



Indications for Lung Transplantation and Patient Selection

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Globally, thousands of patients undergo lung transplantation owing to end-stage lung disease each year. As lung transplantation evolves, recommendations and indications are constantly being updated. In 2021, the International Society for Heart and Lung Transplantation published a new consensus document for selecting candidates for lung transplantation. However, it is still difficult to determine appropriate candidates for lung transplantation among patients with complex medical conditions and various diseases. Therefore, it is necessary to analyze each patient's overall situation and medical condition from various perspectives, and ongoing efforts to optimize the analysis will be necessary. The purpose of this study is to review the extant literature and discuss recent updates.

Keywords: Lung transplantation, Chronic obstructive pulmonary disease, Idiopathic pulmonary fibrosis

Introduction

Globally, thousands of patients undergo lung transplantation owing to end-stage lung disease each year. Lung transplantation is now accepted as a more generally applicable treatment than was the case in its early days, and in 2019, more than 4,500 lung transplants were performed at various centers around the world [1].

Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are important indications for lung transplantation, and the proportion of IPF recipients increased in the 2010s compared to the 2000s [2]. However, it is still difficult to determine appropriate candidates for lung transplantation among patients with complex medical conditions and various disease statuses.

As lung transplantation evolves, recommendations and indications are constantly being updated. In 2021, the International Society for Heart and Lung Transplantation (ISHLT) published a new consensus document for selecting candidates for lung transplantation [3]. Although remarkable advances have been made in various fields of lung transplantation, recipients' clinical course after lung transplantation can still vary depending on their clinical characteristics; hence, individual risk factors reflecting each patient's status must be considered. High mortality, chron-

ic rejection, and the limited use of donor lungs are challenges associated with lung transplantation, compared to other solid organ transplantations, that still need to be overcome, and the selection of recipients who are expected to have survival benefits remains an important issue. The purpose of this study is to review the extant literature and discuss recent updates.

Contraindications and risk factors

The absolute contraindications of lung transplantation introduced in the 2021 ISHLT consensus document for the selection of lung transplant candidates are summarized in Table 1 [3], and the risk factors to be considered are reviewed below.

Age

Determining whether a transplant is possible based on a specific age remains a matter of debate. The 2014 ISHLT guideline suggested that age over 65 years was a relative contraindication for lung transplantation. However, the 2021 ISHLT guideline adjusted this recommendation, instead stating that patients over 70 years of age are relatively contraindicated for lung transplantation. Although age is



Table 1. Absolute contraindications for lung transplantation

Absolute contraindications for lung transplantation
(1) Lack of patient willingness or acceptance of transplantation
(2) Malignancy with a high risk of recurrence or death related to cancer
(3) Glomerular filtration rate <40 mL/min/1.73 m ² unless being considered for multi-organ transplantation, acute renal failure with rising creatinine levels or on dialysis, and low likelihood of recovery
(4) Acute coronary syndrome or myocardial infarction <30 days
(5) Acute liver failure, liver cirrhosis with portal hypertension, or synthetic dysfunction unless being considered for multi-organ transplantation
(6) Stroke <30 days
(7) Septic shock, active extrapulmonary or disseminated infection, or active tuberculosis infection
(8) Human immunodeficiency virus infection with a detectable viral load
(9) Limited functional status with poor potential for post-transplantation rehabilitation
(10) Progressive cognitive impairment
(11) Repeated episodes of non-adherence without evidence of improvement
(12) Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or intravenous drug use
(13) Other severe uncontrolled medical condition expected to limit survival after transplantation

Modified from Leard LE, et al. *J Heart Lung Transplant* 2021;40:1349-79 [3].

still suggested as a relative contraindication, no age is given as an absolute contraindication, and the age of recipients has increased in recent decades [4].

In a 2015 study, selected older patients without significant underlying diseases had acceptable results with no significant difference in short-term survival rates compared to those of younger recipients; however, patients over 70 years of age had lower survival rates [5].

Although the number of older candidates is increasing and more favorable results have been reported for transplantation in older patients than before, recipients should nonetheless be selected carefully according to the assessment of the center and the donor allocation system.

Malignancy

Although malignancy is classified as a contraindication for transplantation, transplantation may be considered depending on the type of malignancy and its characteristics. The recently reported consensus statement on malignant tumors before transplantation of solid organs mentions that transplantation may be considered in patients with a previous cancer history who are well-maintained and without recurrence for more than 5 years, in patients with carcinoma not significantly affected by immunosuppressants, and in those who have no metastasis and a very low risk of recurrence. The consensus report also suggests that careful selection should be made in consideration of current developments in treatment, which have improved patients' survival. In particular, close consultation with an oncologist is necessary to decide whether a patient is likely to receive

survival benefits. However, transplantation should be avoided if a metastatic lesion is present, there is a high risk of recurrence, or the patient's life expectancy is short [6,7].

