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Recipient Management before Lung Transplantation

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Lung transplantation is considered a viable treatment option for patients with end-stage lung disease. Recent decades have seen a gradual increase in the number of lung transplantation patients worldwide, and in South Korea, the case number has increased at least 3-fold during the last decade. Furthermore, the waiting list time is becoming longer, and more elderly patients (>65 years) are undergoing lung transplantation; that is, the patients placed on the waiting list are older and sicker than in the past. Hence, proper management during the pre-transplantation period, as well as careful selection of candidates, is a key factor for transplant success and patient survival. Although referring and transplant centers should address many issues, the main areas of focus should be the timing of referral, nutrition, pulmonary rehabilitation, critical care (including mechanical ventilation and extracorporeal membrane oxygenation), psychological support, and the management of preexisting comorbid conditions (coronary artery disease, diabetes mellitus, gastroesophageal reflux disease, osteoporosis, malignancy, viral infections, and chronic infections). In this context, the present article reviews and summarizes the pre-transplantation management strategies for adult patients listed for lung transplantation.

Keywords: Lung transplantation, Management, Transplant recipient

Introduction

Lung transplantation is a well-established therapeutic option for patients with advanced lung disease that is refractory to maximal medical or surgical therapy. Currently, interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) are the most common indications for lung transplantation, although lung transplantation is also rarely performed in patients with other end-stage lung diseases, such as lymphangioleiomyomatosis, sarcoidosis, and pulmonary arterial hypertension [1]. According to the International Society for Heart and Lung Transplantation (ISHLT), the number of lung transplantations has gradually increased worldwide, with more than 67,000 adult lung transplantations through June 2018 [2]. In South Korea, the number of cases has also shown a nearly 3-fold increase in recent years, from 55 in 2014 to 167 in 2021 [3]. However, despite many advances in surgical techniques and perioperative management, the mortality rate is still higher in lung transplantation patients than in patients who receive transplantation of other organs. Furthermore, the number

of patients added to the waiting list has recently increased in South Korea and the waiting list time is getting longer, with a mean duration of 234 days in 2019 (versus 116 days in 2016) [4]. Hence, to reduce mortality while patients are on the waiting list, careful selection of patients and proper management of pre-transplantation conditions are of paramount importance. This article reviews and summarizes the lung transplantation-specific monitoring and management of adult patients listed for lung transplantation.

Timing of referral

The ISHLT has developed and updated criteria for recipient selection for lung transplantation, which include patients with a high risk of death (>50%) from lung disease without transplantation and a high likelihood of survival (>80%) for at least 5 years after lung transplantation, provided that graft function is adequate [5]. However, it is important for non-transplantation physicians to refer patients with advanced lung disease earlier for lung transplantation. Early referral may allow the identification of modifiable

risk factors, optimization of comorbidities, and improvement of nutritional and functional status, thereby maximizing the chances of meeting the eligibility criteria for transplantation and improving these patients' outcomes [6].

For patients with COPD, a body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity index of 5 or 6 or a forced expiratory volume in 1 second <25% of the predicted value can be considered when determining the timing of referral. For patients with idiopathic pulmonary fibrosis, the time when a confident radiologic or histologic diagnosis is obtained, regardless of lung function, would be appropriate for referral. However, for other ILDs associated with connective tissue diseases, severe limitation with symptoms (New York Heart Association functional class III or IV) or a forced vital capacity <80% of the predicted value, a diffusion capacity for carbon dioxide <40% of the predicted value, or the requirement of oxygen at rest can be considered as criteria for referral [5].

Lung transplantation centers should evaluate potential transplantation candidates to identify risk factors associated with transplantation outcomes and any modifiable factors before placing them on the waiting list. These tests may vary among patients and centers (Table 1). However, following an evaluation at a lung transplantation center, the patient, patient's family, and transplantation specialists will determine together whether the patient will be placed on the transplantation list.

Nutrition and body mass index

The nutritional status of lung transplantation candidates is related to post-transplantation survival. Many studies have identified obesity as a significant risk factor for mortality [7,8], and the current guidelines include class II or III obesity (BMI ≥35 kg/m^2) as an absolute contraindication and class I obesity as a relative contraindication [5]. In particular, Lederer et al. [9] found that obesity was an independent factor in the development of grade 3 primary graft dysfunction. However, a study in the lung allocation system era found that patients with class I obesity (BMI 30–34.9 kg/m^2) had similar survival outcomes to those of normal-weight or overweight patients [10].

