Review Article on Why is the Outcome Good? Secrets of Lung Transplantation in Japan

Long-term management and outcome of lung transplantation in Japan

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Abstract: The long-term survival after lung transplantation (LT) is favorable in Japan. However, long-term survivors after LT are subject to late complications, including chronic lung allograft dysfunction (CLAD), malignancy, infection, and chronic kidney disease (CKD) because of the need for lifelong immunosuppression. The rates of single cadaveric LT (CLT) and living-donor lobar LT (LDLLT) are higher than that of bilateral CLT in Japan. Here, we will describe the management of late complications and long-term outcome after LT in Japan. Attention should be paid to not only the phenotype of CLAD but also the difference in CLAD after CLT and after LDLLT as well as the timing of lung re-transplantation for advanced CLAD, especially after single CLT. Since post-transplant lymphoproliferative disorder is the most common malignancy after LT, infection monitoring for infection-related malignancies and appropriate screening are keys to the early diagnosis and treatment of malignancy after LT. The long-term management of infection after LT is also important, especially with regard to community-acquired pathogens, Aspergillus, and cytomegalovirus. When providing long-term care after LT, physicians should be aware of CKD and the timing of renal replacement therapy in cases with severe CKD. The widespread use of computed tomography and dialysis in Japan are beneficial for long-term survivors of LT. The similar survival outcomes of single CLT and LDLLT, compared with bilateral CLT, might contribute to improved long-term survival in Japan. Pulmonologists are encouraged to become further involved in long-term management after LT in Japan.

Keywords: Lung transplantation (LT); chronic lung allograft dysfunction (CLAD); infection; malignancy; chronic kidney disease (CKD)

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Introduction

Lung transplantation (LT) is the last resort for select patients with end-stage lung diseases even in Japan, which has a persistent problem of extreme donor shortage. Since the first successful living-donor lobar lung transplantation (LDLLT) in Japan was performed at our hospital in 1998 (1), LT has been performed in a total of 931 patients in Japan as of December 31, 2021 (2). After a revision of the Organ Transplant Act in 2010, the number of cadaveric

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LT (CLT) has increased, but the annual number remains small in Japan. According to a recent report from the International Society for Heart and Lung Transplantation (ISHLT), bilateral CLT is performed in approximately 80% of patients worldwide (3). In contrast, compared with bilateral CLT (33.1%, 308 patients), the rate of single CLT (37.6%, 350 patients) and LDLLT (29.0%, 270 patients) are relatively high in Japan because of the extreme donor shortage (2). Worldwide advances in the selection of candidates, surgical techniques, perioperative management, immunosuppression therapy, and long-term management (4) have contributed to a larger number of long-term survivors after LT in Japan also. Generally, the recipients of LT, who require lifelong immunosuppression, are susceptible to various late complications, including chronic lung allograft dysfunction (CLAD), malignancy, infection, and chronic kidney disease (CKD). Among these, CLAD (21.0%), malignancy (17.9%), and infection (16.2%) are the main causes of death at more than 10 years after LT (3). In addition, LT recipients can develop common comorbidities, including hypertension, diabetes mellitus, dyslipidemia, and osteoporosis after LT (5). The long-term management of these complications is key to achieving a good outcome after LT. In Japan, transplant pulmonologists are unavailable at most LT centers because of their rarity, as described elsewhere in this series on "Why is the outcome good? Secrets of lung transplantation in Japan". Accordingly, lung transplant surgeons commonly provide long-term follow-up care for LT recipients, in collaboration with nontransplant physicians at local hospitals. Encouraged by the extensive experience and knowledge obtained from high-volume LT centers throughout the world, a total of 10 LT centers in Japan have evolved, adapting to the unique environment of extreme donor shortage (6,7) and a limited number of LT procedures, with each LT center performing fewer than 50 LT procedures per year (2). In the present review, we will describe the management of late complications, especially for CLAD, malignancy, infection, and CKD, and the long-term outcome of LT in Japan.

