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REVIEW ARTICLE

Recipient selection, timing of referral, and listing for lung transplantation

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Abstract
Recipient selection for lung transplantation is a balance between providing access to transplantation to maximum patients, while utilizing this limited resource in the most optimal way. This review summarizes the current literature and recommendations about referral, listing, and evaluation of lung transplant candidates, with a focus on patients considered to have high risk characteristics.

Keywords Lung transplantation · Recipient selection · Single lung transplant · Bilateral lung transplant

Introduction

Lung transplant is an immensely complicated endeavor for the recipient to undergo and for the transplant team to manage. Careful consideration regarding recipient selection, timing of referral, and timing of listing is crucial in order to improve outcomes and minimize risks for patients. The science as well as survival *after* successful lung transplant still lags *far behind* that of other solid organ transplants. North American 1-year survival rates for double lung, left lung, and right lung transplants are 87.9%, 86%, and 88.4% respectively [1]. Three-year survival is 71.7%, 64.4%, and 65.1%. This is comparable to 1-year and 3-year heart transplant survival of 91% and 81% respectively, as well as renal transplant 1-year and 5-year survival of 93.4% and 72.4% [1, 2]. There is no single factor which affects outcomes, rather a combination of recipient characteristics, donor characteristics, surgical approach, medical management, and fortuity.

Recipient selection considerations are important to minimize risk as much as possible and ensure the best possible outcomes for patients. The optimal timing of referral and listing for transplant is also essential. For a patient to be in the window for a lung transplant, they should be "sick enough to need a transplant, while being well enough to undergo a transplant." Post-transplant complications, especially early in the post-operative period, can be impacted by recipient characteristics. Some patient factors are modifiable (body mass index (BMI), exercise capacity, social situation), while others may not be (non-pulmonary organ dysfunction, prior malignancies, chronic infections).

This review will summarize the current literature and recommendations about timing of referral and listing a patient, evaluation process, and considerations for recipient selection, with a focus on "high-risk" patients.

Evaluation (Table 1)

The transplant evaluation process varies by center, but the goal is always to determine if a patient would be expected to have a longer and/or better quality of life with lung transplant. The transplant team aims to identify the appropriateness of listing and transplanting the patient. If specific modifiable risk factors or obstacles are identified, the transplant center can hopefully outline solutions to overcome said obstacles.

The initial patient encounter at our institution is with a transplant pulmonologist after being referred by the patient's primary pulmonologist. The timing of this referral is crucial since late referrals may result in a patient missing the optimal

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Table 1 Suggested pre-listing consultation and workup

Lung transplant evaluation testing

- Full PFT
- ABG
- 6 Minute Walk
- HRCT chest without contrast
- CT abdomen with and without contrast—patients >65 years and significant CAD regardless of age
- Chest X-ray AP and lateral
- Ultrasound of carotid arteries
- Ankle Brachial Index 0.5, age>50 and/or significant CAD
- Doppler studies of upper and lower extremities
- Panorex
- EKG
- 2D echo with Doppler and color flow velocity mapping
- Right heart catheterization
- Left heart catheterization >45 years
- Speech consult for swallow assessment; MBS if positive swallowing assessment
- PT consult for frailty; strength and endurance; early mobility education
- Ultrasound of kidneys for GFR<50 to assess cortical thickening
- Dexa Scan—if never done or>2 years. After listing decision—not core testing

Lab work

- Comprehensive metabolic profile
- CBC with a differential
- Coagulation profile
- Liver function studies
- Lipid profile
- Vitamin D
- Pre-albumin
- *Hb A1c*
- T3 Uptake, *free and total T4*, TSH
- Serum nicotine and cotinine
- Drug screening
- HLA testing
- Panel reactive antigen (PRA) profiles (luminex)
- G6PD (only for patients with sulfa allergy or renal insufficiency) time of listing
- Immunoglobulins and subclass
- Hepatitis A serology (IgG)
- Hepatitis B serology
- Hepatitis C serology
- Herpes simplex 1,2 serology
- Varicella serology
- CMV serology (IgG)
- EBV serology
- RPR
- Quantiferon Gold
- MMR
- Toxoplasma serology
- Strongyloides serology; add only based on travel history—IgG and 3 stool samples for ova and parasites
- HIV serology
- Coccidioides serology; add only based on travel history; born in Southwest USA, CA, AZ, NM or lived there for prolonged time
- Chagas; if patients are from or visited Latin America: *Trypanosoma cruzi* antibody total
- Urinalysis
- Blood group typing

Health maintenance

- PSA
- PAP smear
- Mammogram
- Colonoscopy pt.>50 or family history or virtual colonography or 2 negative occult fecal test results
- Panorex; dental consult if positive findings

Consults/appointments

- Cardiology
- Cardiothoracic surgery
- GI: endoscopy, pH probe, 24 h manometry for IPF patients or patient's with symptoms of esophageal dysfunction
- Transplant nurse coordinator
- Financial coordinator
- Social worker
- Psychology—by referral only

