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Considering candidates: modifiable and nonmodifiable risk factors for lung transplantation

Julia A. Maheshwari and Lorriana E. Leard

Purpose of review

Evaluation of a candidate's risk profile for lung transplant includes understanding which patient factors can be addressed to minimize transplant risk. Some risk factors can be modified, while others cannot. This review explores current understanding of modifiable and nonmodifiable risk factors for lung transplantation.

Recent findings

Several risk factors for lung transplant can be resolved entirely, thereby minimizing a candidate's transplant risk. Some features cannot be eliminated, though can be optimized to minimize risk. Others cannot be altered and inherently bring risk to transplant, while a subset of nonmodifiable risk factors are considered absolute barriers to transplant.

Summary

Robust research and novel therapies have led to increased ability to modify certain risk factors and thus decrease lung transplant risk. Further studies are needed to better understand how to estimate risk profiles when assessing candidacy and timing for lung transplant.

Keywords

candidate, lung transplant, modifiable, nonmodifiable, risk factor

INTRODUCTION

Lung transplant can be lifesaving for patients with advanced lung diseases. When evaluating candidacy and timing for transplant, it is important to consider risk factors that are present. Whenever possible, a candidate's condition should be optimized to reduce transplant risk. Some risk factors are modifiable or even resolvable, while others are not. This review presents current understanding of these risk factors for lung transplantation based upon literature updates over the past 18 months.

MODIFIABLE RISK FACTORS FOR LUNG TRANSPLANTATION

Several risk factors for lung transplant are modifiable. Some can improve to the point where they no longer constitute a risk factor. These include obesity, low body weight, frailty, and malnutrition. Newer therapies and research have led to an increased ability to address these risk factors.

Obesity

In the most recent consensus statement by the International Society for Heart and Lung Transplantation

(ISHLT) for candidate selection, BMI 30–34.9 kg/m² is considered a risk factor when assessing candidates for lung transplant, while BMI ≥ 35 kg/m² is considered high risk [1] (Table 1). These recommendations are based on prior research showing an association between elevated pretransplant BMI and poor transplant outcomes, including primary graft dysfunction and one-year posttransplant mortality [2,3]. Recent evidence suggests adverse respiratory and renal complications peri-transplant even for patients with BMI ≥ 25 kg/m², suggesting that weight loss should be recommended for all overweight candidates [4[†]].

In addition to traditional recommendations for weight loss such as regular exercise and nutritional counseling, glucagon-like peptide-1 (GLP-1) receptor agonist therapy has recently been identified as an effective treatment for weight loss in

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KEY POINTS

- Several risk factors for lung transplant can be resolved entirely to optimize candidacy; these include obesity, low body weight, frailty, and malnutrition.
- Modifiable risk factors that cannot be resolved, including coronary artery disease, certain pulmonary infections, gastrointestinal reflux disease or gastrointestinal dysmotility, and mental health or cognitive conditions, should be optimized to minimize risk.
- Certain patient factors cannot be altered and therefore bring risk to transplant. These include advanced age, need for extracorporeal life support (ECLS) as a bridge to transplant, renal dysfunction, and history of malignancy.
- Other risk factors may be considered absolute barriers to transplant, such as lack of patient interest, lack of patient understanding, progressive cognitive impairment, episodes of nonadherence, active substance use or dependence, limited functional status with low likelihood of rehabilitation, and severe extrapulmonary organ dysfunction.
- Consideration of each of these risk factors individually and the overall risk profile is important when evaluating a potential candidate for lung transplant.

patients undergoing evaluation for lung transplant. These newer agents have been shown to be more effective in helping patients achieve weight goals and lose a higher percentage of their body weight compared to patients not on GLP-1 receptor agonists [5¹¹]. This treatment presents a less invasive approach, though bariatric surgery remains another option to help potential candidates reach optimal weight for lung transplant [6¹²].

Low BMI

BMI < 16 kg/m² in lung transplant candidates is deemed high risk per the ISHLT consensus statement [1]. Transplant candidates with low body weight may lack the physical reserve to tolerate the rigorous surgery and posttransplant recovery. Treatments such as pulmonary rehabilitation, nutritional counseling, enteral feeding, or pharmacologic treatments such as mirtazapine have proven useful in increasing body weight prior to transplant.