CLAD

Long-term survival is mainly hampered by the development of CLAD after LT (3). CLAD develops within 5 years after LT in approximately 50% of recipients (4). CLAD is characterized by fibrotic changes in the peripheral small airways or interstitial tissue and pleura (8). Known risk factors for CLAD include primary graft dysfunction (9), acute rejection, infection, pseudomonal colonization (10), cytomegalovirus (CMV) mismatch (11), donor-specific antibodies (12), air pollution (13), and gastroesophageal reflux disease (14). According to a consensus report from the ISHLT in 2019, CLAD is defined as an irreversible decline in the forced expiratory volume in 1 s (FEV1) to <80% of the baseline value (8). The baseline values of the pulmonary function test are calculated as the average of the two best values obtained at least 3 weeks apart. To classify the phenotypes of CLAD, bronchiolitis obliterans syndrome (BOS) is defined as CLAD in association with an FEV1/forced vital capacity (FVC) ratio <0.70, whereas restrictive allograft syndrome (RAS) is defined as an irreversible decline of the total lung capacity to <90% of the baseline with the presence of persistent opacities on chest computed tomography (CT) (8). The classification of CLAD phenotypes is important for long-term management because RAS patients have worse survival outcomes than BOS patients (15). At the same time as the pulmonary function testing, a blood examination, chest X-ray, CT of the chest and abdomen, lung ventilation and perfusion scintigraphy, 6-minute walk test, electrocardiography, and echocardiography are also performed at our hospital to enable a differential diagnosis (16). Recently, CT has been shown to be useful for the diagnosis of CLAD (17), including the CT-scan score (18), quantitative CT analysis (19), and machine-learning CT analysis (20). In addition, lung perfusion scintigraphy is valuable for the diagnosis of CLAD after single CLT (21,22), which is performed more often than bilateral CLT in Japan (*Table 1*). Whereas the lung perfusion increases in the transplanted lung because of decreased vascular resistance in non-CLAD patients after a single CLT, the lung perfusion decreases in the CLAD-affected lung, with a perfusion shift toward the native lung in the CLAD patients (21,22).

Similar to the CLT recipients, LDLLT recipients can suffer from CLAD during the long-term (23). The CLAD-free survival and overall survival rates after LDLLT were similar to those after CLT in our hospital (23). Compared with CLAD after CLT, CLAD after LDLLT is characterized by development predominantly in the unilateral lung (24) and a delayed disease onset, compared with CLAD after CLT (23). These unique characteristics of CLAD might reflect the features of the LDLLT procedure. In LDLLT, the immunological features of two different donors may affect the development of CLAD in the unilateral lung (24). Moreover, the small lung grafts morphologically expand to fit the recipient's chest cavity,

Table 1 Management of CLAD in Japan

Characteristics
Attention to the relatively high rate of single CLT (37.6%) and LDLLT (29.0%) as compared to bilateral CLT (33.1%) in Japan
Note the difference in CLAD between CLT and LDLLT, which is characterized by development predominantly in the unilateral lung and a delayed disease onset
Diagnosis
Care for the phenotypes of CLAD, including BOS and RAS
Use CT and lung perfusion scintigraphy for early diagnosis especially after single CLT and LDLLT
Re-LT
Pay attention to the timing of listing for re-LT especially after single CLT
Aware of better survival in CLAD after LDLLT than after CLT

CLAD, chronic lung allograft dysfunction; CLT, cadaveric lung transplantation; LDLLT, living-donor lobar lung transplantation; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; CT, computed tomography; re-LT, lung re-transplantation.

