Review Article

Indications, pre-operative evaluation, and timing for lung transplantation listing

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Abstract: Lung transplantation is an option for those patients with end stage lung disease who have continued to decline and have failed all available surgical and medical therapies. The timing for referral, evaluation, and listing can be critical for this population so as to minimize wait list mortality and also to list when patients are still physically functional. Thus, there is a concept of "window for lung transplantation" that we try to anticipate whereby patients are not transplanted too soon nor are they debilitated by the time they present to a transplant center. Hence, the timing for referral is usually when the projected median survival is 2 years. This article specifically addresses indications, contraindications, and special considerations for patients with interstitial lung disease (ILD), cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and pulmonary vascular diseases. Each one of the aforementioned disease category has different prognosticators to consider for projected survival, which will be covered in this chapter. The median survival after lung transplantation is 5 years, and hence the timing of referral and listing has that post lung transplant survival marker in mind. Over the last two decades, the indications for lung transplantation has expanded. It now includes all lung diseases (except lung cancers) and organ dysfunction outside the lungs is now assessed carefully with some allowance and acceptance of mild extrapulmonary end organ dysfunction in some cases.

Keywords: Lung transplantation referral; listing; prognosis; timing

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Introduction

The decision to refer, evaluate, and list for lung transplantation is a complex process that requires great consideration regarding multiple factors. There is no single protocol to follow as there are multiple physical, clinical, psychosocial and individual factors to consider for each patient. Therefore, understanding the overall process and potential considerations is paramount when considering a patient for lung transplantation.

Indications

Lung transplantation should be considered for any patient with chronic, severe, or end stage lung disease who have been optimized on maximal medical therapy. The following are general criteria for candidacy (1,2):

(I) High risk of death (>50%) from lung disease within 2 years without lung transplantation;
(II) High likelihood of surviving (>80%) at least 90 days after lung transplantation;

(III) High likelihood of survival at 5 years post-transplant (>80%) from an overall medical standpoint as long as there is adequate graft function.

Contraindications

Due to the risks associated with lung transplantation, it is pertinent to consider the absolute and relative contraindications (1,2).

Absolute contraindications

- Recent history of malignancy within the past 2 years is generally a contraindication for lung transplantation. Low risk for recurrence in combination with a 2-year disease-free period is reasonable for consideration (such as low-grade prostate cancer, squamous cell skin cancers). While a 5-year disease-free period is optimal in most cases, consideration will have to be made for the natural history of the lung disease and balance it with the risk of cancer recurrence. It is important to consider that even after a 5-year period, the risk of recurrence may remain too high for lung transplantation to be an option, especially given the added immunosuppression.
- Significant dysfunction of another organ system that is untreatable is considered a contraindication unless combined organ transplantation is an option.
- Coronary artery disease for which revascularization is not an option and/or atherosclerotic disease that is uncorrected and is associated with end-organ ischemia or dysfunction.
- Acute medical instability, such as acute sepsis, myocardial infarction, or acute liver failure (this list is not all inclusive).
- Uncorrectable bleeding disorders.
- Chronic infection pre-transplant, poorly controlled and with highly virulent and/or resistant microorganisms.
- Active *Mycobacterium tuberculosis* infection.
- Significant chest wall deformity or spinal deformity that may cause restriction post-transplantation.
- Body mass index (BMI) ≥35 kg/m^2 (Class II and III obesity).
- Current non-adherence to medical therapy or history of recurrent non-adherence that may increase the risk for non-adherence after transplantation.
- Psychiatric or psychologic conditions that interfere with cooperation with the lung transplant team or adherence to medical therapy.
- Absence of adequate or reliable social support system.
- Severely impaired functional status with limited rehabilitation potential post lung transplantation.
- Substance abuse or dependence (alcohol, illicit/illegal drug use, tobacco).
- Frailty based on screening by physical therapy.

Relative contraindications

- Age should not be considered solely, but rather in combination with overall status and the understanding that increasing age is associated with worsening comorbidities related to absolute or relative contraindications.
  - Over age 65 with other relative contraindications or low physiologic reserve;
  - Over age 75 are generally considered to be poor candidates in the majority of cases.
- BMI 30–35 kg/m^2 (Class I obesity), specifically central obesity.
- Malnutrition that is severe or worsening.
- Osteoporosis that is severe and symptomatic.
- Extensive prior chest surgery with lung resection.
- Previous pleurodesis, either mechanical/chemical.
- Previous cardiac surgery, especially coronary artery bypass graft (CABG) with functioning grafts.
- Significant peripheral vascular disease-potential limb ischemia should intra-operative or post-operative extracorporeal membrane oxygenation (ECMO) be required.
- Esophageal dysmotility/gastroesophageal reflux disease (GERD) associated with Scleroderma related interstitial lung disease (ILD).
- Mechanical ventilation and/or extracorporeal life support (ECLS); may be considered if no other significant acute or chronic organ dysfunction.
- Colonization with highly resistant or virulent microorganisms that would be expected to worsen after transplantation.
- Patients with hepatitis B or C can be considered for transplantation if they have been treated appropriately and show no clinic or radiologic evidence of cirrhosis or portal hypertension; transplantation in a center with skilled hepatology units is recommended.
- Patients with human immunodeficiency virus (HIV) can be considered for transplantation if they have undetectable HIV-RNA, are compliant with their