Nutritional status

Abnormal nutritional conditions, such as overweight or underweight, can affect patients' prognosis after transplantation [8]. A recent report confirmed that primary graft dysfunction and mortality after transplantation may increase in overweight patients and that the prognosis after transplantation may be poor in overweight or obese patients, especially those with a body mass index (BMI) of 35 kg/m² or higher [9-11]. Although low weight is generally accepted as a risk factor in lung transplantation, no significant difference was found in the survival rate of cystic fibrosis (CF) patients according to BMI, even among those with a BMI of 17 kg/m² or less [12,13]. Although BMI is not a definitive criterion for transplantation, adequate nutrition in underweight patients and appropriate weight loss in overweight patients may help improve outcomes.

Major organ dysfunction and other medical conditions

If other organ failure is accompanied by respiratory failure, the post-transplantation process may be adversely affected and the function of the organs may worsen further; hence, a careful approach is required for transplantation in patients with major organ dysfunction. The bleeding that may occur after perioperative surgery and the use of neph-

rotoxic drugs may damage renal function; hence, renal failure may occur to the extent that renal replacement therapy is required after transplantation. Several reports have confirmed that the risk of requiring renal replacement therapy increases in patients above 45 years of age with a glomerular filtration rate less than 60 mL/min/1.73 m². Therefore, a careful approach is required in these patients, and multi-organ transplantation should be considered as well [14-16].

In a previous report, there was no difference in survival and no increase in mortality due to coronary artery disease (CAD) in patients who had undergone coronary intervention before lung transplantation and had preserved left ventricular function. Several recent studies also showed that there was no significant difference in the survival rate of patients with mild to moderate CAD or who underwent coronary intervention before surgery. In patients with peripheral vascular disease (PVD), there may be problems when extracorporeal membrane oxygenation (ECMO) is applied and difficulties with rehabilitation after surgery; however, PVD is not considered an absolute contraindication. As patients with PVD are more likely to have concomitant vascular disease, which can be a problem, various preoperative evaluations are necessary, and a cautious approach must be taken [17-20].

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is associated with allograft dysfunction and rejection after lung transplantation and also reduces the forced expiratory volume in 1 second (FEV1) and survival. For this reason, preoperative anti-reflux surgery in patients with GERD has a good prognosis, but it is not effective in cases where only a proton-pump inhibitor is used or cases accompanied by motility disorders of the stomach or esophagus. Therefore, it can be helpful to accurately evaluate GERD before surgery, control symptoms, and perform pre-transplant fundoplication if necessary [21-24].

Bridge to transplant/extracorporeal life support

Although in the past, the application of extracorporeal life support before transplantation was not recommended owing to poor outcomes, ECMO is now widely used before transplantation owing to advances in ECMO management and experience in countries with an allocation system that prioritizes critically ill patients. In patients awaiting transplantation, ECMO application cannot be avoided when se-

vere hypercapnia and hypoxia are present, and pulmonary hypertension and right ventricular dysfunction can be effectively managed to reduce the burden on the right ventricle and prevent multiple organ damage. Additionally, the application of ECMO enables ambulation or physical therapy. Awake ECMO can also help spare respiratory function. Hence, the accumulation of further experience in ECMO management and continuing technological developments could enable ECMO to be applied more widely [25-27].

Infectious diseases

Active infections are generally contraindications for transplantation. The use of immunosuppressive drugs after transplantation may lead to poor control of infection and progression to sepsis. In cases of CF and non-CF bronchiectasis, the colonization of resistant bacteria progresses, thereby increasing mortality after surgery. However, in recent years, many limitations have been overcome with the development of new antibiotics, advanced regimens, and organism detection and diagnostic technology. Therefore, depending on the characteristics of the infection, a multidisciplinary approach that will be able to sufficiently control infections after transplantation should be implemented at the institutional level for transplantation to proceed. According to a recently reported consensus, transplantation is possible despite infections with non-tuberculous mycobacteria, non-aspergillus molds, and *Burkholderia cepacia* complex if accompanied by appropriate treatment [3,26-28].

Incurable extrapulmonary infections

Human immunodeficiency virus infection is now considered a chronic disease owing to advances in treatment. If antiviral therapy is administered after transplantation in patients with adequate lymphocyte levels and viral load, acceptable results may be obtained [29]. Safe lung transplantation is also possible in patients with hepatitis B virus, similarly to the transplantation of other solid organs, if appropriate antiviral agents are used after transplantation [30].

