Review Article

Patient selection, surgery and perioperative management in lung transplantation in Japan

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Abstract: Lung transplantation (LT) is the final treatment option for end-stage respiratory diseases. The current prognosis of LT recipients in Japan is good, however, the reason for the good prognosis is unclear. In Japan, the waiting time for cadaveric LT is long, which is approximately 900 days on average. A long waiting time affects several aspects of LT. The diseases progress while they await LT in most patients are waiting for LT. Along with the disease progression of the disease, secondary pulmonary hypertension can newly emerge. Some patients suffer from refractory secondary pneumothorax and may receive pleurodesis. Transplant operations can become more difficult, and postoperative management becomes more complicated owing to the disease progression. Thoracic surgeons in Japan have managed the tough difficult situation of LT patients with LT. Possible explanations for how we to maintain a better prognosis in such a situation include sophisticated surgical techniques and ideas, and vigorous postoperative management by thoracic surgeons. Thoracic surgeons are vigorously involved both in operations and in postoperative management in the intensive care unit with or without intensivists in Japan. On the other hand, the long waiting time in Japan and allocation rules with age restriction without considering the severity of patients may have resulted in the selection of recipients to include relatively young recipients, fewer patients with interstitial lung disease and fewer recipients with extracorporeal membrane oxygenation (ECMO) as a bridge to LT. These recipients' characteristics possibly may have affected the prognosis of LT patients with LT in Japan. There is a chance that a future increase in the number of cadaveric donors in Japan may result in a prognosis close that is similar to the international average if the current waiting time in Japan decreases. We review patient selection, surgery and perioperative management in LT in Japan to address the question of why the current prognosis of LT recipients in Japan is good.

Keywords: Lung transplantation (LT); prognosis; Japan

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Introduction

Lung transplantation (LT) is the final option for end-stage respiratory disease. Lung transplant surgery is accompanied by multiple risks, and its long-term survival lags behind most other forms of solid-organ transplantation (1). Candidates of LT should be carefully examined. In Japan, the waiting time for LT is long, with an average time of approximately 900 days as of December 2022 because of the shortage of organ donors (1). Unlike lung allocation scores in the USA and Europe, no system is available to prioritize patients who are progressively worsening in Japan. The waitlist mortality has reached 37% according to data from the Japan Organ Transplant Network (1). To decrease

Table 1 Percentage of waitlist mortality, post-LT one-year survival, and five-year survival

Variable	Japan (2)	USA (3)	ISHLT (4)
Waitlist mortality	37.7%	17.6%	N/A
1-year survival	90.7%	85.3%	85%
5-year survival	73.7%	54.3%	59%

LT, lung transplantation; ISHLT, the International Society for Heart and Lung Transplantation; N/A, not available.

Table 2 Indications and contraindications for cadaveric LT in Japan

A. General considerations
• High risk of death from lung disease if LT is not performed
• High likelihood of return to healthy social life
• Psychologically stable and having social or family support
• Age <60 years for unilateral LT, age <55 years for bilateral LT (at the time of being listed)
• No contraindications
B. Contraindications
• Lack of patient willingness or acceptance of transplant
• Repeated episodes of non-adherence without evidence of improvement
• Active extrapulmonary or disseminated infection
• Irreversible extrapulmonary disease (glomerular filtration rate <50 mL/min/1.73 m^2, liver failure with total bilirubin >2.5 mg/dL, coronary vascular disease, neuromuscular disorder, severe chest wall or spinal deformity)
• Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
• Malignancy with high risk of recurrence or death related to cancer
• Active substance use or dependence including current tobacco use
• Limited functional status with potential for post-transplant rehabilitation
• Severe obesity
• Poor nutritional status
• Extensive pleural adhesion
• Positive HIV antibody

LT, lung transplantation; HIV, human immunodeficiency virus.

the number of deaths during the waiting time as much as possible in Japan, patients need to be listed before they become severely unwell.

Even if a patient on the list survives until LT, a long waiting time causes multiple problems. In most patients, the disease progressively worsens while they are waiting for LT. Secondary pulmonary hypertension can newly emerge, and pneumothorax can repeatedly occur. Some patients develop new respiratory infections such as fungi and non-tuberculosis mycobacteria infection during the waiting time. This situation can possibly make surgery and intra- and postoperative management more difficult.

