Those undergoing transplant for COPD are particularly vulnerable to developing lung cancer, especially in the case of single lung transplantation where a native smoking-exposed lung is still present.

A higher lung cancer risk was demonstrated by Dickson et al⁷⁰ who reviewed outcomes in 262 patients transplanted at Duke University. In this series, eight out of nine patients who developed primary lung cancer were transplanted for emphysema, and each case of primary lung cancer developed in the native lung of SLT recipients. The prevalence of lung cancer in SLT for COPD was 6.9%, and recipient age and smoking history >60 pack-years were associated with its development. A Cleveland Clinic (Cleveland, OH, USA) study of 506 patients by Minai et al⁷¹ found 12 cases of bronchogenic carcinoma, eleven of which developed in patients with emphysema. All but one case were detected in the native lung of SLT recipients.

Yserbyt et al also showed similar occurrence of lung cancer after transplant⁷² and a separate study by the same group noted a significantly increased prevalence in transplant recipients who resume smoking after transplant compared those who do not (10% vs 2%, $P < 0.021$).⁷³ A more recent report, by Grewal et al, from Boston, MA, USA, demonstrated a similar prevalence of lung cancer developing post-transplant in patients with idiopathic pulmonary fibrosis and COPD (3.4% and 3.3%, respectively).⁷⁴ Incidentally, one case was noted in a patient undergoing BLT for COPD which was thought to be of recipient origin, arising from the right mainstem bronchus.

Patients developing cancer after transplant had worse survival than non-transplanted lung cancer patients.⁷⁴ This suggests a role of immunosuppression in the development and progression of lung cancer in transplant recipients. Possible management strategies include reduction of immunosuppression, surgery, radiation, or chemotherapy depending on stage. However, treatment with curative intent was rarely successful, even if the patient presented with stage I disease. A common practice in response to a cancer diagnosis is adjustment of immunosuppression, including discontinuing cell cycle inhibitors (usually mycophenolate mofetil). The use of inhibitors of mammalian target of rapamycin (mTOR), including everolimus and sirolimus, may have antineoplastic effects, but this has not been studied in lung transplant recipients who develop lung cancer, and cannot be recommended definitively. While computed tomography screening of at-risk patients in the general population has shown mortality benefit,⁷⁵ there is no such study in lung transplant patients, and the poor outcomes seen for early-stage disease make it difficult to recommend in the absence of evidence.

Native lung hyperinflation (NLH) after SLT for COPD is another potential complication after transplant. This is seen frequently in the early postoperative period with air-trapping in the native lung while the patient is on positive-pressure ventilation. Although common, the clinical significance of NLH is debated. Several studies have demonstrated that even when NLH occurs, it does not significantly impact mortality or morbidity.^{76,77} Often, the reason for development of NLH is an underlying pathology of the graft such as PGD or acute rejection. These two conditions lead to increased resistance of the transplanted lung and more air-trapping in the native lung. Treatment options available are independent lung ventilation at the time of transplant or either surgical or endobronchial LVR of the native lung.^{78–80} Apart from a lung-protective ventilation strategy to prevent graft injury and limit hyperinflation by using low tidal volumes with a

goal of early extubation and removal of positive pressure, other therapies such as independent lung ventilation and LVR cannot be broadly recommended and should be decided on an individual patient basis.

Conclusion

Although significant advances have occurred in the last few decades, there is still a need for more research to better identify COPD patients who will benefit from lung transplantation and optimize their outcomes.

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Author contributions

C Randall Lane participated in the literature search, writing and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. Adriano R Tonelli participated in the writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted. Both authors contributed toward data analysis and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

- Yusen RD, Edwards LB, Kucheryavaya AY, et al; International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report – 2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014;33(10):1009–1024.
- Shah RJ, Kotloff RM. Lung transplantation for obstructive lung diseases. *Semin Respir Crit Care Med*. 2013;34(3):288–296.
- Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2014;33(2):127–133.
- Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. *Am Rev Respir Dis*. 1979;119(6):895–902.
- Celli BR. Predictors of mortality in COPD. *Respir Med*. 2010;104(6):773–779.
- Martinez FJ, Foster G, Curtis JL, et al; NETT Research Group. Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med*. 2006;173(12):1326–1334.
- Veale D, Chailleux E, Taytard A, Cardinaud JP. Characteristics and survival of patients prescribed long-term oxygen therapy outside prescription guidelines. *Eur Respir J*. 1998;12(4):780–784.
- Ahmedi Z, Bornefalk-Hermansson A, Franklin KA, Midgren B, Ekström MP. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. *Respir Res*. 2014;15:30.