According to a previous report, there was no significant difference in the survival rate among hepatitis C virus seropositive patients who underwent lung transplantation, and there was no increase in mortality in patients without evidence of cirrhosis. Preoperative antiviral treatment is now possible with the use of direct-acting antiviral combi-

nation therapy, and if there is no evidence of liver cirrhosis, hepatitis C virus infection can also be treated after surgery [31,32].

Previous thoracic surgery, pleural procedures, and chest wall and spinal deformities

A history of previous thoracic surgery, pleural disease, and pleural procedures may make the operation difficult and time-consuming and may cause massive bleeding, potentially increasing the incidence of mortality or graft dysfunction. However, these are not contraindications to lung transplantation, and in clinical practice, many such patients are encountered. According to a recent report, about 45% of transplant patients had undergone treatment for chest conditions, and although there was no significant difference in the survival rate, the survival rate was lower in patients who underwent lung re-transplantation [33,34].

Conditions such as chest wall or spinal deformity may also cause difficulties in surgery, and problems such as ventilation or size mismatch may occur. There have been reports of surgery in these patients, according to which appropriate preoperative planning, selection of the donor lung, and postoperative pulmonary toileting are important for these patients [35,36].

Adherence and addiction

In general, after lung transplantation, high-intensity rehabilitation and adherence to lifestyle rules are important; hence, a careful evaluation of social support and compliance is necessary.

Previous studies have indicated that non-adherence is associated with an increased risk of rejection after transplantation. Psychosocial screening is still considered important, and non-adherence without the will to improve is an absolute contraindication. Since compliance and social support are very important for transplant success, socio-economic support at the transplant center should be well provided, and patients should be evaluated with systematic monitoring [37].

Patients with cognitive impairment, such as dementia, have problems with decision-making and self-management, which can lead to adverse results after surgery. As such, cognitive impairment is considered a contraindication [38]. Although affective, anxiety, and depressive disorders are not considered absolute contraindications, they can result in non-adherence, which can lead to poor transplantation outcomes. Therefore, it is necessary to judge

whether the patient's symptoms are well controlled, to actively use psychotropic drugs, and to carefully review the patient's condition [39,40].

Tobacco use, vaping, marijuana smoking, or intravenous drug use are absolutely contraindicated in transplantation. In addition to their direct impacts, these factors may also be associated with non-compliance, which may adversely affect the prognosis. The use of such drugs must be stopped before transplantation, and it is necessary to monitor the patient and provide support through appropriate education [41].

Disease-specific guidelines

Chronic obstructive pulmonary disease

Although COPD remains the most common indication for lung transplantation, it is still difficult to establish an appropriate predictive model because its disease course and prognosis are heterogeneous. Despite these limitations, the BODE score (body mass index, degree of airway obstruction, dyspnea, and exercise capacity score) is still the most important indicator, and along with it, FEV1 and the presence or absence of acute exacerbation determine whether transplantation is possible based on the presence or absence of evidence for pulmonary arterial hypertension (PAH), as summarized in Table 2 [3,42].

Diffusing capacity of the lung for carbon monoxide (DLCO) is not a criterion for lung transplantation, although it can be considered in patients with severe symptoms accompanied by low DLCO or decreased exercise capacity. Cases in which the patient's condition worsens despite maximal treatment or the quality of life deteriorates significantly owing to symptoms may be considered for transplantation [43].

Endoscopic or surgical lung volume reduction (LVR), an important treatment option for patients with COPD, can improve lung function and quality of life and has demonstrated survival benefits in selected patients [44]. Successful LVR can prolong the time for transplantation and preserve nutritional status and motor performance. However, in patients who eventually need transplantation, pleural adhesions can be induced, which can lead to problems such as prolonged operation time and increased bleeding. For this reason, the decision to perform LVR surgery before transplantation should be made after a careful evaluation in patients who will eventually need transplantation [45, 46].

Table 2. Guidelines for patients with COPD

Guidelines	
Guidelines for referral	Patients with a BODE index of 5–6 and at least one additional risk: <ul style="list-style-type: none"> - Frequent acute exacerbations - Increase in BODE index >1 over past 2 years - Pulmonary artery/aorta ratio >1 on CT scan - FEV1 20%–25% predicted
Guidelines for transplantation	Patients with a BODE index of 7–10 and at least one of the following: <ul style="list-style-type: none"> - FEV1 <20% predicted - Moderate to severe pulmonary hypertension - Severe exacerbations - Chronic hypercapnia

Modified from Leard LE, et al. *J Heart Lung Transplant* 2021;40:1349-79 [3]. COPD, chronic obstructive pulmonary disease; BODE, body mass index, degree of airway obstruction, dyspnea, and exercise capacity; CT, computed tomography; FEV1, forced expiratory volume in 1 second.