highly active antiretroviral therapy (HAART), and have no current immunodeficiency-related illness; transplantation in a center with experience in treating HIV-positive patients is recommended.

- Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli*, and multi-drug-resistant (MDR) *Mycobacterium abscessus*, may be considered for transplantation if treated appropriately pre-operatively; transplantation in a center with expertise in treating these infections is recommended.
- Atherosclerotic disease with risk for end-organ dysfunction post-transplantation; may require intervention pre-transplantation and in some cases CABG may be performed at the time of transplantation.
- Chronic diseases should be optimally treated prior to transplantation (i.e., diabetes mellitus, hypertension, peptic ulcer disease or gastric reflux, central venous obstruction, etc.).

Surgical considerations

Many patients who are referred for lung transplant surgery will have already had a chest surgery at some point. This is not necessarily a contraindication for lung transplantation, especially because some procedures are indicated in order to prepare a patient for transplant. Some procedures may have been performed for therapeutic intervention and be unexpected, such as CABG, whereas others may be performed for diagnostics or for pre-transplant optimization, such as video-assisted thoracoscopic (VATS) biopsy or lung volume reduction surgery (LVRS). Recurrent pneumothorax may have been treated with multiple chest tubes, pleurodesis, lung resection, or pneumonectomy. Any previous surgery, specifically pleurodesis, whether surgical or chemical, is associated with higher blood loss, early post-operative morbidity, phrenic nerve damage, chylothorax, and higher incidence of re-exploration. According to the most recent International Society for Heart and Lung Transplantation (ISHLT) consensus document, LVRS had previously been shown to have no effect on outcomes of lung transplantation, however, more recently, patients with chronic obstructive pulmonary disease (COPD) were shown to have poorer outcomes. In addition, for older patients with prior chest procedures, increased rates of bleeding, early morbidity, early graft dysfunction, and poorer results overall are expected (1,2).

- Previous surgery is not an absolute contraindication.
- Pleurodesis is not an absolute contraindication, however, it can contribute to operative challenges, requirement for allogeneic blood transfusion/products and increased ischemia time.
- Pneumothorax should be treated based on best practice recommendations.
- Prior chest procedures may place a patient at risk for increased rates of bleeding, re-exploration, and renal dysfunction; in addition, this may be due to longer operating times/need for extra-corporeal support via., ECMO or cardiopulmonary bypass (CPB).
- In patients who are well-selected for lung transplantation, there is no effect of previous chest procedures on medium and long-term outcomes.
- Patients over 65 should be considered carefully for lung transplantation due to poor outcomes from comorbidities, so previous chest procedures should be a careful consideration.

Disease specific candidate selection

ILD

ILD, specifically idiopathic pulmonary fibrosis, has the worst prognosis for all diseases for which lung transplantation is performed. ILD continues to have the highest mortality on the waiting list. The median survival from time of diagnosis is 2 to 3 years. Therefore, it is essential to refer for evaluation at the time of diagnosis.

Timing for referral and listing

Patients with evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP) should be referred for evaluation upon diagnosis, irrespective of lung function at that time. Abnormal lung function also warrants referral and is defined as forced vital capacity (FVC) less than 80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) less than 40% predicted (3,4). Referral is indicated with any dyspnea, functional decline, or if any oxygen is required. In addition, for patients with inflammatory ILD, continued dyspnea, oxygen requirements, and decline in lung function after medical treatment warrants referral (3,4).

The timing of listing is pertinent for ILD. The following are recommendations for when to proceed with listing: decline in FVC by ≥10% over a 6-month period, consider if FVC drops by more than 5% as this is associated with a poorer prognosis; decline in DLCO ≥15% over

6 months; desaturations less than 88% or distance less than 250 meters on a 6-minute-walk test (6MWT) or more than 50-meter decline on 6MWT within 6 months; pulmonary hypertension per right heart catheterization or echocardiogram; or hospitalization due to respiratory decline, pneumothorax, or acute ILD exacerbation (1,2).