Abbreviations: *ABG* arterial blood gas; *CMV* cytomegalovirus; *CT* computed tomography; *EBV* Epstein-Barr virus; *EKG* electrocardiogram; *G6PD* glucose-6-phosphate-dehydrogenase; *GFR* glomerular filtration rate; *HIV* human immunodeficiency virus; *HLA* human leukocyte antigen; *HRCT* high-resolution computed tomography; *IPF* idiopathic pulmonary fibrosis; *MBS* modified barium swallow; *MMR* measles, mumps, and Rubella; *PAP* Papanicolaou test; *PFT* pulmonary function testing; *PRA* panel reactive antibodies; *PSA* prostate-specific antigen; *PT* physical therapy; *RPR* rapid plasma reagin; *T3* triiodothyronine; *T4* thyroxine; *TSH* thyroid-stimulating hormone

transplant window in relation to his or her disease course. During this initial encounter, considerable time is taken to discuss the various aspects of transplant to establish expectations and identify any absolute contraindications such as active or recent drug use, smoking, or cancer. Patients are then scheduled for several outpatient encounters with members of the multidisciplinary transplant team including the surgery team, social work, nutrition, speech and language pathology, and pharmacy. Social work and transplant psychology are particularly important since many of these obstacles can take time to overcome. Nutrition evaluation and recommendations are necessary since class II or III obesity (BMI 35.0–39.5 and BMI 40.0 or greater) is also often included as an absolute contraindication, and pulmonary cachexia may be difficult to improve [3].

During the evaluation, patients are seen by gastroenterologists to ensure colon cancer screening is up to date. This is particularly important since the incidence of colon cancer has been shown to be elevated in patients with solid organ transplants in comparison to the general population [4]. While an updated colonoscopy is the gold standard, many of the patients may be too fragile for a colonoscopy. In such cases, alternative methods such as computed tomography (CT) colonography, which has a sensitivity of around 89% for adenomas at least 6 mm in size, are utilized and followed by a post-transplant colonoscopy [5]. In addition, high-risk patients undergo motility testing including high-resolution esophageal manometry and pH impedance to assess their risk of reflux and aspiration prior to lung transplant. In severe cases, consideration is given to either pre or post-transplant *gastric*

fundoplication to reduce the risk of bronchiolitis obliterans syndrome [6, 7]. This evaluation is particularly important in patients with suspected scleroderma esophagus; however, the impact of dysmotility in these situations remains unclear.

Patients undergoing evaluation are also referred to cardiology to assess their cardiovascular risk as well as several specific questions related to pulmonary disease and lung transplant. For example, atrial fibrillation is common after lung transplant and has been associated with a prolonged postoperative stay and increased mortality [8]. For this reason, establishing a plan prior to transplant is particularly important for patients at increased risk due to a history of atrial fibrillation. Additional cardiac circumstances that are important to evaluate prior to lung transplant include evaluation for cardiac sarcoidosis, and valvulopathies that may worsen post-transplant pulmonary edema, and establish the likelihood of post-transplant recovery of the right ventricle in patients with severe pulmonary hypertension. A right heart catheterization is always pursued. Several measurements such as pulmonary artery (PA) pressures, cardiac index, and pulmonary capillary wedge pressures impact treatment decisions. In patients with severe pulmonary artery hypertension (PAH), a double lung transplant is preferred. PA pressures and cardiac index are prognostic indicators and impact the *lung allocation score* (LAS) of the patient.

Listing

Initially, patients were transplanted based on length of time on the lung transplantation waitlist. Under this system, the median wait time in the USA ranged from 2 to 3 years [9]. This system also resulted in a discrepancy between severity of lung disease and a hopeful recipient's place on the transplant list [10]. To improve the long waiting period and inequities in the time-based system, a new allocation system was implemented in the USA in 2005 with the goal of capturing those patients with the highest medical urgency. This system is called the LAS and consists of twelve physiologic and demographic components that have been shown to drive mortality in patients with advanced lung disease. The LAS is calculated based on net transplant benefit (1-year survival with transplant minus 1-year survival without transplant) minus medical urgency (1-year survival without transplant); this score is then normalized from 0 to 100 and those patients with the highest score are allotted organs prior to those with a lower score [11]. LAS has also been shown to be a better predictor of waitlist mortality when compared to clinical judgment with a hazard ratio of 1.06 per unit LAS [12].

After the implementation of the LAS system, the absolute number of lung transplant procedures increased by 20% and showed a marked reduction in waitlist mortality. The LAS scoring system has now been adopted by several other countries and transplant organizations given its success in the USA with approximately 60% of transplants being allocated via LAS worldwide [13].

Other countries have variable allocation systems based on clinical judgment, waitlist duration, or a combination of the two. The organ allocation strategy could thus have a significant impact on when a patient should be actively listed for transplant [13].

Disease-specific indications for referral and listing (Table 2)

Chronic obstructive pulmonary disease

The timing of lung transplant referral and listing for patients with chronic obstructive pulmonary disease (COPD) can be challenging. Many patients may remain quite stable despite having advanced disease, and disease progression can often be slow. The BODE index, which is calculated with BMI, airflow obstruction, dyspnea, and exercise capacity, has been shown to be a better predictor of mortality than forced expiratory volume 1 second (FEV1) alone [14]. Therefore, it is frequently relied upon to assess the timing of referral and listing for patients with COPD. In the 2020 update of the International Society for Heart and Lung Transplantation (ISHLT) consensus document, a BODE index of 5–6, with at least one additional risk factor of frequent exacerbations, increased pulmonary artery diameter on CT scan and FEV1 20–25% should be referred. Poor quality of life and deterioration on maximal treatment are more subjective factors which can prompt referral. Listing for transplant should be considered with a BODE index of >7, FEV_1 < 20% predicted, severe exacerbations, chronic hypercapnia, or moderate to severe pulmonary hypertension [3, 15].