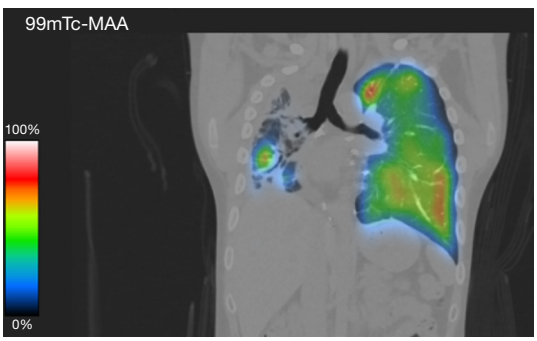

Figure 1 Representative image of unilateral CLAD after bilateral living-donor lobar lung transplantation. Lung perfusion scintigraphy demonstrates a perfusion shift to the left unaffected lung in a patient with right unilateral CLAD. CLAD, chronic lung allograft dysfunction.

leading to a postoperative improvement in FEV1 and FVC during the first 3 years after LDLLT (25) and the delayed onset of CLAD after LDLLT (6). Blood-relative donors for LDLLT have fewer mismatches in human leucocyte antigen (HLA), contributing to the lower and later occurrence of donor-specific antibodies after LDLLT, compared with after CLT (26). Based on the characteristic of the unilateral development of CLAD after LDLLT, lung perfusion scintigraphy can be beneficial for the diagnosis of CLAD after LDLLT, similar to the situation for single CLT (27). The detection of a perfusion shift to the contralateral, unaffected lung using lung perfusion scintigraphy is useful for the early diagnosis of CLAD after both bilateral and single LDLLT (*Figure 1*). Currently, lung perfusion scintigraphy is performed during regular checkups at our hospital as an alternative to lung ventilation scintigraphy using ^{133}Xe, which was discontinued in 2016, to detect washout imaging in the CLAD-affected lung after LDLLT (*Table 2*) (28). Inspiratory and expiratory CT volumetry is also performed to detect unilateral CLAD after LDLLT (29).

Azithromycin is the only prophylactic treatment for CLAD available at present (30,31). Therapeutic options for CLAD are limited and have been reported mostly for BOS patients; these options include the adjustment of maintenance immunosuppression (8), montelukast (32), total lymphoid irradiation (33), and extracorporeal photopheresis (34). Lung re-transplantation is the only therapeutic option for advanced CLAD in carefully selected patients (8). However, the postoperative mortality rate is higher after re-transplantation than after the first LT, especially among RAS patients (35,36). In our hospital, the rate of lung re-transplantation for CLAD was significantly higher among patients after single CLT than among those after bilateral CLT (12.5% *vs.* 2.6%, P=0.046) (37). CLAD may impact lung function in the recipients of single CLT to a greater degree than recipients of bilateral CLT because of the existence of the native lung. Among patients with CLAD after single CLT, contralateral lung re-transplantation is available to avoid surgical difficulty in ipsilateral lung re-transplantation (38). In contrast, patients with CLAD after LDLLT have a better survival outcome than those after CLT (23). The unaffected, functioning contralateral lung in patients with unilateral CLAD may contribute to prolonged survival after LDLLT as well as

Table 2 Annual checkup after lung transplantation in Okayama

Laboratory testing
CBC, CRP, electrolytes, kidney and liver function test, lipid profile, hemoglobin A1c, BNP, CEA, etc.
Immunosuppressive through levels
Fecal occult blood test
Thyroid function test as indicated
Infectious profile
Sputum culture
Serum galactomannan and β-D-glucan
CMV-DNA/pp65 antigenemia
EBV-DNA
HBV-DNA as indicated
Immunologic evaluation
Panel-reactive antibody
Physiological testing
Pulmonary function testing
Electrocardiography
6-minute walk test
Imaging
Chest X-ray
CT of the paranasal sinuses, chest and abdomen
Lung ventilation and perfusion scintigraphy
Bone mineral density
Bronchoscopy as needed
Echocardiography as indicated
Esophagogastroduodenoscopy as indicated
Colonoscopy as indicated
Consultations
Gynecology
Cardiology as needed
Nephrology as needed
Gastroenterology as needed etc.