Therefore, the long waiting time adversely affects every aspect of LT in Japan. However, the 5-year survival of LT patients in Japan is better than that of other societies. Five-year survival was reported to be 71.8% for unilateral cadaveric LT, 75.7% for bilateral cadaveric LT, and 73.8% for living-donor LT in Japan (2). *Table 1* details the waitlist mortality, 1-year survival, and 5-year survival in Japan (2), in the USA (3), and from the International Society for Heart and Lung Transplantation (ISHLT) report (4). We review the process of LT candidate selection, the transplant surgery itself, and perioperative management in Japan to address why the prognosis of LT recipients is better than in other countries.

Patient selection

General rules and guidelines

Table 2 shows the general considerations and contraindications for cadaveric donor LT in Japan. The guidelines of the ISHLT (5) were referred to when this table was created. Several differences can be found between the ISHLT guidelines and the Japanese guidelines.

First, the guidelines in Japan do not mention the disease prognosis, nor do they detail the duration of risk of death, unlike the ISHLT guidelines. One of the general considerations of LT described in the ISHLT guidelines is a "high (>50%) risk of death from lung disease within 2 years if LT is not performed." (5). In Japan, patients need to be listed sooner than the ISHLT guidelines because the waiting time is 900 days on average. If patients are not listed in advance, many patients are lost while they are waiting

Table 3 Recipient diagnosis by types of lung transplantation (transplants: January 1998–December 2022)

	Cadaveric unilateral LT (n=398)	Cadaveric bilateral LT (n=354)	Living-donor LT (n=284)
IIPs	147 (36.9%)	45 (12.7%)	68 (23.9%)
Other IP	71 (17.8%)	43 (12.1%)	28 (9.9%)
p-HSCT	18 (4.5%)	31 (8.8%)	83 (29.2%)
LAM	78 (19.6%)	24 (6.8%)	–
COPD	55 (13.8%)	–	–
IPAH	–	108 (30.5%)	50 (17.6%)
Other	29 (7.3%)	43 (12.1%)	55 (19.4%)
Bronchiectasis	–	41 (11.6%)	–
DPB	–	19 (5.4%)	–

LT, lung transplantation; IIP, idiopathic interstitial pneumonia; IP, idiopathic pneumonia; p-HSCT, post-hematopoietic stem cell transplantation; LAM, lymphangioleiomyomatosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; DPB, diffuse panbronchiolitis.

for LT in Japan (6). Patients need to be sufficiently unwell to undertake the high risk of LT surgery, but if the ISHLT guidelines are adhered to, they cannot survive until LT. Patients who might need LT in 3 years need to be carefully assessed and selected. Hirama *et al.* reported the pulmonary function of LT candidates at the time of listing at Tohoku University Hospital, which is an LT center in Japan (6). According to their report, the predicted forced vital capacity of patients with interstitial lung disease (ILD) at the time of listing was low, with a median of 44.5% (interquartile range, 30.4–59.7%). This demonstrated that the timing of listing was not too early.

Second, there is chronological age restriction of candidates for cadaveric LT in Japan (1). Patients need to be younger than 55 years for listing for bilateral LT and 60 years for unilateral LT and must meet these age criteria at the time of listing. However, patients who are over the age limit at the time of LT are accepted.

Third, impaired renal function and liver function are contraindications for LT. Simultaneous lung and liver transplantation or lung and kidney transplantation from the same cadaveric donor is not currently allowed in Japan.

Unilateral LT instead of bilateral LT is still the first choice in Japan to treat as many patients as possible from a small number of organ donors unless patients suffer from pulmonary arterial hypertension, chronic pulmonary infection such as aspergillus or non-tuberculosis mycobacterium, or infectious diseases such as bronchiectasis (1,2).

Selection of candidates

Lung transplant candidates have to undergo a two-step review by two selection committees (1). One step is completed by a local committee, such as the multidisciplinary committee at each LT center, and the other step is undertaken by a committee that is part of the Japanese Respiratory Society. The second committee consists of five or six respirologists and one or two lung transplant surgeons. After both committees approve a patient for LT, the patient is finally listed for LT. The Japanese Respiratory Society committee is characteristic in Japan because in other countries such as the USA (7) and UK (8), the LT center itself decides whether the patient is a candidate or not, and then they proceed to put the patient on the waiting list.