A subgroup of patients is those with combined pulmonary fibrosis and emphysema (CPFE), which may present with only subtle differences as compared to more isolated COPD cases. This distinction is important given that patients with CPFE, even with only mild concomitant fibrosis, would be expected to have a different disease course and trajectory. For patients with CPFE, their FEV1 may be stable due to the conflicting obstructive and restrictive forces. Despite a stable FEV1, the patient with CPFE's clinical status and risk of mortality may be worsening rapidly. By the same mechanism, the forced vital capacity (FVC) will not decline with disease progression in the manner it changes in idiopathic pulmonary fibrosis (IPF) either. Patients with CPFE are also more likely to develop progressive pulmonary hypertension, which portends a very poor prognosis. Cottin et al. found a 1-year survival of only 60% in patients with CPFE who developed pulmonary hypertension despite relatively preserved predicted FVC and 6-min walk distances [16].

Table 2 Disease-specific indications for referral and listing[31]

Disease	Referral	Listing
Interstitial lung disease	At diagnosis of IPF based on UIP pattern on CT scan or biopsy For all other ILD: • FVC<80% • DLC<40% • 10% decline in FVC/15% decline in DLCO/> 5% decline in FVC with worsening symptoms over 24 months • Supplemental O_2 needs at rest or exertion	Referral criteria plus any of the following: • Absolute decline in FVC>10% in 6 months • Absolute decline in DLCO >10% in 6 months • Absolute decline in FVC>5% with radiographic progression in 6 months • Desaturation to <88% on 6 MWT or >50 m decline in the past 6 months • Pulmonary hypertension • Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.
COPD	BODE Index score of at least 5–6 with additional risk factors: • Frequent exacerbations • Increasing BODE index in the last 2 years • PH on CT scan (pulmonary artery/aorta ratio>1) • FEV1 20–25% predicted Clinical worsening on maximal treatment Unacceptable quality of life	• BODE Index 7–10 • FEV1<20% • Moderate to severe pulmonary hypertension • Severe exacerbations • Chronic hypercapnia
Cystic fibrosis	• FEV1<30% • FEV 1<40% AND ◦ 6MWD<400 m ◦ PCO2>50 ◦ Hypoxemia at rest or exertion ◦ Pulmonary hypertension ◦ Recurrent exacerbations (>2/year) ◦ Worsening nutrition ◦ Massive hemoptysis ◦ Pneumothorax • FEV1<50% AND ◦ Rapid decline ◦ Exacerbation requiring PPV	Any of the above referral criteria in combination with any of the following: • FEV1<25% predicted • Rapid decline in lung function or progressive symptoms • Frequent hospitalization, (> 28 days in the last year) • Any exacerbation requiring mechanical ventilation • Chronic respiratory failure with hypoxemia or hypercapnia • Pulmonary hypertension • Worsening nutritional status BMI<18 kg/m^2 • Recurrent massive hemoptysis despite bronchial artery embolization • World Health Organization functional class IV symptoms
Pulmonary arterial hypertension	• ESC/ERS high risk or REVEAL risk score>8 on appropriate PAH therapy • RV dysfunction despite appropriate therapy • Need for IV or Sc prostacyclin therapy • Progressive disease on appropriate therapy • Recent hospitalization • PVOD or PCH, scleroderma or large pulmonary artery aneurysm • Liver or kidney dysfunction due to PAH • Recurrent hemoptysis	• ESC/ERS high risk or REVEAL risk score>10 on appropriate PAH therapy • Progressive hypoxemia • Progressive, but not end-stage, liver, or kidney dysfunction due to PAH • Life-threatening hemoptysis

Abbreviations: *6MWT* 6 minute walk test; *BMI* body mass index; *BODE* body mass, airflow obstruction, dyspnea, and exercise; *CT* computed tomography; *COPD* chronic obstructive pulmonary disease; *DLCO* diffusion capacity for carbon monoxide; *ERS* European Respiratory Society; *ESC* European Society of Cardiology; *FEV1* forced expiratory volume 1second; *FVC* forced vital capacity; *ILD* interstitial lung disease; *IPF* idiopathic pulmonary fibrosis; *PAH* pulmonary arterial hypertension; *PCH* pulmonary capillary hemangiomatosis; *PH* pulmonary hypertension; *PPV* positive pressure ventilation; *PVOD* pulmonary veno-occlusive disease; *REVEAL* Registry to Evaluate Early and Long-Term PAH Disease Management; *UIP* usual interstitial pneumonia

Adapted from the 2020 ISHLT Consensus document for the selection of Lung Transplant Candidates

Interstitial lung disease

The rate of lung transplantation for interstitial lung disease (*ILD*) has increased since the implementation of the LAS system. Despite this change, patients with diffuse parenchymal lung diseases still have the highest waitlist mortality rate compared to all other common lung transplant indications [17]. Therefore, patients with ILD should be considered for referral much earlier than those with other diagnoses [18, 19]. For patients with IPF, transplant discussion and referral should generally be made at the time of diagnosis. The same approach has been argued for non-specific interstitial pneumonitis; however, this disease tends to be very heterogeneous and consideration should be given as to the radiographic pattern, propensity for exacerbations, rate of decline, and most importantly establishing if there is a response to anti-inflammatory

therapies if appropriate. For all non-IPF ILD patients, an FVC <80% predicted or DLCO<40% (diffusing capacity of lungs for carbon monoxide) predicted as well as any degree of hypoxemia with or without functional limitations disease warrants referral to a transplant center. A decline in pulmonary function (FVC > 10% and DLCO >15%) over the past 2 years has been shown to be an indicator of poor prognosis and warrants referral [3]. It should be emphasized that referral to a transplant center does not always mean the patient is ready to be listed for transplant. However, establishing the relationship earlier, rather than later, in the patient's disease course is crucial in order to provide adequate time to overcome barriers to transplant, before the patient becomes too deconditioned to be expected to survive and recover from the procedure. In addition, exacerbations in ILD can be unpredictable. A transplant center will be much more likely to successfully transplant a critically ILD patient if the relationship has been established, as well as if the majority of the evaluation process have been completed.