Although a low BMI alone should not preclude listing or transplantation, several studies have shown malnutrition

Table 1. Pre-transplant tests and evaluation

Category	Tests
Laboratory tests	CBC, BUN/Cr, liver function tests, electrolytes, iron, TIBC, HbA1c and glucose, urinalysis, pregnancy test, thyroid function test, ABGA, coagulation tests, ABO with Rh
Serology for infections	HBcAb, HBeAg, anti-HBe, HBV-DNA, anti-HCV, anti-HAV (IgG & IgM), HIV Ag/Ab, HSV (IgG & IgM), CMV (IgG & IgM), CMV-PCR, EBV (IgG & IgM), EBV-PCR, VZV (IgG & IgM), Toxoplasma (IgG & IgM); interferon-gamma release assays, TB/NTM-PCR; serology for syphilis
Serology for connective tissue diseases	Rheumatoid factor, complements, anti-nuclear Ab, anti-dsDNA
Staining and cultures	Routine cultures (blood, sputum, urine), stool exam & occult blood test, CMV culture (blood/throat), fungus culture (sputum), and AFB stain and cultures
PFT	PFT with DLCO, 6-minute walk test
Image	Chest and abdomen CT
Cardiac tests	BNP, NT-proBNP, troponin, CK-MB, electrocardiogram echocardiogram, cardiac catheterization (patients >45 years)
Tumor markers	PSA (male patients), CEA, AFP, and CA19-9
HLA tests	HLA A/B/C and DR; HLA Ab tests: panel reactive antibody class I & II; HLA cross-matching (when a new donor is listed)
Other health evaluations	Bone mass density (DEXA), esophagogastroduodenoscopy, colonoscopy, dental examination, and evaluation for psychosocial factors
Vaccinations	Pneumococcal vaccination; seasonal influenza vaccination; DTP vaccination; hepatitis A and B (if not already immune)

CBC, complete blood count; BUN, blood urea nitrogen; Cr, creatinine; TIBC, total iron-binding capacity; HbA1c, hemoglobin A1c; ABGA, arterial blood gas analysis; HBcAb, hepatitis B core antibody; HBeAg, hepatitis B e-antigen; anti-HBe, hepatitis B e antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HAV, hepatitis A virus; IgG, immunoglobulin G; IgM, immunoglobulin M; HIV Ag/Ab, human immunodeficiency virus antigen/antibody; HSV, herpes simplex virus; CMV, cytomegalovirus; PCR, polymerase chain reaction; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; TB, tuberculosis; NTM, nontuberculous mycobacterium; AFB, acid-fast bacilli; PFT, pulmonary function test; DLCO, diffusion capacity of lung for carbon monoxide; CT, computed tomography; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; CK-MB, creatine kinase–myocardial band; PSA, prostate-specific antigen; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; HLA, human leukocyte antigen; DEXA, dual-energy X-ray absorptiometry; DTP, diphtheria, tetanus, pertussis.

to be associated with poor outcomes, especially in patients with cystic fibrosis or COPD [11,12]. Post-transplantation immunosuppressive therapy may exacerbate the preexisting risk of infection in patients with malnutrition. Hence, physicians are encouraged to optimize the nutritional status of these patients, with appropriate steroid tapering, nutritional counseling, dietary modifications, and lifestyle changes [1]. However, importantly, BMI is not a valid parameter for obesity in lung transplantation candidates due to its poor correlation with body composition [9]. Alternative methods such as adipose tissue characterization or biomarkers (e.g., leptin) may provide more valuable information [13,14].

Psychosocial problems

All lung transplantation candidates should be screened for psychological problems which might cause nonadherence to their post-transplantation management. A history of psychiatric diseases and substance dependence (e.g., alcohol and tobacco) should also be examined. Interventions including cognitive therapy and behavioral counseling may have a positive impact on long-term medication adherence.

The current literature shows that the prevalence of depression or anxiety in patients with end-stage lung disease is higher than the level in the general population [15]. It was reported that approximately 25% and 10% of patients who were listed for lung transplantation met the diagnostic criteria for anxiety and depressive symptoms, respectively [16,17]. Therefore, interventions addressing these issues, as well as family support, during the waiting period are important.