Frailty

Frailty, often described as a state of low physiologic reserve and increased vulnerability to stressors, is cited as a rationale for exclusion from lung

transplant. It has been associated with increased risk of delisting or death while on the waiting list [7]. Pretransplant frailty has also been associated with increased risk of death following transplant [8]. The physical aspect of frailty is represented in the ISHLT consensus statement as 'limited functional status'. Candidates having limited functional status with potential for posttransplant rehabilitation are considered to be at substantially increased risk for poor outcomes following transplant, while nonambulatory patients with poor potential for rehabilitation are considered unsuitable candidates [1].

Newer data supports this, noting that lung transplant candidates with higher frailty index scores experienced prolonged ICU, ward, and rehabilitation center lengths of stay, a higher total number of hospitalization days, and increased mortality following transplant than those categorized as less frail. When frailty is combined with additional comorbidities, it is associated with increased 1-year posttransplant mortality. In a recent study, 38% of frail patients with 6 or more comorbidities died within the first year posttransplant [9¹³]. Thus, frailty should be evaluated together with other risk factors when assessing candidacy.

Exercise therapy has emerged as a powerful tool to improve pretransplant frailty. 'Prehabilitation' – dedicated rehabilitation prior to transplant – is intended to optimize candidates' cardiovascular fitness and muscle strength in order to tolerate the stress of surgery and facilitate speedy recovery [10¹⁴]. Prehabilitation has been shown to improve exercise tolerance, quality of life, and posttransplant outcomes in solid organ transplant candidates [11¹⁵].

Malnutrition

Poor nutritional status, represented in the ISHLT consensus statement by 'hypoalbuminemia,' is associated with decreased waiting list and posttransplant survival [12,13]. Early identification of malnutrition allows for treatment with oral nutritional supplementation and high calorie, high protein foods or more aggressive measures such as medication or enteral feeding.

Coronary artery disease

Risk factors that cannot be resolved should be optimized to minimize risk. These include coronary artery disease, pulmonary infections, gastrointestinal reflux disease or gastrointestinal dysmotility, and mental health or cognitive conditions.

The degree to which coronary artery disease is viewed as a risk factor for lung transplant varies

Table 1. Risk factors for lung transplantation**Absolute contraindications**

- Lack of patient willingness or acceptance of transplant
- Malignancy with high risk of recurrence or death related to cancer
- Glomerular filtration rate < 40 mL/min/1.73 m² unless being considered for multiorgan transplant
- Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia)
- Stroke within 30 days
- Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multiorgan transplant
- Acute liver failure
- Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
- Septic shock
- Active extrapulmonary or disseminated infection
- Active tuberculosis infection
- HIV infection with detectable viral load
- Limited functional status (e.g. nonambulatory) with poor potential for posttransplant rehabilitation
- Progressive cognitive impairment
- Repeated episodes of nonadherence without evidence of improvement
 - Footnote: For pediatric patients this is not an absolute contraindication and ongoing assessment of nonadherence should occur as they progress through different developmental stages.
- Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or IV drug use
- Other severe uncontrolled medical condition expected to limit survival after transplant

Risk factors with high or substantially increased risk

- Age > 70 years
- Severe coronary artery disease that requires coronary artery bypass grafting at transplant
- Reduced left ventricular ejection fraction $< 40\%$
- Significant cerebrovascular disease
- Severe esophageal dysmotility
- Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
- BMI ≥ 35 kg/m²
- BMI < 16 kg/m²
- Limited functional status with potential for posttransplant rehabilitation
- Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
- Unreliable support system or caregiving plan
- Lack of understanding of disease and / or transplant despite teaching
- *Mycobacterium abscessus* infection
- *Lomentospora prolificans* infection
- *Burkholderia cenocepacia* or *gladioli* infection
- Hepatitis B or C infection with detectable viral load and liver fibrosis
- Chest wall or spinal deformity expected to cause restriction after transplant
- Extracorporeal life support
- Retransplant < 1 year following initial lung transplant
- Retransplant for restrictive CLAD
- Retransplant for AMR as etiology for CLAD