Patients' characteristics in Japan

Table 3 shows the diagnoses of pulmonary diseases of patients who underwent LT in Japan from January 1998 to December 2022 (2). Patients with non-infectious pulmonary complications following hematopoietic stem cell transplantation are not a small population as an indication for LT in Japan, unlike the ISHLT registry report (9). Post-hematopoietic stem cell transplantation (p-HSCT) pulmonary diseases, comprising obliterative bronchiolitis or ILD, are the major indication for living donor LT in Japan. This reflects that the living donor must be a spouse or a blood relative and that there is age restriction to be a

living donor, which is usually from 20 to 60 years old. The best combination of a recipient and living donor(s) is a child and his/her parent/parents. The most common pulmonary disease that requires LT in childhood is p-HSCT pulmonary disease. Therefore, patients with p-HSCT are the largest group of living donor LTs. Conversely, according to the ISHLT registry report (4), the leading cause of LT in North America between 2010 and 2018 was idiopathic pulmonary fibrosis, followed by chronic obstructive pulmonary disease and cystic fibrosis. In Japan, cystic fibrosis is very rare.

Idiopathic pulmonary arterial hypertension (PAH) is the major entity for cadaveric bilateral LT, while lymphangioleiomyomatosis is the second major entity for cadaveric unilateral LT. This large proportion of PAH and lymphangioleiomyomatosis among LT recipients reflects the long waiting time. Patients with idiopathic PAH and lymphangioleiomyomatosis can usually survive until they receive a new lung(s) with the help of medication, in contrast to idiopathic interstitial pneumonia (IIP). With the aid of available medication, they can survive until they have the opportunity for LT.

Pleuroparenchymal fibroelastosis (PPFE) is a rare entity of interstitial pneumonia (IP) characterized by fibrosis that has upper lobe and subpleural predominance. PPFE is related to a low body mass index and a "flat chest", as described in a previous report (10). This usually mild-to-moderate chest deformity as well as nutritional status needs to be carefully assessed at the time of evaluation for LT listing, especially in patients with PPFE because the chest deformity affects LT surgery and postoperative management. In the Tokyo Lung Transplant program, which started in 2015, 109 cases of cadaveric LT were performed up to December 2022, including 39 cases of IIP. Nine (23%) of 39 IIP cases were PPFE. The number of patients with PPFE who are LT recipients is not small in Japan. According to a review of LT for PPFE, the long-term outcomes are similar to those of patients with other IPs (11), but PPFE may result in a complicated intraoperative and short-term post-LT course.

Living donor LT

Living donor LT is an important type of LT in Japan. In patients who cannot await cadaveric donors and who have a spouse or relatives who would willingly donate part of their lungs, living donor LT is a viable option.

Multiple studies have reported on living donor LT in Japan (12,13). Adult patients usually require two donors for living donor LT, with one donor for the right side and another for the left side. All living-donor LT are unilateral or bilateral lobar transplantations. Graft size calculations and matching are important factors of living donor LT. Right-to-left inverted and native upper lobe-sparing living donor lobar LT have been created to maximize the postoperative respiratory function of the recipient (14,15). Nakajima *et al.* reported six cases of living donor segmental LT in pediatric patients with a median age of 7 years (range, 4–15 years) and a median height of 112.7 cm (range, 95–125.2 cm). (16). They performed six cases of bilateral LT under cardiopulmonary bypass. A basal segment and a lower lobe were implanted in three patients, and a basal segment and an S6 segment were implanted in the other three. There was one hospital death (at 14 days) due to sepsis and one late death (at 9 years) due to leukoencephalopathy. The remaining four patients have been alive for over 9 months. The researchers concluded that living-donor segmental LT was a technically difficult but feasible procedure with acceptable outcomes for small pediatric patients.

Even though all living donor LTs were lobar LT and many challenging cases have been performed, the 5-year survival of living donor LT is 73.8%, which is comparable to cadaveric LT in Japan.

