



# A narrative review on the management of patients awaiting lung transplantation in Japan

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**Background and Objective:** The number of lung transplantations performed in Japan is increasing, and post-transplant outcomes are relatively favorable. A major concern is the extremely long waiting time and the high mortality rate on the waitlist. The management of patients before transplantation is very important and essential for further improvement of outcomes. In this review, we summarize the management of patients awaiting lung transplantation in Japan.

**Methods:** A literature search was conducted via PubMed in November 2022 using the following keywords: lung transplantation, waiting, management, recipient, and Japan. Peer-reviewed academic journal articles published in English were also included.

**Key Content and Findings:** A growing number of studies have evaluated the management of pre-transplant patients. This includes infection control, vaccination, respiratory disease-specific treatment, malignancy, nutrition, rehabilitation, psychosocial assessment, and health-related quality of life (HRQOL) for patients on the waitlist. Each is important, and various evaluation methods and strategies to improve outcomes have been reported.

**Conclusions:** Proper and multifaceted management of pretransplant patients is extremely important to reduce the mortality of candidates for lung transplantation. Integrated management is crucial to the success and survival of lung transplant recipients.

**Keywords:** Lung transplantation; recipient; Japan; management

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## Introduction

### Background

Lung transplantation is an established procedure for patients with end-stage respiratory failure. However, the shortage of donor lungs is one of the most critical issues in lung transplantation, which is a particularly serious problem in Japan. Although the number of brain-dead

donors and lung transplantations has increased since the revised Japanese transplantation law took effect in 2010 (1), the number of newly registered candidates for lung transplantation has increased at a pace far exceeding the number of donors. The average waiting time was more than 900 days, resulting in a nearly 50% mortality rate on the waiting list. Marginal or extended criteria lungs have sometimes been used, considering the recipient's

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**Table 1** The search strategy summary

Items	Specification
Date of search	2022/11/24
Databases and other sources searched	PubMed
Search terms used	Lung transplantation, waiting, management, recipient, and Japan
Timeframe	2000–2022
Inclusion and exclusion criteria	Inclusion criteria: articles retrieved from search term in PubMed and related transplant management articles or guideline judged by authors to be related to it  Exclusion criteria: case reports and articles unrelated to transplant management were excluded
Selection process	Two authors conducted selection

condition. However, lung transplantation in Japan shows favorable outcomes, with 5-year survival rate was 73.72% for cadaveric lung transplantation and 73.84% for living lung transplantation (2), which is getting better year by year (3-5) and also better than that reported by the International Society for Heart and Lung Transplantation registry.

### Objective

Favorable outcomes of lung transplantation in Japan can be attributed to several factors, but there is no doubt that management during waiting periods is important. This article reviews the management of candidates listed for lung transplantation, especially in Japan. We present this article in accordance with the Narrative Review reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1690/rc>).

### Methods

A literature search was conducted via PubMed in November 2022 using the following keywords: lung transplantation, waiting, management, recipient, and Japan from 2000 to 2022 (*Table 1*). Eleven papers were retrieved by search. We have also added the peer-reviewed paper from Japan which is related to the management of patients who are waiting on the list for lung transplantation selected by 2 authors. We may have missed some important literature. Peer-reviewed academic journal articles published in English including International Society for Heart and Lung Transplantation registry report were also included.

## Results

### *Listing and de-listing candidates*

An age limitation is enforced for recipients of lung transplantation in Japan, due to severe donor shortage. At the time of registration to be on the waiting list, the recipient must be under 60 for a single lung transplantation or under 55 for a bilateral lung transplantation. To save as many recipients as possible from one donor, single lung transplantation is a priority in Japan. Unless the candidates have pulmonary artery hypertension (PAH) or chronic respiratory infection, a single lung transplantation is usually the first option, and a bilateral lung transplantation is the second option. There is no priority system such as allocation system, based on severity or urgency in Japan. Once candidates are on the list, they must wait their turn. Due to the extremely long waiting time, earlier registration may be necessary in considering disease progression and age, rather than the timing of registration presented internationally (6). Once a recipient is enrolled, we may consider removing them from the waiting list if they no longer meet the eligibility criteria during the waiting time, such as when a vital organ remains irreversibly damaged, a malignancy which is difficult to treat, is diagnosed, rehabilitation is not possible after transplantation, or family members are not available.

### *Assessment of infections*

Chronic infections or colonization with resistant organisms are sometimes a problem for lung transplantation and may

be contraindications to lung transplantation. This problem is particularly important in patients with bronchiectasis, such as cystic fibrosis, which is uncommon in Japan, or diffuse panbronchiolitis (DPB) (7). *Aspergillus* species (8), nontuberculous mycobacteria (8), and multidrug-resistant bacteria, such as *Burkholderia* species or *Pseudomonas aeruginosa*, are sometimes cultured from these patients (9). These patients tend to have a more rapid decline in respiratory function during the waiting period (10). In addition to sinus surgery and nasal care for chronic rhinosinusitis, long-term macrolide antibiotic therapy has been shown to significantly improve the survival of patients with DPB (11).