The decision to list a patient with ILD is usually more straightforward than patients with COPD. Physiologic parameters tend to be more reliable with regard to predicting mortality. Rapid decline in FVC has been found to be a marker for increased risk of mortality when compared to otherwise similar patients with stable FVC [20–22]. Patients should generally be listed if over a 6-month period they experience a decline in FVC >10%, decline in DLCO>10%, or > 50-m drop in 6 minute walk test (6MWD) [19, 23]. A diagnosis of pulmonary hypertension on echocardiography or heart catheterization is a poor prognostic sign and can prompt listing. Additional indications for listing include any hospitalization for acute respiratory decline, pneumothorax, or acute exacerbation. Composite scores like *Gender, Age Physiology Index*, Composite Physiologic Index, and Risk Stratification Score can help with prognostication of individual patients based on baseline parameters and progression over time. These can be helpful in making listing decisions, but should be looked at in combination with other clinical factors [24].

Cystic fibrosis and non-CF bronchiectasis

Patients with cystic fibrosis (CF) should be considered for lung transplantation when they reach a predicted 2-year survival of less than 50%. However, their younger age means the center should ensure transplant listing and transplantation are not premature. Based on the 2020 update of the ISHLT consensus document, patients with FEV1 < 30% should be referred for transplant. Additionally, patients with FEV1 < 40% and additional risk factors (6MWD < 400 m, PCO2 > 50, pulmonary hypertension, BMI < 18, frequent exacerbations or massive hemoptysis) should be referred. Listing is suggested if FEV1 drops to <25%, rapidly worsening lung function, frequent hospitalizations, chronic respiratory failure, need for mechanical ventilation, recurrent massive hemoptysis, or severe dyspnea (World Health Organization (WHO) functional class 4).

In addition, the systemic nature of cystic fibrosis offers additional obstacles that need to be considered during the evaluation period. Malabsorption and pulmonary cachexia predispose this population to low BMI, and a BMI < 18.5 has been associated with lower survival [25]. Strategies to optimize the nutritional status of patients with CF are limited. Patients with a G551D mutation have demonstrated improved nutritional status after Ivacaftor treatment [26]. There may be additional strategies to optimize the nutritional status that a specialized team can employ such as titration in pancreatic enzyme supplementation, addition of choline supplementation, or potentially lipid matrix supplementation [27, 28]. Additional chronic complications of cystic fibrosis that should be evaluated and optimized as much as possible prior to transplant including diabetes, liver disease, bone disease, gastroesophageal reflux, and depression [29].

Non-cystic fibrosis bronchiectasis can be caused by chronic infections, immune dysregulation, and genetic disorders, and may be idiopathic. It accounts for 2.7% of all lung transplants [15]. Patients with non-CF bronchiectasis tend to do better when compared to CF patients with similar lung function, with a lower mortality. This has led some authors to recommend a higher transplant threshold. Regardless, the current accepted standards for non-CF bronchiectasis regarding referral and listing for transplant are the same as those for CF [3]. And as with CF, a low FEV1 has been associated with higher mortality, and an FEV1 < 30% predicted can be associated with a 4-year mortality of up to 39% [30].

Pulmonary vascular disease

Lung transplantation for pulmonary vascular disease is a continuously evolving area especially with regard to timing and surgical approach. Due to several advancements in the management of pulmonary hypertension and a greater understanding of right ventricular function, lung transplantation can often be delayed longer than previously recognized. Pulmonary arterial hypertension, group 1 of World Symposium of Pulmonary Hypertension classification, represents the most frequent indication for lung transplant among the five pulmonary hypertension groups. Group 2 pulmonary hypertension would not be expected to improve with lung transplantation since the pathology is secondary to left heart disease. Group 3 pulmonary hypertension secondary to an underlying lung parenchyma pathology plays an important role when considering the timing and risks of lung transplantation.

Two composite risk stratification tools are now widely used in PAH patients—Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL 2.0) and 2015 European Society of

Cardiology/European Respiratory Society (ESC/ERS). An intermittent/high-risk status on ESC/ERS score or a REVEAL score > 8 on appropriate PAH therapy should prompt transplant referral. Other situations which should prompt referral include progression on appropriate therapy, need for systemic prostacyclin treatment, liver or kidney dysfunction due to PAH or recurrent hemoptysis. Listing can be considered if high risk per ESC/ERS score or REVEAL score > 10. Progressive hypoxia, worsening renal or liver dysfunction from PAH, and life-threatening hemoptysis are other triggers for listing. Patients with pulmonary venous occlusive disease, scleroderma-associated PAH, concomitant PAH-ILD, and familial PAH are considered at higher risk for worsening and should be considered for earlier referral [15].

COVID-19 and other viral illnesses

The Covid Virus Disease-19 (COVID-19) pandemic has posed an unprecedented challenge to global health infrastructure. Acute respiratory failure in otherwise healthy individuals as well as progressive fibrotic lung disease as a sequel of this disease is well recognized. As the pandemic continues to evolve, lung transplantation is emerging an option for a small subset of patients. Cases reporting bilateral lung transplantation for COVID-19-related acute respiratory distress syndrome have begun to emerge [31]. *At* our center, single and double lung transplantation for this indication has been performed. Some experts have recommended waiting 4–6 weeks after the onset of respiratory failure before transplant. It is important to note that these patients are usually critically ill and may be dependent on Extracorporeal Membrane Oxygenation (ECMO), and this should be considered before an evaluation is started [30].