Risk Factors

- Age 65–70 years
- Glomerular filtration rate 40–60 mL/min/1.73m²
- Mild to moderate coronary artery disease
- Severe coronary artery disease that can be revascularized via percutaneous coronary intervention prior to transplant
- Patients with prior coronary artery bypass grafting
- Reduced left ventricular ejection fraction 40–50%
- Peripheral vascular disease
- Connective tissue diseases (scleroderma, lupus, inflammatory myopathies)
- Severe gastroesophageal reflux disease
- Esophageal dysmotility
- Thrombocytopenia, leukopenia, or anemia with high likelihood of persistence after transplant
- Osteoporosis
- BMI 30–34.9 kg/m²
- BMI 16–17 kg/m²
- Frailty
- Hypoalbuminemia
- Diabetes on insulin that is poorly controlled
- Edible marijuana use
- *Scedosporium apiospermum* infection
- HIV infection with undetectable viral load
- Previous thoracic surgery
- Prior pleurodesis
- Mechanical ventilation
- Retransplant > 1 year for obstructive CLAD

From International Society for Heart and Lung Transplantation consensus document for the selection of lung transplant candidates.

Source: 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. doi:10.1016/j.healun.2021.07.005.

based upon its severity and potential for revascularization. Mild to moderate coronary artery disease (CAD) and a history of coronary artery bypass graft (CABG) are risk factors, but not barriers. These patients should have their medical therapy for CAD optimized. Cardiology consultation before transplant is essential, especially given the accelerated atherosclerosis observed in transplant recipients driven by the posttransplant immunosuppression regimen. Severe CAD is also considered a risk factor; thus, eligible candidates should undergo percutaneous coronary intervention prior to transplant, provided time allows for the completion of dual antiplatelet therapy. CAD requiring CABG at the time of transplant inherently brings risk to the transplant surgery, though may be an option depending on center experience. This may require referral to a center with expertise in performing CABG at the time of transplant [14[¶]]. In a recent propensity-matched analysis, in-hospital mortality and overall posttransplant survival were similar between matched lung transplant candidates with CAD (defined as coronary artery stenosis $> 50\%$, prior PCI or CABG, or prior myocardial infarction) and non-CAD patients [15[¶]].

Pulmonary infections

Several pretransplant infections are associated with increased posttransplant morbidity and mortality. *Mycobacterium abscessus* infection is associated with development of CLAD and increased mortality posttransplant [16,17]. *Burkholderia cenocepacia* causes severe disseminated infection and increases risk of death posttransplant when compared to other *Burkholderia* species and lung transplant recipients without pretransplant infection [18]. *Lomentospora prolificans* infections are often challenging to treat given intrinsic resistance to antifungal therapy, predisposing to fulminant infections following lung transplant [19]. Treatment of these infections should be conducted at specialized centers with infectious disease experience managing these infections peritransplant.

Gastroesophageal reflux disease and gastrointestinal dysmotility

Pretransplant gastroesophageal reflux disease (GERD) predisposes to the development of chronic rejection in the lung allograft due to aspiration of harmful gastric contents [20]. Implementation of reflux precautions such as sitting upright or going for a short walk after meals, eating dinner at least 2–3 hours before bed, and using a wedge pillow or elevating the head of the bed are important interventions to physically prevent esophageal reflux of gastric contents and promote forward motility through the GI tract. Fundoplication is a surgical option in select lung transplant recipients to control reflux and retrograde aspiration [21].

Lack of effective esophageal peristalsis, often seen in patients with scleroderma, increases the risk of reflux and aspiration of food matter and gastrointestinal secretions into the lung. In addition to reflux precautions, management of these patients may include a postpyloric feeding tube in the peritransplant period. Delayed gastric emptying also may be a risk factor for aspiration. Evaluation with a nuclear medicine gastric emptying study and management with pro-motility agents may be warranted in these patients.