CBC, complete blood cell count; CRP, C-reactive protein; BNP, brain natriuretic peptide; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; CT, computed tomography.

allowing optimal treatment for late complications after LDLLT. In fact, the first recipient of LDLLT in Japan has survived for more than 24 years, despite the development of unilateral CLAD 3 years after LDLLT (39). In three patients treated at our hospital, lung re-transplantation for CLAD was performed more than 10 years after LDLLT (6). Considering the characteristics of CLAD after single CLT and LDLLT, which are frequently performed in

Japan, physicians should pay attention to the timing of lung re-transplantation. The number of cases of lung re-transplantation for CLAD has been increasing in Japan (6,40,41), and a national survey is required for the detailed evaluation of lung re-transplantation.

Malignancy

Recipients of solid organ transplantation are associated with an increased risk of malignancy related to oncogenic infections as well as an increased risk unrelated to known infections because of long-term immunosuppression (42,43). Infection-related malignancies can include non-Hodgkin and Hodgkin lymphoma; nasopharyngeal cancer (associated with Epstein-Barr virus, EBV); cancers of the cervix, vulva, vagina, penis, anus, and oropharynx (associated with human papillomavirus); liver cancer (associated with hepatitis B and C viruses); Kaposi sarcoma (associated with human herpesvirus 8); some forms of leukemia (associated with human T lymphotropic virus) and stomach cancer (associated with *Helicobacter pylori*) (42,43). Among these, Kaposi sarcoma, non-Hodgkin lymphoma, and cancers of the skin, lip, liver, vulva, and anus develop with a fivefold or greater frequency in recipients of solid organ transplantation, compared with the general population (42). Furthermore, the incidence of each malignancy is dependent on the transplanted organs (42,43). Compared with recipients of other solid organ transplantation, LT recipients have an approximately twofold increased risk of non-Hodgkin lymphoma because of EBV, i.e., post-transplant lymphoproliferative disorder (PTLD), and an approximately threefold increased risk of lung cancer (42). Generally, LT recipients require more immunosuppression to avoid a higher risk of lung allograft rejection than patients undergoing other solid organ transplantation, which likely contributes to the higher incidence of PTLD. Lung cancer might be attributable to the underlying diseases of the LT recipients, such as interstitial pneumonia and chronic obstructive pulmonary disease—both of which are known risk factors for lung cancer (44).

The first national survey of the incidence of *de novo* malignancy after LT in Japan was conducted in 179 recipients who underwent transplantations between 2001 and 2010. The incidence of *de novo* malignancy was 10.1% (18 patients), and the most common disease was PTLD (12 patients), followed by cervical cancer (4 patients), breast cancer (2 patients), and tongue cancer (1 patient) (44). Updated data showed that the incidence of *de novo* malignancy was 6.0% (36 patients) of 596 recipients transplanted between 2001 and 2017 in Japan, and the most common disease was also PTLD (17 patients). Unlike the results in the US described previously (42), no recipients of LT developed skin cancer, including either melanoma or Kaposi sarcoma, in these past surveys conducted in Japan. This difference may reflect the lower incidence of dermatologic malignancies in the general population in Japan (45,46), compared with the US (47). In 2019, the most common sites of malignancy in the general population in Japan were the colon, lung, stomach, breast, and prostate (45). Whereas surveillance for skin cancer with dermatologic examinations every 6 or 12 months is recommended in the US, since dermatologic malignancies are the most frequent malignancies in recipients of solid organ transplantation (48), skin cancer surveillance is not emphasized in Japan. In general, screening for malignancy, including chest and abdominal CT, gynecological examination, tumor markers, and viral load monitoring for EBV, is performed annually, while esophagogastroduodenoscopy and colonoscopy are performed once every several years at our hospital. Currently, cancer screening using ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/CT is not covered by the national health insurance program in Japan. The common sites of malignancy vary among countries and races; thus, appropriate screening for malignancy depending on the situation in each country and infection monitoring for infection-related malignancies are needed for long-term management after LT. Regular screening allows patients to receive aggressive treatment and management for earlier-stage malignancy, even after they have undergone LT.