High-risk recipients(Table 3)

Elderly patients

An age greater than 65 years was considered a relative contraindication by the ISHLT. Reflecting the evolving experience in older patients, the 2020 update, lists age > 70 years as a risk factor with "high or substantially increased" risk. The age of lung transplant recipients has increased in recent years, especially in the USA. As centers become more comfortable with this population, patients 65 years or older are now becoming the age group with the highest rate of transplant. While short-term survival is similar in older patients, long-term survival is decreased. Pragmatically, the lesson to be learnt from these data is twofold. Careful selection of the recipient is paramount, and improved survivorship is likely derived from selection bias. Secondly, denying otherwise suitable candidates, based solely on age, may be too restrictive. Ethical arguments based on utility and equity can be made either way, and transplant centers would be best suited to make protocols based on the catchment population, individual patient suitability, and broader societal, cultural, and ethical values. Our practice is to not consider age in isolation as a contraindication. Other factors such as comorbidities, frailty, and functional capacity play a more important role. It is important to discuss with the patient that the expected survival varies based on age and is lower than at advanced ages.

Human immunodeficiency virus

Infection with the human immunodeficiency virus (HIV) is not considered a contraindication to transplant by the United Network for Organ Sharing (UNOS) [3]. Until recently, HIV-infected individuals did not have the opportunity to donate organs; this changed with passing of the *HIV Organ Policy Equity Act* (HOPE act) in 2013 that legalized HIV positive donation to HIV-positive recipients. HIV-positive recipients of liver and kidney transplant have been observed to have similar survival, but increased incidence of acute rejection [32]. HIV-positive lung transplant recipients have similar 1-, 3-, and 5-year survival rates when compared to non-infected patients. However, these patients are more likely to develop bacterial infections, with an incidence approaching 86%. Additionally, 28% of patients will develop acute rejection [33]. The management of an HIV positive recipient is an extraordinarily complex task that needs coordination with infectious disease experts. Use of Highly Active Antiretroviral Therapy (HAART) is the rule; however, interactions with calcineurin inhibitors are common and require frequent dose adjustments. These appear to be most common with efavirenz and ritonavir, and the use of these agents is discouraged. Additionally, drop in CD 4 counts post-transplant is usual, but the risk of development of acquired immune deficiency syndrome (AIDS) remains low.

Scleroderma and esophageal disease

Connective tissue disease–associated interstitial lung disease (CTD-ILD) account for 1% of all lung transplants in the USA [34]. Esophageal dysmotility is common in this subgroup and some degree of dysfunction exists in almost 80% of patients with CTD, with gastroesophageal reflux (GER) being the most common. GER confers a high risk towards the development of *chronic lung allograft dysfunction* (CLAD). Scleroderma and associated esophageal disease are not considered contraindications to transplant. However, the UNOS database reports a higher 1-year mortality [35]. This has not been observed in most high-volume centers, where survival appears to be similar. A detailed evaluation of gastrointestinal anatomy and function is necessary including pH monitoring, *esophagogastrodudenoscopy*, and a gastric-emptying study.

Table 3 High risk recipient characteristics

	Special considerations	Management
Advanced Age	Frailty and Functional status Cardiac and vascular disease Cognitive impairment	Intensive rehabilitation pre and post LTX, focus on nutrition Extensive workup Neurocognitive testing to identify early, alter immunosuppression, neuro rehab
HIV	Ensure viral suppression and optimal CD4 count Higher risk of post LTx infection Monitoring for interactions between HAART and CNI	Stable HAART regimen and ID evaluation pre LTX Collaboration with ID and pharmacy for close monitoring
Scleroderma	Digital ulcers Esophageal dysmotility GERD	Minimize pressors and decrease arterial lines, use CCB if needed Aspiration precautions, NPO and post pyloric feeds for 3 months Consider anti reflux surgery
CAD	Moderate CAD Severe CAD	Aggressive medical management in moderate disease Concomitant CABG or pre LTX PCI based on recipient factors (ability to tolerate surgery, ability to wait to complete DAPT pre transplant)
Critical illness	Non pulmonary organ dysfunction common High risk of infection/sepsis Deconditioning and debility Sedation and mentation Risk of thrombosis and bleeding	Multidisciplinary critical care team with routine evaluation for appropriate candidacy Establish clear expectations with patient and family given high chance of clinical worsening
HIV	Ensure viral suppression and optimal CD4 count Higher risk of post LTx infection Monitoring for interactions between HAART and CNI	Stable HAART regimen and ID evaluation pre LTX Collaboration with ID and pharmacy for close monitoring
High allosensitization	Longer wait list duration Increased risk of acute rejection (ACR and AMR) Increased risk for CLAD	List earlier anticipating higher wait list duration Surveillance with regular DSA and bronchoscopies Optimize immunosuppression post-transplant

Abbreviations: *ACR* acute cellular rejection, *AMR* antibody-mediated rejection, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CLAD* chronic lung allograft dysfunction, *LTX* lung transplant, *CNI* calcineurin inhibitor, *DAPT* dual anti-platelet therapy, *DSA* donor-specific antibodies, *GERD* gastroesophageal reflux disease, *HAART* highly active antiretroviral therapy, *ID* infectious disease, *NPO* nothing by mouth, *PCI* percutaneous intervention