- Martinez FJ, Kotloff R. Prognostication in chronic obstructive pulmonary disease: implications for lung transplantation. *Semin Respir Crit Care Med*. 2001;22(5):489–498.
- Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest*. 1996;109(3):741–749.
- Lima DF, Dela Coleta K, Tanni SE, Silveira LV, Godoy I, Godoy I. Potentially modifiable predictors of mortality in patients treated with long-term oxygen therapy. *Respir Med*. 2011;105(3):470–476.
- Foucher P, Baudouin N, Merati M, et al. Relative survival analysis of 252 patients with COPD receiving long-term oxygen therapy. *Chest*. 1998;113(6):1580–1587.
- Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest*. 2002;121(5):1434–1440.
- Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J*. 1959;2(5147):257–266.
- [No authors listed]. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(5 Pt 2):S77–S121.
- Wilke S, Jones PW, Müllerova H, et al. One-year change in health status and subsequent outcomes in COPD. *Thorax*. 2015;70(5):420–425.
- Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med*. 2003;167(4):544–549.
- Yoshimura K, Maekura R, Hiraga T, et al. Identification of three exercise-induced mortality risk factors in patients with COPD. *COPD*. 2014;11(6):615–626.
- Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. *Chest*. 2007;132(6):1778–1785.
- Casanova C, Cote C, Marin JM, et al. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. *Chest*. 2008;134(4):746–752.
- Galiè N, Humbert M, Vachiery JL, et al; Authors/Task Force Members. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2015. pii: ehv317. [Epub ahead of print].
- Solidoro P, Boffini M, Lacedonia D, Scichilone N, Paciocco G, Di Marco F. Pulmonary hypertension in COPD and lung transplantation: timing and procedures. *Minerva Med*. Epub 2014 Mar 11.
- Cuttica MJ, Kalhan R, Shlobin OA, et al. Categorization and impact of pulmonary hypertension in patients with advanced COPD. *Respir Med*. 2010;104(12):1877–1882.
- Hurdman J, Condliffe R, Elliot CA, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J*. 2013;41(6):1292–1301.
- Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005–1012.
- Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. *Respir Med*. 2009;103(5):692–699.
- Singer JP, Peterson ER, Snyder ME, et al. Body composition and mortality after adult lung transplantation in the United States. *Am J Respir Crit Care Med*. 2014;190(9):1012–1021.
- Eberlein M, Garrity ER, Orens JB. Lung allocation in the United States. *Clin Chest Med*. 2011;32(2):213–222.

29. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. *Am J Transplant.* 2006;6(5 Pt 2): 1212–1227.
30. Egan TM, Kotloff RM. Pro/con debate: lung allocation should be based on medical urgency and transplant survival and not on waiting time. *Chest.* 2005;128(1):407–415.
31. Stavem K, Bjørtuft Ø, Borgan Ø, 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(1):75–84.
32. 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(9095):24–27.
33. Lahzami S, Aubert JD. Lung transplantation for COPD – evidence-based? *Swiss Med Wkly.* 2009;139(1–2):4–8.
34. Thabut G, Ravaud P, Christie JD, 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(10): 1156–1163.
35. Lahzami S, Bridevaux PO, Soccia PM, et al. Survival impact of lung transplantation for COPD. *Eur Respir J.* 2010;36(1):74–80.
36. Cerón Navarro J, de Aguiar Quevedo K, Ansótegui Barrera E, et al. Functional outcomes after lung transplant in chronic obstructive pulmonary disease. *Arch Bronconeumol.* 2015;51(3):109–114.
37. Tanash HA, Riise GC, Ekström MP, Hansson L, Piitulainen E. Survival benefit of lung transplantation for chronic obstructive pulmonary disease in Sweden. *Ann Thorac Surg.* 2014;98(6):1930–1935.
38. Zerjoub M, Mohite PN, Sabashnikov A, et al. Lung transplantation in chronic obstructive pulmonary disease: long-term survival, freedom from bronchiolitis obliterans syndrome, and factors influencing outcome. *Clin Transplant.* 2015;29(4):383–392.
39. Inci I, Schuurmans M, Ehrsam J, et al. Lung transplantation for emphysema: impact of age on short- and long-term survival†. *Eur J Cardiothorac Surg.* Epub 2015 Jan 18.
40. Hayanga AJ, Aboagye JK, Hayanga HE, et al. Contemporary analysis of early outcomes after lung transplantation in the elderly using a national registry. *J Heart Lung Transplant.* 2015;34(2):182–188.
41. Diamond JM, Lee JC, Kawut SM, et al; Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med.* 2013;187(5):527–534.
42. Parada M, González D, Parente I, et al. Surgical risk factors associated with lung transplantation. *Transplant Proc.* 2009;41(6):2218–2220.
43. Singh VK, Patricia George M, Gries CJ. Pulmonary hypertension is associated with increased post-lung transplant mortality risk in patients with chronic obstructive pulmonary disease. *J Heart Lung Transplant.* 2015;34(3):424–429.
44. Yusef RD, Christie JD, Edwards LB, et al; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report – 2013; focus theme: age. *J Heart Lung Transplant.* 2013;32(10):965–978.
45. Castleberry AW, Martin JT, Osho AA, et al. Coronary revascularization in lung transplant recipients with concomitant coronary artery disease. *Am J Transplant.* 2013;13(11):2978–2988.
46. Sherman W, Rabkin DG, Ross D, et al. Lung transplantation and coronary artery disease. *Ann Thorac Surg.* 2011;92(1):303–308.
47. Lakey WC, Spratt S, Vinson EN, Gesty-Palmer D, Weber T, Palmer S. Osteoporosis in lung transplant candidates compared to matched healthy controls. *Clin Transplant.* 2011;25(3):426–435.
48. Hariman A, Alex C, Heroux A, Camacho P. Incidence of fractures after cardiac and lung transplantation: a single center experience. *J Osteoporos.* 2014;2014:573041.
49. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34(1): 1–15.
50. Thabut G, Mornex JF, Pison C, et al. Performance of the BODE index in patients with α 1-antitrypsin deficiency-related COPD. *Eur Respir J.* 2014;44(1):78–86.
51. Banga A, Gildea T, Rajeswaran J, Rokadia H, Blackstone EH, Stoller JK. The natural history of lung function after lung transplantation for α 1-antitrypsin deficiency. *Am J Respir Crit Care Med.* 2014;190(3): 274–281.
52. Tiriveedhi V, Banan B, Deepti S, et al. Role of defensins in the pathogenesis of chronic lung allograft rejection. *Human Immunol.* 2014;75(4): 370–377.
53. Kenn K, Gloeckl R, Soennichsen A, et al. Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. *Transplantation.* 2015;99(5):1072–1077.
54. Li M, Mathur S, Chowdhury NA, Helm D, Singer LG. Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant.* 2013;32(6):626–632.
55. Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003;348(21):2059–2073.
56. Nathan SD, Edwards LB, Barnett SD, Ahmad S, Burton NA. Outcomes of COPD lung transplant recipients after lung volume reduction surgery. *Chest.* 2004;126(5):1569–1574.
57. Backhus L, Sargent J, Cheng A, Zeliadt S, Wood D, Mulligan M. Outcomes in lung transplantation after previous lung volume reduction surgery in a contemporary cohort. *J Thorac Cardiovasc Surg.* 2014;147(5): 1678.e1–1683.e1.
58. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. *Thorax.* 2014;69(11):980–986.
59. Fuehner T, Clajus C, Fuge J, et al. Lung transplantation after endoscopic lung volume reduction. *Respiration.* Epub 2015 Jul 2.
60. Singer JP, Blanc PD, Hoopes C, et al. The impact of pretransplant mechanical ventilation on short- and long-term survival after lung transplantation. *Am J Transplant.* 2011;11(10):2197–2204.
61. Braune SA, Kluge S. Extracorporeal lung support in patients with chronic obstructive pulmonary disease. *Minerva Anesthesiol.* 2013;79(8): 934–943.
62. Turner DA, Cheifetz IM, Rehder KJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. *Crit Care Med.* 2011;39(12):2593–2598.
63. Garcia JP, Kon ZN, Evans C, et al. Ambulatory veno-venous extracorporeal membrane oxygenation: innovation and pitfalls. *J Thorac Cardiovasc Surg.* 2011;142(4):755–761.
64. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD. Single vs bilateral, sequential lung transplantation for end-stage emphysema: influence of recipient age on survival and secondary end-points. *J Heart Lung Transplant.* 2001;20(9):935–941.
65. Thabut G, Christie JD, Ravaud P, 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(9614):744–751.
66. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. *JAMA.* 2015;313(9):936–948.
67. Wang Q, Rogers CA, Bonser RS, Banner NR, Demiris N, Sharples LD; UK Cardiothoracic Transplant Steering Group. Assessing the benefit of accepting a single lung offer now compared with waiting for a subsequent double lung offer. *Transplantation.* 2011;91(8): 921–926.
68. von Boehmer L, Draenert A, Jungraithmayr W, et al. Immunosuppression and lung cancer of donor origin after bilateral lung transplantation. *Lung Cancer.* 2012;76(1):118–122.
69. Verleden GM, Fisher AJ. Lung transplantation and lung cancer: is there a link? *Respiration.* 2011;81(6):441–445.