#### ***Pulmonary complications after hematopoietic stem cell transplantation (HSCT)***

HSCT is a highly invasive treatment for hematologic malignancies. Late-onset noninfectious pulmonary complications (LONIPCs) are life-threatening complications after HSCT. Five types LONIPCs were reported, including bronchiolitis obliterans (BOs), BOs with organizing pneumonia, diffuse alveolar damage, lymphocytic interstitial pneumonia, and non-classifiable pneumonia (12). Pleuroparenchymal fibroelastosis (PPFE) has been reported as an LONIPCs. Some patients with PPFE suffer from recurrent pneumothorax, which is resistant to treatment, leading to poor prognosis. Lung transplantation is not indicated for up to 2 years after the eradication of a hematological malignancy, and a disease-free interval of 5 years is ideal. In addition, there must be no severe damage to vital organs such as the liver and kidneys, and no uncontrollable graft versus host disease (GVHD). If the condition progresses too quickly to wait for a cadaveric lung transplant, living donor lung transplantation is considered according to the standards of each transplantation center. In fact, a report from Japan found that 17 patients received a cadaveric lung transplant while 45 patients received a living donor lung transplant (13).

#### ***Management of registered disease-specific treatment***

Interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) are the major registered respiratory diseases for lung transplantation in the world. However, lung transplantation is rarely performed in patients with other end-stage lung diseases, such as lymphangioleiomyomatosis (LAM) or PAH (14). In Japan,

ILD, LAM, and COPD are common indications for single-lung transplantation, and PAH, ILD, and bronchiectasis are common indications for bilateral lung transplantation. Cystic fibrosis is a rare disease in Japan, and COPD is not a major indication due to the upper age limit, which is less than 55 years old for bilateral lung transplantation and 60 years old for single lung transplantation. Non-infectious pulmonary complications after HSCT are important cause of morbidity and mortality. Lung transplantation is one of the treatments option for selected HSCT recipients. To reduce the mortality rate of these patients on the waiting list, proper pre-transplantation management is very important.

#### **ILD**

ILD is a major indication for lung transplantation in Japan. Approximately one-third of ILD patients underwent cadaveric lung transplantation, whereas approximately 50% died while on the waiting list regardless of their specific diagnosis (15). This outcome is similar to the mortality rate of all Japanese candidates on the waiting list (16). Idiopathic PPFE and LONIPC with radiological PPFE has better survival on the wait list for lung transplantation than fibrotic ILD without radiological PPFE (17). A history of pneumothorax and a short 6-min walk distance were independent predictors of waitlist mortality in lung transplantation candidates with ILD. Recent advances in antifibrotic therapy may potentially reduce mortality in patients with ILD on the waiting list for lung transplantation (16).

#### **LAM**

LAM is a rare neoplastic disease characterized by the proliferation of abnormal smooth muscle-like cells, leading to cystic destruction of the lungs. Due to its rarity, LAM was a minor indication (0.9%) for lung transplantation in an international survey (18). However, it is one of the major indications (approximately 20%) in Japan. The prognosis after registration was similar to that after lung transplantation, which is 73.7% survival rate at 5 years, being favorable in LAM patients. Greater use of sirolimus is expected to improve the circumstances of pre-transplantation life in patients with advanced LAM (19).

#### **PAH**

PAH is a common indication for bilateral lung transplantation and the fourth leading cause of necessity for lung transplantation worldwide. Recent developments in PAH-

specific drugs, such as prostacyclin, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, soluble guanylate cyclase stimulators, and prostacyclin receptor agonists, have substantially improved the prognosis of PAH. Only about 10% of PAH patients died within 1 year after diagnosis of PAH. Even after registration for lung transplantation, patients receiving prostacyclin infusion soon after PAH diagnosis had a marked reduction in pulmonary artery pressure and long-term survival before lung transplantation (20). Nocturnal hypercapnia is prevalent among patients with advanced PAH who are waiting for lung transplantation and is associated with a percentage of total lung capacity (21).

### ***Mechanical ventilation or extracorporeal membrane oxygenation (ECMO)***

The lung allocation score (LAS) system was implemented in the United States in 2005. The number of patients who undergo lung transplantation while on mechanical ventilation or ECMO has increased. The purpose of the LAS system is to reduce waiting time and mortality and prioritize patients based on urgency (22). In contrast, the algorithm for donor lung allocation in Japan is based primarily on accrued time on the waiting list, which favors patients with slowly progressive diseases rather than rapidly progressive diseases (23). ECMO has been increasingly used as a bridge to lung transplantation since most patients undergo lung transplantation within a few weeks. However, the waiting time is longer in Japan owing to the severe shortage of donors. The indication of ECMO as a bridge to transplant is quite rare, and only a few cases have been reported (24).