Transplant surgery

The "basic" surgical techniques of LT in Japan are not different from reported standard techniques (17). Bilateral LT is performed via a clam-shell incision, while unilateral LT is often performed with anterolateral or posterolateral thoracotomy in the lateral position in most LT centers in Japan unless the patient requires central vessel cannulation for extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. If the recipient cannot tolerate one lung ventilation at the lateral thoracotomy, veno-arterial (VA)-ECMO can be initiated with cannulation of the femoral vein and artery. Bilateral LT is performed under ECMO with central cannulation in most cases. Pediatric cases are often performed under cardiopulmonary bypass. The number of patients who need concomitant cardiac surgical procedures is small.

In Japan, a flat chest and a small thoracic cavity are not rare. The thoracic cage becomes smaller as fibrosis progresses in some patients. This typically occurs in patients with PPFE. Lateral thoracotomy allows for better exposure, especially at the posterior side of the hilum because the heart moves toward the contralateral side. We consider

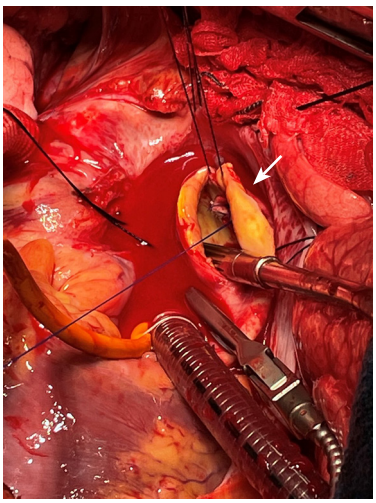

Figure 1 Intraoperative image showing a thick pulmonary arterial wall (arrow) in a patient with pulmonary hypertension. This 40-year-old patient had patent ductus arteriosus and severe pulmonary hypertension, and underwent bilateral lung transplantation. This image was taken at the time of ductus arteriosus patch closure from inside the pulmonary artery at the time of lung transplantation.

graft volume reduction or delayed chest closure if closing the chest causes hemodynamic instability in patients with a small chest cavity.

Pleural adhesion is common in patients with LT in Japan. A history of pleurodesis for pneumothorax or infectious adhesion in bronchiectasis or ILD is not rare in these patients. During the long waiting time, some patients experience secondary pneumothorax, which is often refractory. Some of them have had surgeries or pleurodesis to control the pneumothorax. Thirteen (11.9%) of 109 cadaveric LT cases in the Tokyo Lung Transplant Program had surgery or pleurodesis for pneumothorax before they underwent LT. This rate is higher than that in a previous study from the USA, which reported 10 patients (2.2%) who underwent pleurodesis before LT among 453 patients with LT (18). Chronic pulmonary infection, such as non-tuberculosis mycobacterium and aspergillus, can also occur during the long waiting time. These infections can cause inflammation and pleural adhesion. Because of these problems that occur as the disease progresses during the long waiting time, surgeons in Japan often encounter extensive pleural adhesion at the time of LT. A small chest cavity and pleural adhesion are pulmonary complications that emerge with disease progression, especially in patients with ILD. Intrapulmonary colonization and infection are considered to be relative contraindications worldwide (19). We consider transplantation for a patient with intrapulmonary infection if there is a reasonable expectation that antibiotics or antifungal therapy will adequately control the infection.

The long waiting time also affects the condition of patients with idiopathic PAH. The pulmonary artery (PA) in these patients is continuously exposed to high pressure, and the wall of the PA becomes fragile. Furthermore, the wall of the PA in patients with PAH often appears thick, and there are yellowish-like atherosclerotic arteries at the time of LT (*Figure 1*). This fragile PA is easily torn, and surgeons need to perform each stitch carefully at PA anastomoses in patients with PAH. Other problems in patients with PAH are heart failure and a high dosage of intravenous/subcutaneous prostacyclin. In Japan, almost all patients receive a continuous infusion of prostacyclin when they undergo LT. The dosage of prostacyclin has been increased by cardiologists to help with disease progression during the waiting time. Prostacyclin, which is a potent vasodilator, has an anti-platelet effect, making hemostasis difficult. Moreover, the long-term high-dose (>100 ng/kg/min, and often >200 ng/kg/min) use of prostacyclin causes prominent mediastinal and peri-bronchial angiogenesis, similar to racemose hemangioma, causing massive bleeding during surgery. Surgeons tend to spend a lot of time attempting to maintain hemostasis at LT for patients with idiopathic PAH in Japan.