70. Dickson RP, Davis RD, Rea JB, Palmer SM. High frequency of bronchogenic carcinoma after single-lung transplantation. *J Heart Lung Transplant*. 2006;25(11):1297–1301.
71. Minai OA, Shah S, Mazzone P, et al. Bronchogenic carcinoma after lung transplantation: characteristics and outcomes. *J Thorac Oncol*. 2008;3(12):1404–1409.
72. Yserbyt J, Verleden GM, Dupont LJ, Van Raemdonck DE, Dooms C. Bronchial carcinoma after lung transplantation: a single-center experience. *J Heart Lung Transplant*. 2012;31(6):585–590.
73. Ruttens D, Verleden SE, Goeminne PC, et al. Smoking resumption after lung transplantation: standardised screening and importance for long-term outcome. *Eur Respir J*. 2014;43(1):300–303.
74. Grewal AS, Padera RF, Boukedes S, et al. Prevalence and outcome of lung cancer in lung transplant recipients. *Respir Med*. 2015;109(3):427–433.
75. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395–409.
76. Weill D, Torres F, Hodges TN, Olmos JJ, Zamora MR. Acute native lung hyperinflation is not associated with poor outcomes after single lung transplant for emphysema. *J Heart Lung Transplant*. 1999;18(11):1080–1087.
77. Mal H, Brugière O, Sleiman C, et al. Morbidity and mortality related to the native lung in single lung transplantation for emphysema. *J Heart Lung Transplant*. 2000;19(2):220–223.
78. Ruberto Franco F, Zullino V, Congi P, et al. Independent lung ventilation in the postoperative management of single lung transplantation: case report. *Transplant Proc*. 2014;46(7):2357–2359.
79. Crespo MM, Johnson BA, McCurry KR, Landreneau RJ, Sciarba FC. Use of endobronchial valves for native lung hyperinflation associated with respiratory failure in a single-lung transplant recipient for emphysema. *Chest*. 2007;131(1):214–216.
80. Perch M, Riise GC, Hogarth K, et al. Endoscopic treatment of native lung hyperinflation using endobronchial valves in single-lung transplant patients: a multinational experience. *Clin Respir J*. 2015;9(1):104–110.

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