Table 3. Guidelines for patients with ILD

Guidelines	
Guidelines for referral	(1) Pulmonary fibrosis on CT scan with FVC of <80% predicted or DLCO <40% predicted (2) Pulmonary fibrosis on CT scan with one of the following in the past 2 years: <ul style="list-style-type: none"> - Decline in FVC >10% or decline in DLCO >15% - Decline in FVC >5% in combination with worsening of respiratory symptoms or radiographic progression (3) Supplemental oxygen needed at rest or on exertion (4) Inflammatory ILD, progression of disease (imaging or pulmonary function test result) despite treatment
Guidelines for transplantation	(1) Pulmonary fibrosis on CT scan with one of the additional risk factors in the past 6 months <ul style="list-style-type: none"> - Absolute decline in FVC >10% or in DLCO >10% - Absolute decline in FVC >5% with radiographic progression (2) Desaturation to <88% on 6-minute walk test or >50 m decline in 6 months (3) Pulmonary hypertension (4) Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation

Modified from Leard LE, et al. *J Heart Lung Transplant* 2021;40:1349-79 [3]. ILD, interstitial lung disease; CT, computed tomography; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

Interstitial lung disease

Interstitial lung disease (ILD) remains an important indication for lung transplantation, and the number of patients with this disease is increasing. Despite several new treatments, ILD still has a poor prognosis and the highest mortality rate during lung transplantation. For this reason, patients with ILD should be referred to a transplant center earlier than those with other lung transplant indications. The survival benefit and various evaluation tools for lung transplantation in patients with ILD are relatively well established [47,48].

If there is evidence of histopathological or radiographic usual interstitial pneumonia, it is important to refer the patient to a transplant center at the time of diagnosis. In addition, referral should be considered if there are signs of a decrease of forced vital capacity or DLCO. Even though there are other factors that predict the course of ILD, such

as PAH and evidence of right ventricular failure, accurate predictions are difficult and several risk factors must be considered [3,49,50] (Table 3).

In cases of ILD with extrapulmonary involvement, such as familial fibrosis, sarcoidosis, and connective tissue disease, special consideration is needed because several additional evaluations are required. An additional consideration is the use of anti-fibrotic agents during transplantation. Theoretically, the use of these drugs is thought to cause problems in wound healing, but some studies have shown no notable effects of anti-fibrotic agents on wounds, anastomosis, or bleeding [51-53].

CF and non-CF bronchiectasis

CF is a disease involving multiple organs that occurs in young patients, and lung transplantation has been consistently demonstrated to yield greater survival benefits in

general for CF over other diagnoses warranting transplantation [54].

The most important predictor for CF is FEV1, and a recent report showed a median survival of 6.6 years in patients with FEV1 <30% of the predicted value. The use of CF transmembrane conductance regulator modulators is expected to further increase median survival. However, individual differences still exist, and a high risk of death was reported when FEV1 was <30% of the predicted value [55].

Listing and referral may be based on worsening lung function, severe symptoms, decreased exercise capacity, frequent hospitalizations, and hemoptysis (Table 4) [3]. An additional consideration in patients with CF is infection with multi-drug-resistant organisms. These organisms may recolonize after transplantation and increase the risk of graft dysfunction. Although the evidence is insufficient, sinus surgery before transplantation can be considered, and even if surgery is not performed, accurate evaluation and treatment are required before and after transplantation [56].

Non-CF bronchiectasis can be caused by various factors, such as chronic infection or genetic disease. Although the characteristics of the patient and the course of the disease are heterogeneous, the results after transplantation are bet-

ter than those in CF patients. However, it is recommended that the referral and listing criteria be applied in the same way as for CF patients [57,58].

Pulmonary arterial hypertension

The timing of lung transplantation for PAH and related surgical methods have changed, and many developments have been made. In the World Symposium of Pulmonary Hypertension classification of PAH, group 1 is the most common indication. Group 2, with decreased left ventricular function, is not an indication for transplantation, but group 3 with PAH and accompanying pathological changes in the lung parenchyma can be considered for transplantation. The current consensus is based on 2 tools for referral and listing: the REVEAL Registry 2.2 (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management 2.0) and 2015 European Society of Cardiology/European Respiratory Society. Additionally, transplantation may be necessary if prostacyclin treatment is required for an appropriate intervention, there is accompanying liver or renal failure, or severe hemoptysis is present [3,59-62] (Table 5).