Unilateral LT remains the first choice in Japan for patients without PAH or chronic intrapulmonary infection because of the shortage of organ donors, as described above. Thoracic surgeons sometimes encounter a situation in which bilateral LT is ideal, but there is often no other choice than unilateral LT. This problem has been addressed with several techniques, such as a simultaneous lung volume reduction for native lung, native lung PA banding, or "hybrid lung transplantation". We previously reported simultaneous unilateral LT and contralateral lung volume reduction in patients with emphysema (20). We also reported contralateral PA banding after single LT for patients with bronchiolitis obliterans (21,22). Kurosaki *et al.* reported two cases of "hybrid lung transplantation" combining living donor and cadaveric LTs (23). Careful evaluation and consideration of each patient's condition leads to these ideas and solutions to problems, which can be caused by a native lung after unilateral LT.

Perioperative management

Patients are managed by local respirologists until LT, and they are seen by the LT team once or twice a year during the waiting time. Home oxygen therapy is started for almost all patients with LT, except for those with idiopathic PAH. In some patients, mechanical ventilation (MV) with tracheostomy or non-invasive positive pressure ventilation is required during the waiting time. In the Tokyo Lung Transplant Program, 7 of 109 (6.4%) patients were on ventilator support with tracheostomy while waiting for LT. Maintaining a good nutritional status and activity level on a ventilator is not easy, but is important to ensure survival from lung transplant surgery and to promote recovery after LT.

Patients are managed in the intensive care unit (ICU) after LT. Although critical care doctors are actively involved in postoperative management along with thoracic surgeons, in some hospitals in Japan, their degree of involvement appears to vary. This is probably because the number of critical care specialists is insufficient in Japan, at only 2115 in 2021 according to the data from the Japanese Society of Intensive Care Medicine (24). This equates to 16.8 critical care doctors per 1 million population, whereas in the USA, there were 90.4 critical care specialists per 1 million in 2015 according to the American Hospital Association report (25). At all hospitals, thoracic surgeons are extensively involved in the management of patients after LT in the ICU.

The basic principles of postoperative management in the ICU in Japan are similar to worldwide standards (26). Standard postoperative management in the early phase is correction of fluid balance with diuresis, which aims to achieve the preoperative body weight and ensure appropriate medical therapy including immunosuppression. If graft function is satisfactory, the early phase of management is usually uneventful.

The current rate of donated cadaveric lung use is >80% because of the severe shortage of organ donors in Japan (1), which is much higher than the world standard. An example of this rate in other countries is 17.6% use of lungs from donation following neurological death in the USA in 2021 (27). One of the reasons for the high lung utilization rate is the "medical consultant system" in Japan, which is a unique partnership between transplant consultant physicians and local physicians that has been developed to maximize the organ utilization rate in Japan since 2002 (28). Consequently, many cadaveric donors in Japan contain at least one marginal factor, such as a heavy smoking history, unclear chest X-ray, positive sputum culture, old age, and specific cause of death, including hanging. These marginal factors can affect the postoperative course. We often observe copious airway secretions in grafts from heavy smokers or donors of an older age. While a patient is intubated, thoracic surgeons frequently perform bronchoscopy, usually daily. If the purulent secretion is copious, we perform bronchoscopy twice a day until appropriate antibiotics start working and the secretions decrease. This procedure is valuable for airway toileting and the evaluation of the fluid status from secretions. If extubation is not feasible within 1 week after LT or sputum is still abundant at 1 week, tracheostomy is considered to allow effective rehabilitation. Miyoshi *et al.* reported the efficacy of early tracheostomy in LT recipients (29). Frequent bronchoscopy for airway toileting performed by thoracic surgeons is an important part of post-transplantation for managing LT in Japan. Likely because of this management, we have not experienced an increase in MV duration, ICU stay, or post-op ECMO use in patients receiving transplants from donors with marginal factors in Tokyo.