The reduction of immunosuppression is preferred for the treatment of *de novo* malignancy after LT, especially for PTLD, although the optimal approach is unknown (44,49). Care must be taken to avoid lung allograft rejection when reducing immunosuppression. Switching from a calcineurin inhibitor to a mammalian target of rapamycin (m-TOR) inhibitor has been shown to be associated with the regression of Kaposi sarcoma after kidney transplantation (50). Immunosuppressed recipients after LT who develop *de novo* malignancy can safely undergo surgery despite the increased risk of infection, and they can be managed with the same therapeutic approaches used in the general population (44). Of note, the use of immune checkpoint inhibitors in cancer patients after solid organ transplantation is reportedly associated with an increased risk of allograft rejection (51).

Infection

Infection is the most important cause of morbidity and mortality throughout the clinical course of LT (3). LT recipients are at a constant risk of infection with bacteria, fungi, and viruses. Infection in LT recipients can be attributed to the following factors: the high level of immunosuppression required to avoid allograft rejection; a reduction in airway defense mechanisms (loss of lymphatics, impaired mucociliary clearance, and blunted cough reflux), and continuous environmental exposure to microorganisms (5). The impact of infection on LT in Japan is described elsewhere in this series; here, we will briefly describe the key points regarding infectious complications during long-term care after LT. During the chronic phase (6 to 12 months or more after LT), LT recipients receive minimal levels of immunosuppression and are subject to community-acquired pneumonia caused by respiratory viruses, pneumococcus, Legionella, or other common pathogens, rather than opportunistic infections (52,53). Among bacterial infections, community-acquired bacteria, such as *Streptococcus pneumoniae*, are important as they can cause invasive disease when infection occurs more than 6 months after LT (54). The colonization of *Pseudomonas aeruginosa* and *Staphylococcus aureus* may lead to lower respiratory disease during the chronic phase after LT (55,56). In addition, attention should be paid to mycobacterial infection, including tuberculosis and nontuberculous mycobacteria, during the chronic phase after LT. Drug interactions among immunosuppressive agents, especially calcineurin inhibitors, and antitubercular drugs, such as rifampicin, can complicate the treatment of mycobacterial infection after LT.

Regarding fungi, aspergillosis is the most common result of invasive fungal infection after LT (57). Whereas aspergillosis occurs within the first 6 months in 72% of patients (57), infection with non-Aspergillus molds can occur later than Aspergillus infection (median, 419 *vs.* 363 days after LT) (58). Nebulized amphotericin and systemic triazole can be used for antifungal prophylaxis (59). The selection of triazole varies depending on the patients' risk factors for infection. Physicians must be aware of drug interactions between triazole, especially voriconazole, and calcineurin inhibitors, and adjust the dose of calcineurin inhibitors accordingly. The duration of antifungal prophylaxis varies from during the hospital stay only to lifelong prophylaxis in the US (59), and prophylaxis is performed for more than 1 year (60) or indefinitely at our hospital (61). Aspergillus infection can invade neighboring structures, such as the pulmonary artery, causing massive hemoptysis (62). Care must be taken especially when aspergilloma occurs in the native lung of recipients of single LT (63), which is often performed in Japan. In our hospital, the galactomannan antigenemia assay and the beta-D-glucan assay are regularly used to monitor for signs of fungal infection. The risk of *Pneumocystis jirovecii* pneumonia (PCP) is greatest during the first 6 months after solid organ transplantation if prophylaxis is not administered (64,65). Although the incidence of PCP was 70% to 88% after LT before the adoption of universal prophylaxis with trimethoprim-sulfamethoxazole (64,65), the use of universal prophylaxis, which is typically given indefinitely, has enabled a dramatic decrease in the incidence of PCP (66).