Preexisting human leukocyte antigen antibodies (sensitized candidates)

Pregnancy, blood transfusion, and prior transplantation can predispose transplantation candidates to the development of antibodies to human leukocyte antigen (HLA), which is associated with worse graft and patient survival. Panel reactive antibodies (PRAs) have been used to measure the degree of sensitization, and many testing centers now use a multiplexed bead-based flow cytometric assay (i.e., Luminex). The development of this solid phase-based assay has greatly increased the ability to detect HLA-specific antibodies, with high sensitivity and specificity. If HLA antibodies are present, even at low levels, there is a risk of hyperacute rejection, chronic rejection, or death. Previous studies have suggested that recipients who have a

PRA >25% before lung transplantation have an increased risk of death [18]. In an analysis of the United Network for Organ Sharing database, the prevalence of lung transplantation candidates with positive PRA was 17% [18]. However, the results of PRA testing are highly variable depending on the technique. Some centers reported poor post-transplantation outcomes, while other centers reported comparable overall or chronic lung allograft dysfunction-free survival rates. Although avoidance of donors with reactive HLA antigens can be a solution, it is associated with a longer waiting time and increased risk of death on the waiting list for sensitized recipients.

Many strategies have been developed to facilitate transplantation in candidates with preexisting HLA antibodies. One approach is lowering the HLA antibody titers before lung transplantation, which is referred to as a "desensitization protocol," consisting of plasmapheresis, methylprednisolone, bortezomib (or rituximab), and intravenous immunoglobulin. However, the results of desensitization protocols in lowering the HLA antibody titers in heart or lung transplantations remain disappointing [19,20].

However, pre-transplantation screening for HLA antibodies is very valuable in lung transplantation candidates. Despite variation among transplantation centers, a recommended screening method is the combination of solid-phase immunoassays and cross-matching tests (complement-dependent lymphocytotoxicity/flow cytometry) [21].

Mechanical ventilation and extracorporeal membrane oxygenation

Since the implementation of the lung allocation score in 2005, more patients who are sicker and older have been listed, and the number of patients who underwent lung transplantation while on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) has substantially increased in the United States [22,23].

Mechanical bridging to lung transplantation may prolong patients' survival on the waiting list and subsequently their chances of being able to receive transplantation from a suitable donor. However, post-transplantation outcomes were found to be worse in patients who received lung transplantation while on mechanical ventilation than in those without mechanical ventilation [22,23]. As is well known, mechanical ventilation is associated with an increased risk of ventilation-induced lung injury and ventilator-associated pneumonia. Furthermore, the use of sedatives may place patients at high risk for deconditioning, malnutrition, and infection. Hence, the best scenario

would be for transplantation candidates to undergo lung transplantation before requiring mechanical ventilation. However, importantly, potential transplantation candidates should be fully evaluated, including medical and psychological assessments, before they receive mechanical ventilation; furthermore, they need to understand transplantation as a therapeutic option, and its complications and outcomes.

Although early experiences with ECMO-bridged lung transplantation were disappointing, multiple studies published after 2010 have reported that patients with ECMO had similar 1-year post-transplantation survival rates to those not supported with ECMO [24-26]. In fact, technical advances in ECMO devices (e.g., small biocompatible oxygenators, heparin-coated circuits, centrifugal pumps, etc.) have decreased patients' morbidity and allowed patients to receive ECMO for extended periods while awaiting lung transplantation. In particular, when implemented in awake and ambulatory patients, ECMO allows patients to actively participate in nutrition and rehabilitation programs, which is linked to a reduction of post-transplantation complications. However, ECMO utilization is associated with increased resource use, high costs, and complications, which can be a barrier for many centers to use ECMO as a bridge.

Frailty and rehabilitation

Patients with end-stage lung disease frequently experience muscle weakness, deconditioning, and inactivity. In particular, reduced muscle mass and reductions in quadriceps strength are frequently observed in lung transplantation candidates. These reductions, along with the resultant decreased quality of life, can persist for years after lung transplantation [27-29].

Rehabilitation plays an important role in the pre-transplantation period by enhancing exercise capacity and optimizing functional status before lung transplantation. After lung transplantation surgery, further reductions in muscle strengths and slow recovery of exercise capacity are observed despite the immediate improvement in respiratory symptoms and ventilatory function [30]. Hence, participation in a rehabilitation program before lung transplantation may lead to more favorable outcomes, with shorter hospitalization. Previous studies have consistently shown that pre-transplantation rehabilitation was feasible and associated with improved functional exercise capacity and quality of life [31-33]. From this standpoint, Rochester et al. [34] proposed elements of exercising training before lung transplantation, which included progressive aerobic exer-cise and upper- and lower-extremity strengthening under close supervision, as well as continuous monitoring. They suggested that exercise should begin at a low intensity and gradually progress to the highest capacity tolerated, while maintaining adequate oxygenation [34].