Post-LT medication including immunosuppression, antimicrobial, and antifungal therapies slightly differ among LT centers, but basic regimens are quite similar. Immunosuppressive therapy consists of calcineurin inhibitor, anti-metabolites, and corticosteroids. Antimicrobial antibiotics are selected on the basis of the sputum cultures of the donor and recipient. Oral itraconazole is administered as a prophylactic antifungal therapy and sulfamethoxazole and trimethoprim mixture as a prophylaxis for pneumocystis infection. Oral valganciclovir is given for 6 to 12 months depending on the sero-status of cytomegalovirus in the Tokyo Lung Transplant Program.

ECMO is required for some patients in perioperative management. Multiple situations require ECMO for patients with LT, and preoperative ECMO is a bridge to LT. However, ECMO can cause multiple complications. Short-term complications include bleeding, thrombosis, hemolysis, renal and neurological injury, concomitant infections, and technical and mechanical problems. Long-term complications reflect the physical, functional, and neurological sequelae of critical illness. Taking into consideration the long waiting time for LT without a system that prioritizes patients on ECMO, the introduction of ECMO as a bridge to LT needs to be carefully considered. Furthermore, once ECMO is performed in a patient, the cessation or withdrawal of ECMO is not legally allowed in Japan. The cessation of treatment such as ventilation or ECMO is currently considered to be homicide from a legal

Table 4 Bridge ECMO cases in Tokyo

Patient	Age, years	Sex	Diagnosis	ECMO type	Bridge ECMO days	LT
1	29	Male	Post-HSCT pulmonary disease	VV	136	Cadaveric bilateral
2	40	Male	Idiopathic interstitial pneumonia	VA	108	Cadaveric bilateral
3	39	Male	Post-HSCT pulmonary disease	VV	5	LD bilateral
4	49	Male	Idiopathic interstitial pneumonia	VV	7	LD bilateral
5	36	Female	Diffuse panbronchiolitis	VA	16	LD bilateral
6	62	Male	Idiopathic interstitial pneumonia	VV	20	Cadaveric unilateral

ECMO, extracorporeal membrane oxygenation; LT, lung transplantation; HSCT, hematopoietic stem cell transplantation; VV, veno-venous; VA, veno-arterial; LD, living donor.

perspective in Japan. We have experienced 6 bridge ECMO cases out of 135 LT cases, which comprised 26 living donor LTs and 109 cadaveric LTs, since we started the Tokyo Lung Transplant Program in 2015 until December 2022 (*Table 4*). Three of these cases were LTs from cadaveric donors and the remainder were LTs from living donors. The interval between initiating ECMO and LT from a cadaveric donor is longer than that in living donor cases. One recipient was on VA-ECMO for 109 days because he had severe pulmonary hypertension and right heart failure (30), and one patient was on veno-venous ECMO for 136 days (31). Both patients required multiple exchanges of ECMO circuits and extremely intensive care at a specialized ECMO center until they received a donor call. Whether a patient has the option for living donor LT is an important factor when we consider bridge ECMO for the deteriorating patient. There are no determined indications for the initiation of bridge ECMO for patients without the choice of living donor LT. We take into consideration how long the patient has already been on the waitlist and his/her physical strength. The ability for rehabilitation under bridge ECMO is very important to not lose the physical tolerance for LT surgery; therefore, physical ability is carefully assessed at the time of consideration of bridge ECMO.

Intraoperative ECMO provides cardiopulmonary support (32), and femoral cannulation or central cannulation is selected depending on the case. There are two major indications for postoperative ECMO use. One indication is for primary graft dysfunction. The other is cardiac support for patients with idiopathic PAH to prevent left heart failure and sudden collapse. The latter indication is planned prolongation of intraoperative ECMO (33,34). In Tokyo, we (35) have used prolonged VA-ECMO for multiple PAH patients, like the Vienna group (33).

Discussion

The quality of surgeons' skills and the vigorous postoperative care by thoracic surgeons in Japan may affect patient survival. Excellent surgical skills lead to a low rate of complications of bronchial and vessel anastomoses. The incidences of airway complications after LT range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8% (36). In the Tokyo lung transplant program, we have only experienced one airway complication out of 109 cadaveric LT cases (from January 2015 to December 2022), which was bronchus intermedius stenosis. The percentage was as low as 0.9%, which possibly reflects the quality of our surgeons' skills.