Psychiatric, psychological, or cognitive conditions

Mental health issues which threaten to interfere with medical adherence can be problematic following lung transplant. Lung transplant recipients are expected to manage complicated medication regimens, attend frequent medical appointments, and undergo regular surveillance testing. Missed medication doses and surveillance tests can predispose to infection or rejection of the lung allograft. Thus, it is

critical to ensure that each candidate with mental health or cognitive conditions has both an optimized therapeutic plan and a reliable caregiver plan established prior to transplant. Recent data highlights the additional benefit of mental health services (social workers, psychiatrists, psychologists) in promoting adherence to medical treatment, decreasing the risk of complications posttransplant. Expansion of psychiatry support from the candidate evaluation phase to the waiting list and posttransplant periods could also help recipients navigate anxiety and depression that often become more apparent during these phases [22].

NON-MODIFIABLE RISK FACTORS FOR LUNG TRANSPLANTATION

Certain patient factors cannot be altered and thus bring risk to transplant recipients. These include advanced age, need for extracorporeal life support (ECLS) as a bridge to transplant, renal dysfunction, and history of malignancy.

Age

The average age of patients undergoing lung transplant is rising, driven by factors such as implementation of the lung allocation score, increasing life expectancy, and delay in need for transplant due to treatments such as antifibrotic therapy. Given the increased likelihood of frailty and higher number of comorbidities with advanced age, patients between 65–70 years carry risk of complication when undergoing lung transplant, while patients >70 years are deemed high risk [1]. Newer studies examining transplant outcomes and risk factors for increased 3- and 5-year mortality in this population may help to further stratify transplant risk in these patients [23,24].

Extracorporeal life support

Extracorporeal life support (ECLS) is used to bridge critically ill patients to lung transplant. Inherent risks with ECLS include the possibility of ischemic or hemorrhagic stroke, bleeding, blood product transfusions which may lead to sensitization, and kidney injury. The likelihood of developing complications increases the longer one is supported by ECLS. Studies evaluating ECLS as a bridge to transplant (BTT) provide insight into its impact on peri-transplant outcomes. Shou *et al.* showed that a longer duration of venovenous extracorporeal membrane oxygenation (VV ECMO) BTT was associated with higher waitlist mortality, though patients with varying lengths of ECMO duration had similar 1-year posttransplant mortality if they were successfully bridged to

transplant [25¹¹]. Whether patients remained on VV ECMO until transplant, changed configuration from venovenous to venoarterial (VA ECMO) in the setting of right ventricular (RV) failure, or were initially cannulated on VA ECMO or right ventricular assist device with oxygenator did not affect 5-year posttransplant survival [26¹²]. Another recent study showed that patients age ≥ 65 years who required ECLS BTT had a higher risk of 3-year posttransplant mortality compared to patients in this age group who required only mechanical ventilation or no mechanical support prior to transplant [27¹³]. Factors associated with positive outcomes in ECLS BTT patients include patients who can be bridged while remaining awake and/or ambulatory on ECLS [28,29]. Given the risks with ECLS as well as the need for specialized care at a center familiar with ECLS management, its use characterizes patients as high risk for lung transplant [1].

Chronic kidney disease

Chronic kidney disease (GFR 40–60 ml/min/1.73 m²) brings risk to lung transplant surgery and recovery [1]. Optimization of blood pressure control, blood sugar measurements, and minimizing use of injurious medications can improve renal function to an extent. However, the presence of chronic kidney disease despite these efforts heightens a patient's peri-operative risk profile and increases the chance of severe renal dysfunction following transplant, particularly when coupled with typical peri-transplant hemodynamic changes and posttransplant nephrotoxic medications. Renal dysfunction with GFR < 40 ml/min/1.73 m² has been viewed as a barrier to lung transplant unless a patient was being considered for simultaneous lung–kidney transplant. Due to the recent implementation of a 'safety net' policy in the United States, which allows a lung transplant recipient who develops kidney failure within 1 year of lung transplant to be prioritized on the waiting list for kidney transplant, some centers may be willing to proceed with lung transplant in patients with decreased renal function [30¹⁴].