Surgical corrective options should be kept in mind and caution regarding GER and aspiration be exercised in the immediate post-operative period. There is no consensus on how best to manage these patients to mitigate early rejection. Most centers recommend a strict exclusion from oral diet for at least 3 months post-transplant. The use of a post-pyloric feeding tube is then recommended until anti-reflux surgery can be safely performed [30]. We do not consider any degree of esophageal dysmotility to be a contraindication to transplant. Patients are carefully evaluated by a multidisciplinary team to assess and mitigate aspiration risk post-transplant. This often includes prolonged nil per oral (NPO) for several months' post-surgery with a post pyloric feeding tube. Patients often undergo partial fundoplication if there is concomitant acid reflux noted.

Coronary artery disease

Coronary artery disease (CAD) is prevalent in about 10% lung transplant candidates. The prevalence is higher in patients with interstitial lung disease than it is in COPD. Since corticosteroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors may contribute to the development of metabolic syndrome, lung transplant recipients are at an increased risk of developing worsening CAD. An increase in 30-day mortality was reported in a series of 539 patients, where patients with CAD had a mortality of 4.2% versus 3.3% in those without [36]. A left heart catheterization with coronary angiography is routinely recommended for patients aged 40 and above. For severe CAD, a concomitant coronary artery bypass graft (CABG) procedure may be considered. Mixed results are reported with this technique, where one center reported longer intensive care unit stay, whereas this was not observed in other centers. There was no difference in survival reported in these studies [36, 37]. The impact of patient selection and tailoring the management approach to the individual patient needs cannot be unstated. It is important to take factors such as age, frailty, and other comorbidities, and must be considered at the time of listing. A multimodality approach discussing the need for pre-transplant coronary intervention and optimal duration of antiplatelet therapy and detailed consideration to the type of transplant (single vs

double) must be performed, considering the severity of coronary disease and the potential impact on post-op recovery. In our experience, carefully selected patients tolerate combined lung transplant and CABG surgeries well with similar short-term outcomes [38, 39]. In patients with a prior CABG, the patency of the graft is a key determinant. For patients with patent graft, no concurrent intervention is required. The presence of patent graft does not preclude left lung transplant; however, if V/Q scan is equivocal or shows less perfusion on the right, a single right lung transplant makes the surgery relatively easier. Previous midline sternotomy for any reason should not impact the laterality decision, as both are technically feasible. In patients with atherosclerotic disease affecting the graft, a multidisciplinary discussion involving cardiothoracic surgery and cardiology is recommended to make a case-by-case determination of the best therapeutic option. In patients with severe aortic valve disease, our institution prefers a pre-transplant *transcatheter aortic valve replacement*, with complete recovery before actively listing the patient. Concomitant lung transplant and aortic valve replacement or repair has been reported in single center studies, with acceptable outcomes.

Critically ill patients

Over the past two decades, the number of critically ill patients that have been transplanted has steadily increased. Critically ill patients constituted 3.7% of all lung transplants in 2003, a number that rose to 14.1% in 2013 [40]. As can be expected, these patients require urgent evaluation and listing due to the nature of their illness. In keeping with this, the mortality in this group while on the waitlist is high and approaches 50% [41]. Most patients requiring a lung transplant in the critical care context require cannulation and maintenance on veno-venous ECMO. Large transplant centers have had mixed results, and published data indicate that about 50% of listed patients are able to get transplanted [42]. Clinicians should be wary of factors associated with poor outcomes in patients on ECMO. High physiologic debility, as codified by a high Acute Physiology, Age, and Chronic Health Evaluation or Sequential Organ Failure Assessment score, or age more than 60 years are harbingers of worse outcomes. Organ system–specific indicators such as *serum bilirubin* more than 3 mg%, high pulmonary artery pressures, and complications of ECMO are also not well tolerated. Additionally, since critical illness myopathy and muscle wasting are particularly common in patients on ECMO, an inability to tolerate ambulatory ECMO is a poor sign [40, 43]. In this context, a patient requiring complete sedation to tolerate ECMO is less likely to be able to tolerate transplant, and the postoperative recovery period. It is important for a transplant program to consider these factors and management should be aimed at allowing the patient the best possible chance to thrive. Planning and implementation of awake and ambulatory ECMO must be paramount, while waitlist duration should be anticipated, and goals and expectations of the team and the family be defined and managed. Although the configuration of ECMO is decided on a case-by case basis, a venous configuration that spares the femoral veins is usually preferred to allow for ambulation and "awake" ECMO. Configurations which allow sparing of the femoral vessels include dual lumen catheter (Avalon), Protec duo and central cannulation of the aorta, and inferior vena cava.

Allosensitization

The presence of *human leucocyte antigen* (HLA) antibodies to non-self-antigens can have a significant impact on organ availability and post-transplant outcomes. Based on the presence of *HLA* antibodies and population HLA studies, calculated panel reactive antibodies provide an estimate of percent of potential donors a recipient will have antibodies to. The presence of antibodies to a large percent of the population can make it difficult to find an acceptable organ for the patient. In a recent study [44], the likelihood of transplant decreased (HR 0.71) and an increased likelihood of death (HR 1.66) on the waitlist was observed for patients with allosensitization [44]. Anti-HLA antibody development prior to transplant was associated with an increased risk of development of donor-specific HLA antibodies post-transplant [45].