Table 4. Guidelines for patients with CF

Guidelines	
Guidelines for referral	(1) FEV1 <30% predicted (2) FEV1 <40% predicted and - 6-Minute walk distance <400 m - PaCO ₂ >50 mm Hg - Hypoxemia at rest or with exertion - Pulmonary hypertension - Worsening nutritional status despite supplementation - 2 Exacerbations per year requiring intravenous antibiotics - Massive hemoptysis requiring bronchial artery embolization - Pneumothorax (3) FEV1 <50% predicted and - Rapidly declining based on pulmonary function testing or progressive symptoms - Any exacerbation requiring positive pressure ventilation
Guidelines for transplantation	(1) Any of the above referrals with any of the following: - FEV1 <25% predicted - >30% relative decline in FEV1 over 1 year - Frequent hospitalizations, particularly if hospitalized for >28 days in the last year - Requiring mechanical ventilation - Chronic respiratory failure with hypoxemia or hypercapnia - Pulmonary hypertension - Body mass index <18 kg/m ² despite nutritional interventions - Recurrent massive hemoptysis despite bronchial artery embolization - World Health Organization functional class IV

Modified from Leard LE, et al. J Heart Lung Transplant 2021;40:1349-79 [3].
 CF, cystic fibrosis; FEV1, forced expiratory volume in 1 second; PaCO₂, partial pressure of carbon dioxide.

Table 5. Guidelines for patients with PAH

	Guidelines
Guidelines for referral	(1) ESC/ERS intermediate or high risk or REVEAL risk score 8 despite appropriate PAH therapy (2) Significant RV dysfunction despite appropriate PAH therapy (3) Need for IV or SC prostacyclin therapy (4) Progressive disease despite appropriate therapy (5) PVOD/PCH, scleroderma, large and progressive pulmonary artery aneurysms (6) Secondary liver or kidney dysfunction (7) Potentially life-threatening complications such as recurrent hemoptysis
Guidelines for transplantation	(1) ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH therapy, including IV or SC prostacyclin analogues (2) Progressive hypoxemia, especially in patients with PVOD or PCH (3) Progressive, but not end-stage, liver or kidney dysfunction due to PAH (4) Life-threatening hemoptysis

Modified from Leard LE, et al. *J Heart Lung Transplant* 2021;40:1349-79 [3].

PAH, pulmonary arterial hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; RV, right ventricle; IV, intravenous; SC, subcutaneous; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis.

Lymphangiomyomatosis

Although lymphangiomyomatosis (LAM) is not a common indication for transplantation, it has better outcomes after transplantation than other diseases. Even though it is rare for LAM patients to require transplantation owing to the use of the mechanistic target of rapamycin (mTOR) inhibitors, transplantation can be performed in cases of severe pulmonary function deterioration and the presence of severe symptoms. An important issue to consider is that these patients usually have had a prior pleural procedure, which can cause a large amount of bleeding during transplantation. The use of mTOR inhibitors in patients being considered for transplantation remains a matter of debate, but the current consensus is that they should be used until transplantation is considered, and the patient should be thoroughly educated about the risks involved [63-65].

Acute respiratory distress syndrome

In patients with acute respiratory distress syndrome (ARDS) without underlying lung disease, transplantation may be indicated if the patient is not withdrawn from the ventilator or if there is evidence of irreversible lung injury. Transplantation has recently become an important option in cases of irreversible fibrotic changes of the lungs in ARDS caused by coronavirus disease 2019 [66,67]. Several studies have indicated that when lung transplantation is performed in patients with ARDS, the prognosis is better in those with no comorbidities, a young age, and no other organ failure. Transplantation in patients with ARDS

should be preceded by a determination that the patient's condition is irreversible. Transplantation is considered when the patient is not weaned from a ventilator or ECMO even 1 month after ARDS occurs, parenchymal infiltration is not recovered, and pulmonary compliance is severely deteriorated [68,69].

Conclusion

Owing to the accumulation of many experiences and advances in technology, the selection of appropriate candidates for lung transplantation has undergone many changes and developments, which are still in progress. The patient's medical condition and psychosocial support, as well as the center's experience and support, will be important in selecting candidates for transplantation. However, as the clinical characteristics of candidates are still very diverse and there are many variables, it is necessary to analyze each patient's overall situation and medical condition from various perspectives. Continuing efforts to optimize the analysis will be necessary.

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Writing–original draft: JS. Writing–review & editing: CS.

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