Comorbid conditions

Coronary artery disease

Lung transplantation candidates are frequently at risk of coronary artery disease (CAD) because of their age, smoking history, and other risk factors. In a study of lung transplantation patients, 21% of patients had CAD and 15% underwent revascularization before or at the time of lung transplantation [35]. Another study demonstrated that pre-transplantation CAD was an independent risk factor for cardiovascular events after lung transplantation [36]. Hence, lung transplantation candidates should be screened for CAD during the pre-transplantation period.

However, satisfactory outcomes were recently reported in patients with CAD who underwent lung transplantation [37]. Because the risk imposed by CAD can be minimized with adequate medical or surgical interventions, lung transplantation can be considered in patients if they do not have end-organ dysfunctions. Percutaneous or surgical revascularization may be an option in patients with preserved left ventricular function, but occasionally, heart-lung transplantation may be considered in carefully selected patients with advanced CAD [38].

Diabetes mellitus

Although diabetes mellitus (DM) is not a contraindication to lung transplantation, existing studies found that pre-transplantation DM was associated with an increased risk of mortality [39,40]. Most transplantation centers recommend that blood glucose be well controlled (e.g., hemoglobin A1C of 7% or less). However, physicians should be aware that preexisting DM can worsen after transplantation because of the use of steroids and calcineurin inhibitors. Furthermore, after lung transplantation, caution should be exercised regarding the use of metformin (usually contraindicated in patients with renal or hepatic dysfunction), glucagon like peptide-1 agonists (due to gastrointestinal problems and altered immunosuppressant levels), and sodium-glucose cotransporter-2 inhibitors (due to diabetic ketoacidosis) [1].

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD), a common extrapulmonary manifestation of systemic sclerosis, requires careful evaluation and treatment because of its progressive nature after lung transplantation [41]. GERD is thought to aggravate the decline of lung function before transplantation and also in allografts after transplantation. The ISHLT guidelines indicate that severe esophageal dysmotility is a risk factor for poor post-transplantation outcomes [5]. A previous study suggested early fundoplication in lung transplantation patients to protect against GERD-induced lung injury [42]. Fundoplication may slow the decline of lung function in allografts.

Viral infections

As the management and outcomes of patients with human immunodeficiency virus (HIV) infection continue to improve, those with HIV may be considered for receiving lung transplantation. While HIV infection with a detectable viral load is considered a contraindication to lung transplantation, patients with an undetectable viral load (<20 copies/mL), CD4+ lymphocyte count >200/mm^3, no acquired immunodeficiency syndrome-defining illness, and adherence to antiretroviral treatments can be eligible for lung transplantation [5]. However, importantly, special attention is needed to avoid drug-drug interactions between antiretroviral and immunosuppressive agents after transplantation. In the United States, the passage of the HIV Organ Policy Equity Act permitted transplantation of HIV-positive donor organs to HIV-positive recipients [43].

Infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) with a detectable viral load and liver cirrhosis are increased risk of poor post-transplantation outcomes [5,44]. Because antiviral therapies for HBV are effective and safe, HBV infection does not preclude lung transplantation in the absence of liver cirrhosis. Similarly, although treatment for HCV prior to transplantation is recommended, patients with detectable HCV who do not have liver cirrhosis may also be treated after lung transplantation [5,45]. Two recent studies reported lung transplantations from HCV viremic donors into uninfected recipients [46,47]. They showed good outcomes in cases treated with direct-acting antiviral agents after transplantation. This suggests that post-transplantation antiviral treatments may also be curative in recipients who receive organs from HCV-positive donors.

Malignancy

Screening for cancer is an important part of the pretransplantation evaluation. In patients with a history of cancer, the risk of cancer recurrence should be considered before placing the patient on the waiting list. Although malignancy with a high risk of recurrence is an absolute contraindication to lung transplantation, patients where the risk of recurrence is very low may be able to undergo lung transplantation. In an analysis of the ISHLT data by Beaty et al. [48], pre-transplantation malignancy was not associated with an increased risk of mortality at 5 years. This suggests the current process for patient selection is appropriate [48]. However, several factors, including the type and stage of cancer and negative evidence of metastasis, should be taken into consideration [49,50].