Pre- and post-transplant desensitization may provide a viable option to improve outcomes in these patients. While no single standardized regimen exists, the use of plasmapheresis, corticosteroids, intravenous immunoglobulin, and rituximab has been reported with some degree of success, by some centers in the USA [46]. Most transplant programs will have developed institutional protocols in this regard.

Contraindications to transplant listing (Table 4)

Absolute contraindications for transplant are determined by institutional guidelines and clinical experience in some determinants, whereas there exist clear limitations in others. Controversial contraindications include age and body mass index. As discussed at detail in preceding sections, an age of more than 65 years is considered an absolute contraindication by some centers. Our experience with transplanting older individuals has been encouraging, and as described above, an absolute age limit may be needlessly restrictive. Candidacy should be determined by an in-depth review of all pertinent factors and not age alone.

Obesity with a BMI of more than 30 kg/m^2 is used as a contraindication to transplant by some centers. We allow a BMI up to 35 kg/m^2, with an overall assessment taking the center stage. In a 2014 study analyzing the survival of 9000

Table 4 Contraindications[31]

Absolute contraindications to Lung Trasplantation
•Lack of patient willingness
• Recent malignancy with high risk of recurrence
• Kidney disease
◦ Glomerular filtration rate<40
◦ Worsening acute kidney disease or need for dialysis
• Acute coronary syndrome <30 days
• Stroke <30 days
• Liver disease
◦ Liver cirrhosis with portal hypertension or synthetic dysfunction
◦ Acute liver failure
• Infectious diseases
◦ Septic shock
◦ Active extra pulmonary infection
◦ Active tuberculosis infection
◦ HIV infection with detectable viral load
• Limited functional status and low rehabilitation potential
• Progressive cognitive impairment
• Psychosocial factors
◦ Repeated episodes of non-adherence without evidence of improvement,
◦ Active substance use or dependence
• Severe uncontrolled medical condition expected to limit survival after transplant

Adapted from the 2020 ISHLT Consensus document for the selection of Lung Transplant Candidates

patients from the UNOS database, no difference in 1-year mortality was associated with a BMI of 30–34.9 [47]. However, there are mixed data in this regard. It is prudent to treat an obese or overweight candidate as a high-risk patient and take all patient factors into consideration.

A history of malignancy, except for localized non-melanomatous skin tumors, less than 2 years prior to transplant, is an absolute contra-indication. A 5-year disease-free interval is recommended, whereas a 2-year interval may be acceptable in rare situations [3]. This is due to an unacceptably high risk of recurrence in the post-transplant period.

Significant major organ dysfunction, i.e., brain, heart, liver, or kidney, also precludes the patient from being considered for transplant. The risk of perioperative complications and organ failure is unacceptably high [3].

Infections with highly virulent organisms, or current chronic incurable infections, active tuberculosis, or ongoing sepsis would not allow for adequate immunosuppression and mortality would be expected to be high.

Significant chest wall or spinal deformity, such as kyphoscoliosis or severe or symptomatic osteoporosis, would be at a high surgical risk, and at increased risk of perioperative morbidity and mortality.

Ongoing substance abuse, including alcohol and tobacco, that is either active or within the last 6 months, is also deemed to be an absolute contraindication. The practices with cannabis are evolving given increased legalization of medical and recreational cannabis across the USA and Europe. Local legislation and practices dictate whether this would be considered a contraindication. Inhalation of cannabis continues to be considered a contraindication to transplant.

And finally, the lack of psychosocial stability and support not only would make post-transplant management challenging, but would also lead to poor patient outcomes, and would therefore preclude transplant.

Contraindications continue to evolve over the past several years. While several recipient characteristics, like advanced age, HIV, obesity, and multidrug-resistant infections, were considered an absolute contraindication in the past, patients with these characteristics are being increasingly transplanted across the world. Referral and collaboration with an experienced transplant center can help increase access to patients who may be turned down at one program. The absolute contraindications per the 2020 ISHLT consensus document update are listed in Table 4.

Conclusions

The indications and contraindications to lung transplant continue to evolve with more experience and improved medical and surgical management. Timely referral can help candidate optimization and increase chances of successful transplantation especially in high-risk groups. While individual practices may vary based on experience, expertise, and resources, the overarching goal remains optimal utilization of this limited resource to provide maximal benefit to patients.