Malignancy with high risk of recurrence or cancer-related death

As the average age of lung transplant recipients rises, candidates with a history of malignancy are more common. Previously, a 5-year cancer-free interval was required prior to listing a candidate for transplant, given concern that posttransplant immunosuppression would increase the chance of cancer recurrence [31¹⁵]. Recent recommendations advocate consideration of each malignancy in coordination with Oncology. Some malignancies with a favorable

prognosis may pose less of a risk; thus, a shorter cancer-free interval may be acceptable prior to lung transplant or may be managed with diligent follow-up and adjustment of immunosuppression. Current guidance is available through two cancer-specific consensus statements [32,33].

Early-stage non-small cell lung cancer has been noted as an incidental finding in some native lung explants. Contrary to prior studies showing lower survival in these patients [34,35], a recent study of Stage I non-small cell lung cancer incidentally discovered in explanted lungs found comparable survival to lung transplant recipients without incidentally-identified cancer [36¹⁶]. The implications of this finding warrant further study.

Finally, a few risk factors remain that present an absolute barrier to transplant. Some could in fact evolve over time – for example, a patient who is not willing to pursue transplant later becomes amenable if less aggressive treatments are excluded, or a patient who is actively smoking cigarettes pursues smoking cessation. However, when present at the time of candidacy evaluation, these risk factors are viewed as contraindications.

Lack of patient interest

A patient who is not interested in lung transplant should not be convinced to pursue evaluation testing or undergo transplant surgery. Alongside physical health and stamina to endure transplant surgery and recovery, mental readiness and resilience are essential. In fact, patients deemed to have 'mental toughness' have decreased hospital length of stay following transplant [37¹⁷].

Lack of patient understanding

A patient must be alert and able to fully understand the prognosis of the underlying disease and the fundamentals of lung transplant in order to provide informed consent to proceed. A patient who is unable to understand both of these, despite teaching from physicians, nurses, social workers, and coordinators, and following exhaustion of strategies to aid patients with lower health literacy or educational limitations when present, is not a suitable candidate for transplant.

Progressive cognitive impairment

While a patient with progressive cognitive impairment (diagnosed by neurocognitive testing or evaluation) could be buttressed by robust caregiver support to manage medications and post-transplant care, poor neurocognitive performance

pretransplant has been associated with adverse post-transplant outcomes [38].

Repeated episodes of nonadherence without evidence of improvement

Missing medication doses or follow up appointments increases the chances of developing complications such as acute or chronic rejection, opportunistic infections, and toxicity from the post-transplant medication regimen. Diligent adherence to care is key to a successful outcome posttransplant. The risk of nonadherence is challenging to quantify in lung transplant candidates, given the lack of standardized methods or guidelines to do so. Providers must also be aware of how implicit bias can impact perceptions of adherence [39].

Active substance use or dependence

Ongoing use of substances, such as tobacco, vaping, or use of intravenous (i.v.) drugs poses risk to the lung allograft. In our current system where donor lungs are a limited resource, lung transplant programs must allocate these organs to patients who would serve as optimal stewards of their transplanted lungs. Resources for smoking cessation and drug rehabilitation should be provided to patients to help them achieve abstinence prior to lung transplant.

Limited functional status with poor potential for posttransplant rehabilitation

A nonambulatory patient with minimal potential for posttransplant rehabilitation is not an ideal candidate for lung transplant surgery. Prior to and while active on the waiting list, functional status should be repeatedly assessed. Optimized functional status improves the candidate's chance of a smooth post-transplant recovery with a greater likelihood of hospital discharge.

Severe extrapulmonary organ dysfunction (including chronic kidney or liver disease)

The ideal lung transplant candidate has single organ disease – that is, lung disease without other organ dysfunction. Severe extrapulmonary organ dysfunction is a contraindication to lung transplant.

CONCLUSION

Evaluation of a candidate's risk profile for lung transplant includes understanding which risk factors can be addressed to minimize transplant risk.

Some risk factors may be resolvable, while others can be only optimized. Still other nonmodifiable factors must simply be recognized as placing the candidate at increased risk for adverse outcomes. The full constellation of risk factors must be considered when evaluating each candidate for lung transplant.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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