Cystic fibrosis (CF)

In general, lung transplantation should be considered for patients with CF who have a 2-year predicted survival of less than 50% and who have functional limitations that are classified according to the New York Heart Association (NYHA) as Class III or IV. It is difficult to predict survival; however, it has been shown that measurement of lung function, particularly forced expiratory volume in 1 second (FEV_1), over time is the predictor that is most useful in clinical practice (1,2).

Timing for referral and listing

Patients with CF should be referred for lung transplantation evaluation for the following (5):

- FEV_1 less than 30% or with rapidly declining FEV_1 despite optimal therapy (particularly female patients), infected with non-tuberculosis mycobacterial (NTM) infection or *B. cepacia* complex, and/or with diabetes.
- 6-minute walk distance less than 400 meters.
- Pulmonary hypertension not associated with an acute hypoxic event (systolic pulmonary artery pressure >35 mmHg on echocardiography or >25 on right heart catheterization.
- Clinical decline with increasing number of exacerbations that are associated with any one of the following:
  - Acute respiratory failure requiring non-invasive ventilation;
  - Worsening of both antibiotic resistance and recovery from exacerbations;
  - Declining nutritional status in spite of dietary supplementation;
  - Life-threatening hemoptysis even with embolization.

A patient should be placed on the list for lung transplantation for the following:

- Chronic respiratory failure with hypoxia (PaO_2 <60 mmHg) or hypercapnia ($PaCO_2$ >50 mmHg).

Special considerations

Infectious processes in this population lend themselves for special consideration, particularly NTM disease and *B. cepacia* complex. Due to the increasing prevalence of NTM in patients with CF, all patients who are referred for lung transplant evaluation should be screened for NTM infection. If found to be positive for NTM, the organism should be confirmed and treatment initiated prior to listing. Progressive disease despite appropriate treatment or an inability to tolerate treatment is a contraindication to transplantation and the patient should not be listed or should be removed from the list. In addition, all treatment for NTM should be led by providers with expertise in this area (1,2).

For patients with *B. cepacia* complex, there is a more rapid decline in lung function and respiratory disease. Any patient referred for lung transplantation should be screened for *B. cepacia*. *B. cenocepacia* has worse outcomes after transplantation than other species and therefore it is recommended to determine which organism is present. If any other species than *B. cenocepacia*, the patient can be listed for transplant. For those with *B. cenocepacia*, there is increased risk of recurrence post-transplantation, therefore, they have an increased risk of mortality (1,2).

COPD

According to the Centers for Disease Control and Prevention (CDC), COPD was the third leading cause of death in the United States as of 2014.

In addition, comprising 40% of all lung transplants worldwide, COPD (non-α_1-antytrypsin deficiency and α_1-antytrypsin deficiency) remains the most common single indication for lung transplantation (1).

Multiple methods of evaluation have been used to determine survival in patients with COPD, to include FEV_1, FVC, hypoxemia, hypo- or hypercapnia, pulmonary artery pressure wedge pressure, cardiopulmonary exercise testing (CPET), and the 6MWT. Although each of these indices provides insight as to expected mortality in patients with COPD, one cannot be used as a stand-alone in decision making. The BODE index, which is comprised of BMI, obstruction, dyspnea, and exercise capacity, presents itself as a useful tool in determining survival. In order to calculate the score, the following are evaluated: BMI, FEV_1, the Modified Medical Research Council dyspnea scale, and the 6MWT are combined to determine a 10-point score. According to Celli *et al.* (6), for a BODE score of 7 to 10,

the mortality rate is 80% at 52 months. In addition, the C statistic for predicting risk of death using the BODE index compared to FEV_1 alone was 0.74 and 0.65, respectively (6). In addition to using this index as an indicator for mortality, hospitalizations in patients with COPD also lend weight to their mortality risk.

Although lung transplant is primarily performed for survival benefit, quality of life evaluation is also pertinent in this population when determining timing for evaluation and listing. The COPD patient remains complex as the natural progression of the disease process is slower than that for other indications requiring transplant. One must consider estimated survival for this population since the median survival post-transplant is between 5 to 6 years and patients with COPD may have a longer survival without transplant. Even with using these tools, waiting too long for transplant may lead to worsening debility and functional decline, which can be contributing factors to poor outcomes and shorter survival post-transplant. Due to the lengthy trajectory of the disease process, for patients with COPD, consideration of quality of life is an important factor, and remains an issue in determining whether or not this should be a factor in deciding to evaluate and list for transplant.

Timing of referral and listing

The most recent ISHLT Consensus Document for Lung Transplant Candidate Selection (1) lists both timing of referral and timing of listing for patients with COPD, which are as follows:

Timing of referral:

- Progressive disease despite maximal treatment (which includes medication, pulmonary rehabilitation, and oxygen therapy);
- Not a candidate for bronchoscopic lung volume reduction (BLVR) or LVRS; concurrent referral lung transplant evaluation and LVR evaluation is appropriate;
- BODE index score 5–6;
- $PaCO_2$ >50 mmHg and/or PaO_2 <60 mmHg;
- FEV_1 <25% predicted.