Typical technical challenges in LT in Japan include the following: living donor LT, which essentially uses all lobar grafts but sometimes segmental grafts; bilateral LT for idiopathic PAH, in which patients have been exposed to continuous long-term infusion of a vasodilator; LT for patients with a small and flat chest; and LT for patients with severe pleural adhesions. These challenging cases can improve the surgical techniques of thoracic surgeons.

In addition to LT surgery, thoracic surgeons are actively involved in ICU management with or without critical care doctors in Japan. Findings of bronchoscopy, which is frequently performed by surgeons in the ICU, provide information about the patient's fluid status and the condition of their graft. This information leads to more appropriate postoperative management. However, this vigorous management requires the surgeon's dedication. Whether this management is sustainable, even if the number of LT increases in the future, remains unclear.

A relatively good prognosis might be affected by the patient's characteristics. The first possible factor is recipient

age. As previously described, patients need to be younger than 55 years for bilateral LT and 60 years for unilateral LT at the time of listing in Japan. This age restriction is probably one of reasons for the good prognosis in Japan because, according to the ISHLT registry report, 5-year mortality increases in older recipients (9). According to the Scientific Registry of Transplant Recipients data from the USA, 36.7% of recipients were over 65 years old, while most recipients (46%) were 50 to 64 years old among LT recipients in 2021 (3). This demonstrates that LT recipients in Japan are younger than in other countries, and this age factor is one of the reasons for the good prognosis in Japan.

Another recipient characteristic that may affect prognosis is the patient's diagnosis. Because the waiting time is long, patients with rapidly progressive disease cannot survive until LT. There is a possibility that sicker patients die on the waitlist and outcomes look better because only healthier patients are living long enough to undergo LT. Such patients who cannot survive until LT include those with idiopathic pulmonary fibrosis (6).

In the first era of cadaveric LT in Japan, which started in 2000, most recipients had idiopathic PAH for bilateral LT and lymphangioleiomyomatosis for unilateral LT as a result of "natural selection" of the waiting list (2). In recent years, the number of patients with ILD has been increasing, probably reflecting a relative increase in the number of donors and a decrease in the requirement for LT for idiopathic PAH and lymphangioleiomyomatosis in both diseases, for which effective medications have been developed and are widely used. In Japan, we have started experiencing the occurrence of primary lung cancer in the native ILD lung after unilateral LT, similar to other countries (37,38). The change in recipient characteristics may alter the long-term prognosis of LT recipients in the future.

Because of the long waiting time, caution needs to be taken when determining if bridge ECMO or bridge MV is initiated for patients with a rapidly progressive condition. Therefore, the number of recipients on bridge ECMO or MV for cadaveric LT is lower in Japan than in other countries. A study reported that the 5-year survival of recipients with bridge ECMO was lower than that of recipients without bridge ECMO or MV (39). Another study reported that bridge ECMO was an independent risk factor for bronchial anastomotic dehiscence (40). The lower ratio of bridge ECMO could be one of the reasons for the good prognosis in Japan.

This review has several limitations. First, an appropriate legal and social system in each country is required for transplantation. LT requires expensive medical resources. The health insurance system largely affects actual care for patients with LT, and legislation and health insurance systems differ among countries. Therefore, accurate comparisons of the quality of care for transplant patients in Japan with that in other countries are difficult. Second, no established method is available to compare surgical techniques or ICU management between surgeons in Japan and those in other countries. The information in this report was mainly obtained from our experiences. We have identified that there are differences in patient characteristics and ICU management among countries through our own experience and numerous reports. Objective evaluation and assessment of the surgical techniques and ICU management are important to address whether this difference affects the prognosis.

Conclusions

Age restrictions for LT candidates and natural patient selection during the long waiting time for transplantation may result in long-term prognoses that appear to be better. However, sophisticated surgical techniques with low rates of airway complications, surgical practices including segmental grafts, and vigorous postoperative management by thoracic surgeons may have positively affected the prognosis of LT patients in Japan. Further assessment is needed because the number of cadaveric donors is increasing in Japan. An increase in sicker recipients and a change in patient characteristics may change the long-term prognosis in Japan in the future.

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