Localized skin cancer (non-melanoma) is not considered a contraindication to lung transplantation, and a 2-year disease-free interval may be acceptable for skin cancers other than melanoma [51]. However, in most cases (hematologic malignancy, sarcoma, or cancers of the bladder, kidney, or breast), a 5-year disease-free interval should be demonstrated [52]. In particular, the risk of recurrence may be high in patients with bronchial carcinoma even after a 5-year disease-free interval, which warrants further research [52,53].

Osteoporosis

Severe osteoporosis is considered a relative contraindication to lung transplantation [5,38]. End-organ failure and steroid use before transplantation may contribute to a reduction in bone mass, which is especially common in the elderly. Hence, all transplantation candidates are encouraged to be monitored for osteoporosis and fracture risk, and if indicated, therapy should be initiated early before transplantation [54]. In particular, patients with cystic fibrosis are at high risk of developing bone disease and fracture due to their suboptimal vitamin D levels [55].

Chronic infections

Colonization or chronic infections with highly resistant organisms are considered a relative contraindication to lung transplantation, and this issue is especially common in patients with bronchiectasis and cystic fibrosis. *Aspergillus* species, *Burkholderia* species, and nontuberculous mycobacteria (NTM) are frequently cultured in sputum samples from these patients [56,57]. Although some centers

may decline to perform transplantation in patients with these organisms, high-volume or experienced transplantation centers may consider transplantation in these patients if there is a reasonable expectation of pre- or post-transplantation control of the infection.

Aspergillus species are isolated in sputum cultures in 20%–50% of patients with cystic fibrosis on the waiting list. Because patients colonized with *Aspergillus* species before transplantation are at high risk for tracheobronchitis or infections at anastomosis sites after transplantation, most centers initiate antifungal agents when these organisms are isolated before transplantation [58]. Patients with cystic fibrosis with NTM infections before transplantation are also at high risk of infection after transplantation, especially among those infected with *Mycobacterium abscessus* [57,59]. Hence, it is prudent to screen lung transplantation candidates for NTM, and in cases of NTM infections, eradication of these organisms should be attempted before transplantation. However, persistent positive cultures despite adequate treatment are a relative contraindication to lung transplantation [5].

Among patients with cystic fibrosis, infections or colonization with multidrug-resistant (MDR) bacteria such as *Burkholderia* species or *Pseudomonas aeruginosa* are not uncommon [60,61]. These patients with MDR pathogens tend to show a more rapid decline in lung function [62]. Data on the impact of these MDR pathogens are very limited, but a multicenter study reported poor outcomes after transplantation in recipients infected with pan-resistant organisms before transplantation [63]. In general, infection with the *Burkholderia cepacia* complex is considered a relative contraindication to lung transplantation, but some centers consider those infections an absolute contraindication [59].

Vaccination

All transplantation candidates, close contacts, and healthcare providers should complete the recommended vaccinations before transplantation. Non-transplantation or transplantation centers should review the vaccination status of transplantation candidates. Of note, patients receiving high-dose steroids or immunosuppressants should avoid live attenuated vaccines such as intranasal influenza, rotavirus, varicella zoster, measles, mumps, and rubella: but the inactivated influenza vaccine is safe [1]. Household contacts should also avoid these live vaccines.

Removal from the waiting list

The clinical conditions of patients on the waiting list can change rapidly, which may lead to delisting from the lung transplantation waiting list. Common reasons for delisting are as follows: progression of disease to the point where the patient becomes too sick to undergo the operation, the development of new organ failure, sepsis, nonadherence to treatment, and improvement of clinical status. In particular, those on mechanical ventilation or ECMO are at high risk of delisting due to the sudden deterioration of their condition. Therefore, all lung transplantation candidates should be assessed regularly for their suitability for lung transplantation.

Conclusion

Proper management during the pre-transplantation period is crucial for transplantation success and patient survival. Older and sicker patients have recently been receiving lung transplantation. Hence, early referral to transplantation centers, optimization of nutritional status, psychosocial support, rehabilitation to maintain good functional status, and management of comorbid conditions are all important to maintain lung transplantation candidacy. Additionally, bridging to lung transplantation (mechanical ventilation or ECMO) may be used to increase the likelihood of receiving suitable organs.

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