Timing of listing: (one or more criteria)

- BODE index ≥7;
- FEV_1 <15% to 20% predicted;
- Three or more severe exacerbations within the past year;
- One severe exacerbation with acute hypercapnic respiratory failure;
- Moderate to severe pulmonary hypertension.

Special considerations

Lahzami *et al.* (7) demonstrated a global survival benefit for those with a BODE score of 7 to 10. Although, those with a score of 5 to 6 were not expected to have a survival benefit from lung transplantation, they were shown to have similar quality of life benefits as those in the more severe category. Therefore, this tool can be useful when determining survival benefit versus quality of life benefit as indications for lung transplantation in patients with COPD. Also, of note, BLVR and LVRS may help to improve nutritional status and functional status or physical deconditioning in order to make the candidate more suitable for transplant (1).

Pulmonary vascular diseases

Due to improved therapy with prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors for idiopathic pulmonary arterial hypertension (PAH) and pulmonary hypertension, there has been a change in the timing for referral of this population. The current recommendation is to refer for evaluation with the following: NYHA Class III or Class IV, even if still intensifying therapy; rapidly progressing disease; need for parenteral therapy regardless of symptoms or NYHA Class; and known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis) (8,9).

The patient should be placed on the list for transplantation with any of the following: NYHA Class III or IV despite treatment with combination therapy (including prostanoids); cardiac index less than 2 liters/min/m^2; mean right atrial pressure above 15 mmHg; 6MWT less than 350 meters; or hemoptysis, pericardial effusion, or progressively worsening right heart failure (signs may include renal insufficiency, hyperbilirubinemia, elevated brain natriuretic peptide, or recurrent ascites) (1,2).

Coal workers' pneumoconiosis (CWP)

Patients with CWP with end stage respiratory failure should be referred for lung transplantation evaluation. This population is most commonly seen in Appalachian regions including eastern Kentucky, southwestern Virginia, and southern West Virginia. Although this is currently a preventable disease, the incidence continues to increase and there is currently no definitive treatment. Therefore, as with the aforementioned disease processes, patients should be referred for evaluation upon diagnosis.

According to Hayes *et al.* (10), there is currently no demonstrated difference between single and bilateral lung transplantation in this population, therefore, either is appropriate. The degree of massive pulmonary fibrosis and ease of explantation of the lungs will weigh into the decision of performing single *vs.* bilateral lung transplantation in this population.

Pre-operative evaluation

When a decision is made to proceed with lung transplantation evaluation, the following tests are routinely ordered to screen for potential contraindications:

- Blood type;
- Serum serology (HIV, hepatitis C, hepatitis B);
- Preformed antibodies;
- CT chest;
- Imaging of abdomen (CT or ultrasound);
- Carotid duplex and ankle-brachial index (ABI) (>50 years old);
- Right heart catheterization in all potential candidates;
- Coronary angiogram (>45 years old);
- Cancer screenings per published guidelines (i.e., colonoscopy, mammogram, pap smear, etc.);
- Consult with physical therapy to screen for frailty;
- Consult with social worker, psychologist, psychiatrist, or psychiatric nurse practitioner to screen for psychosocial profile;
- Consult with financial office to screen for insurance coverage;
- Consult with dietitian to optimize weight and caloric intake.

Additional testing may be considered based on the patient's clinical status, other co-morbidities, and other risk factors.

Removal from the waiting list

All patients who are listed for lung transplantation should continue to be monitored as they wait in order to determine if there have been changes significant enough to warrant removal from the waiting list, which can be either temporary or permanent removal. The continued evaluation should include both subjective and objective parameters. This reevaluation is especially pertinent for those who are inpatient and awaiting transplant or who are on mechanical ventilation or ECLS as their clinical status may change more abruptly. If there is any concern that one of the aforementioned contraindications to transplantation has occurred, then reevaluation is pertinent. According to the ISHLT consensus document, the most common reasons for removing a patient from the waitlist are as follows: weight changes (loss or gain), rehabilitation changes or inability to participate in rehabilitation, renal failure, microorganism that is unresponsive to treatment, non-compliance, or patient uncertainty regarding lung transplantation. In addition to removing from the waitlist for worsening clinical criteria, it is also important to consider that occasionally patients will no longer be candidates for transplantation because of a positive response to medical treatment. There is then the potential that the risk of transplantation would then outweigh the benefits if improving from a medical standpoint (1,2).

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