### ***Malignancy***

Screening for malignancy is essential when considering the indications for lung transplantation. The risk of malignancy recurrence should be considered in patients with a history of cancer prior to registration. Although malignancy with a high risk of recurrence is a contraindication to transplantation, patients with a low risk of recurrence are candidates for lung transplantation. Pre-transplantation malignancy was associated with the risk of *de novo* malignancy after lung transplantation (25) but was not associated with an increased risk of mortality at 5 years (26). According to the Japanese national survey, *de novo* malignancy after lung transplantation was 10.1% and post-

transplant lymphoproliferative disorder (PTLD) was the most common malignancy (27). PTLD occurred after both living-donor lobar lung transplantation and cadaveric lung transplantation (28). Among 40 cases undergoing lung transplantation after HSCT, 13 patients who had less than 5 years of disease-free interval experienced no recurrence (29). The waiting time is apparently longer than that in other countries, and periodic screening for malignancy might be important in Japan.

### ***Nutrition***

The nutritional status of patients on the waiting list is related to post-transplant survival. Several studies have identified obesity (30), low body mass index (31) and low serum albumin concentration (32) as significant risk factors for mortality after lung transplantation. Immunosuppressive therapy after lung transplantation can exacerbate the pre-existing risk of infection in patients with malnutrition. Physicians in charge need to optimize the nutritional status of these patients with lifestyle changes, appropriate steroid tapering, nutritional counseling, and dietary modifications (14).

### ***Rehabilitation***

Although respiratory function can improve after lung transplantation, which takes up to 6 months (33), exercise capacity may not return to normal after 18 months (34). This might be associated with the negative effect of chronic underlying diseases, mostly musculoskeletal and cardiopulmonary function. Pre-transplant rehabilitation could contribute to improving muscle strength, enhancing exercise capacity, and reducing dyspnea. This would positively influence the candidate's health-related quality of life (HRQOL) (35). Pre-transplant rehabilitative interventions mainly focus on motor and breathing exercises (36) and have been integrated into an education program. Lung transplant candidates should be encouraged to attend pre-transplant rehabilitation to preserve and improve their HRQOL (37).

### ***Psychosocial assessment***

Lung transplant candidates are screened for psychological problems that may cause poor adherence to the management of lung transplants, such as medication or rehabilitation. Patients with end-stage respiratory diseases tend to

experience more depression or anxiety over their lifetime (38). Lung transplant candidates could become more fearful of death during the waiting time and tend to be emotionally unstable (39). Even if transplantation is successful, anxiety and fear of problems, such as rejection or infection, will follow. Therefore, psychiatric and psychosocial aspects, as well as family support, are extremely important throughout the pre- and post-transplant periods.

### *Quality of life*

The ultimate goal of lung transplantation is not only to improve survival but also to improve functional outcomes. Improving the HQROL of end-stage lung disease is an important aspect of the physical, psychological, and social limitations due to severe respiratory disease. Poor sleep quality due to anxiety and respiratory symptom was common among candidates who were on the waitlist in Japan (40). Since it is the most appropriate evaluation or questionnaire to assess HQROL, some studies have been reported. Both modified Medical Research Council dyspnea and St. George's Respiratory Questionnaire scores were significantly associated with waitlist mortality (41). Another study showed that the Mageri Respiratory Failure Questionnaire-26 and the Severe Respiratory Insufficiency Questionnaire were effective and useful measures of HRQOL (42). These parameters can be utilized to improve the allocation system or waiting period mortality in the future.

### *Inactive system*

The Japanese organ-transplant registration system allows recipients to self-determine whether they want to have an "inactive status", i.e., temporary removal from the waiting list for lung transplantation; when they prefer restoration to an "active status", they can resume their position on the waiting list where they were originally registered. Common reasons for an inactive status are the stable conditions of recipients with medical care, and the clinical features of LAM patients with a history of inactive status have also been reported (19). Currently the outcome of treatment for PAH has improved, there are many patients of PAH with inactive status. The patients of PAH had higher mortality risk in the first 3 months after lung transplantation than other major diagnoses (18), they need to think about the timing of lung transplantation or optimal drug therapy (43).

## **Conclusions**

The survival outcome of lung transplantation in Japan is favorable, but major concerns are the long waiting time and high mortality rate during the waiting period. Pre-transplant management of candidates is important to improve transplant outcomes by increasing the probability of patients reaching transplantation. It is important to provide proper and multifaceted support by various professionals to reduce mortality while patients are on the waiting list.

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