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References

1. ISHLT Transplant Registry Quarterly Reports for Heart in North America
. 2018. https://www.ishltregistries.org/registries/quarterlyDataReportResults.asp?organ=HR&rptType=all&continent=4.
2. Wang JH, Skeans MA, Israni AK. Current status of kidney transplant outcomes: dying to survive. Adv Chronic Kidney Dis. 2016;23:281–6.
3. 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: 1–15.
4. Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF Jr, Engels EA. Risk of colorectal cancer after solid organ transplantation in the United States. Am J Transplant. 2016;16:960–7.
5. Plumb AA, Halligan S, Pendsé DA, Taylor SA, Mallett S. Sensitivity and specificity of CT colonography for the detection of colonic neoplasia after positive faecal occult blood testing: systematic review and meta-analysis. Eur Radiol. 2014;24:1049–58.
6. Hartwig MG, Anderson DJ, Onaitis MW, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg. 2011;92:462–8.
7. Davis RD Jr, Lau CL, Eubanks S, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg. 2003;125:533–42.
8. Orrego CM, Cordero-Reyes AM, Estep JD, et al. Atrial arrhythmias after lung transplant: underlying mechanisms, risk factors, and prognosis. J Heart Lung Transplant. 2014;33:734–40.
9. Yusen RD, Edwards LB, Dipchand AI, et al. The registry of the international society for heart and lung transplantation: thirty-third adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35:1170–84.
10. Travaline JM, Cordova FC, Furukawa S, Criner GJ. Discrepancy between severity of lung impairment and seniority on the lung transplantation list. Transplant Proc. 2004;36:3156–60.
11. Egan TM, Edwards LB. Effect of the lung allocation score on lung transplantation in the United States. J Heart Lung Transplant. 2016;35:433–9.
12. Hirji A, Zhao H, Ospina MB, et al. Clinical judgment versus lung allocation score in predicting lung transplant waitlist mortality. Clin Transplant. 2020;34:e13870.
13. Gottlieb J. Lung allocation. J Thorac Dis. 2017;9:2670–4.
14. 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;350:1005–12.
15. Kreider M, Hadjiliadis D, Kotloff RM. Candidate selection, timing of listing, and choice of procedure for lung transplantation. Clin Chest Med. 2011;32:199–211.
16. Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J. 2010;35:105–11.
17. Valapour M, Lehr CJ, Skeans MA, et al. OPTN/SRTR 2017 Annual Data Report: Lung. Am J Transplant. 2019;19:404–84.
18. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
19. du Bois RM, Weycker D, Albera C, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184:459–66.
20. Richeldi L, Kolb M, Azuma A, et al. FVC decline over 1 year predicts mortality but not subsequent FVC decline in patients with IPF. Eur Respir J. 2017;50: PA 4892.
21. Paterniti MO, Bi Y, Rekić D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2017;14:1395–402.
22. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
23. Flaherty KR, Andrei A-C, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med. 2006;174:803–9.
24. Fernández Fabrellas E, Peris Sánchez R, Sabater Abad C, Juan SG. Prognosis and follow-up of idiopathic pulmonary fibrosis. Med Sci (Basel). 2018;6:51.
25. Kapnadak SG, Pilewski JM, Gries CJ. Underweight patients with Cystic Fibrosis (CF): A risk worth taking. J Heart Lung Transplant. 2014;33:S185.
26. Borowitz D, Lubarsky B, Wilschanski M, et al. Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor. Dig Dis Sci. 2016;61:198–207.
27. Schall JI, Mascarenhas MR, Maqbool A, et al. Choline supplementation with a structured lipid in children with cystic fibrosis: A randomized placebo-controlled trial. J Pediatr Gastroenterol Nutr. 2016;62:618–26.
28. Stallings VA, Schall JI, Maqbool A, et al. Effect of oral lipid matrix supplement on fat absorption in cystic fibrosis: A randomized placebo-controlled trial. J Pediatr Gastroenterol Nutr. 2016;63:676–80.
29. Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. Front Endocrinol (Lausanne). 2018;9:20.
30. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021;40:1349–79.
31. Bharat A, Querrey M, Markov NS, et al. Lung transplantation for patients with severe COVID-19. Sci Transl Med. 2020;12: eabe4282.
32. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update–a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:745–55.
33. Kern RM, Seethamraju H, Blanc PD, et al. The feasibility of lung transplantation in HIV-seropositive patients. Ann Am Thorac Soc. 2014;11:882–9.
34. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020;8: 304–20.
35. De Cruz S, Ross D. Lung transplantation in patients with scleroderma. Curr Opin Rheumatol. 2013;25:714–8.
36. Zanotti G, Hartwig MG, Castleberry AW, et al. Preoperative mild-to-moderate coronary artery disease does not affect long-term outcomes of lung transplantation. Transplantation. 2014;97:1079–85.
37. Castleberry AW, Martin JT, Osho AA, et al. Coronary revascularization in lung transplant recipients with concomitant coronary artery disease. Am J Transplant. 2013;13:2978–88.
38. DeFazio D, Kashem M, Sunagawa G, et al. Younger patients show acceptable outcomes after undergoing concomitant coronary bypass grafting with lung transplantation. J Heart Lung Transplant. 2020;39:S370.
39. DeFazio D, Kashem M, Sunagawa G, et al. Patients over 70 years old show acceptable outcomes after undergoing concomitant coronary artery bypass grafting with lung transplantation. J Heart Lung Transplant. 2020;39:S370–1.
40. Weig T, Irlbeck M, Frey L, et al. Parameters associated with short- and midterm survival in bridging to lung transplantation with extracorporeal membrane oxygenation. Clin Transplant. 2013;27: E563–70.
41. Hayanga JWA, Lira A, Aboagye JK, Hayanga HK, D'Cunha J. Extracorporeal membrane oxygenation as a bridge to lung transplantation: what lessons might we learn from volume and expertise? Interact Cardiovasc Thorac Surg. 2016;22:406–10.
42. Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg. 2013;145:1065–71.
43. Biscotti M, Gannon WD, Agerstrand C, et al. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: A 9-year experience. Ann Thorac Surg. 2017;104:412–9.

44. Tague LK, Witt CA, Byers DE, et al. Association between Allosensitization and waiting list outcomes among adult lung transplant candidates in the United States. Ann Am Thorac Soc. 2019;16:846–52.
45. Verleden SE, Vanaudenaerde BM, Emonds M-P, et al. Donor-specific and -nonspecific HLA antibodies and outcome post lung transplantation. Eur Respir J. 2017;50:1701248.
46. Snyder LD, Gray AL, Reynolds JM, et al. Antibody desensitization therapy in highly sensitized lung transplant candidates. Am J Transplant. 2014;14:849–56.
47. 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;190:1012–21.

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