Among viral infections, cytomegalovirus (CMV), EBV, and community-acquired respiratory viruses including SARS-CoV-2 are important in the chronic phase after LT (53). CMV is one of the most common infections after LT and occurs in approximately 30% of recipients within the first year after LT, despite universal prophylaxis (5). CMV infection can involve the central nervous system, lung, liver, and gastrointestinal tract. Importantly, CMV infection is associated with the development of acute rejection and CLAD (67). Universal prophylaxis against CMV decreases the incidence of CMV infection and the severity of disease (68,69). Universal prophylaxis using induction with intravenous ganciclovir or oral valganciclovir followed by maintenance with oral valganciclovir is recommended for LT recipients who are CMV seropositive or who have received a lung from a CMV seropositive donor (CMV D^+/R^+, D^-/R^+, D^+/R^-) (68,69). Prophylaxis for 12 months is recommended for CMV D+/R- recipients and for 6 to 12 months for CMV D^+/R^+ and D^-/R^+ recipients after LT (68-70). The CMV is routinely monitored with viral load using quantitative nucleic acid amplification tests (NAAT) or pp65 antigenemia assays (68,69), even after the administration of universal prophylaxis, at our hospital. When ganciclovir resistance is suspected based on clinical treatment failure or breakthrough viremia, foscarnet should be used (68,69). Other than CMV, EBV is associated with PTLD, as described above. After the SARS-CoV-2 pandemic, a fully automated NAAT platform to detect viral and atypical bacterial pathogens in nasopharyngeal specimens has been frequently used for the diagnosis of community-acquired respiratory viruses in our hospital. In addition, vaccines are available for influenza virus and SARS-CoV-2 (71,72).

Japan has the largest number of CT scanners in the world, according to data from the Organization for Economic Co-operation and Development (73). To diagnose and manage infectious complications during long-term care, CT has been aggressively used, in addition to sputum culture and bronchoscopy, after LT throughout Japan. The widespread use of CT in Japan might contribute to the management of infections, in addition to CLAD and malignancy, as described above. Hypogammaglobulinemia is associated with an increased risk of infection with fungus, CMV, and community-acquired respiratory viruses (74,75). The level of immunoglobulin G is regularly monitored and measured if infection occurs, and intravenous immunoglobulin is administered for patients with hypogammaglobulinemia even during the chronic phase (76). Periodic intravenous or subcutaneous immunoglobulin is given to patients with persistent hypogammaglobulinemia who had received a hematopoietic stem cell transplantation prior to LT (77,78). Additionally, patients who receive enhanced immunosuppression for CLAD are at risk for opportunistic infections. Because fatal infections may develop in patients suffering from other late complications, the control of subsequent infection is important for long-term management after LT (6). In the case of suspected infection, nontransplant physicians at local hospitals should contact transplant physicians at LT centers (5).

CKD

CKD commonly develops after non-renal organ transplantation, which is caused mainly by calcineurin inhibitors (79-81). To optimize renal function after LT, lung transplant physicians try to manage LT recipients by recommending optimal salt and water intakes and to avoid nonsteroidal anti-inflammatory drugs as well as the adequate control of diabetes, hypertension, hyperlipidemia, and hyperuricemia (82). When the creatinine level is elevated, nephrotoxic agents should be minimized and the dose of calcineurin inhibitors should be reduced, while the dose of mycophenolate mofetil should be increased (82). Unfortunately, m-TOR inhibitors, including sirolimus and everolimus, are not covered for immunosuppression after LT by the Japanese national health insurance program. Despite the maximum effort, irreversible CKD ultimately necessitates renal replacement therapy, including chronic dialysis and kidney transplantation (KT). According to a registry report from the ISHLT, the cumulative incidence of severe renal dysfunction (creatinine level >2.5 mg/dL) was 24.6% of patients within 10 years after LT; moreover, the prevalence of patients with CKD requiring chronic dialysis or KT was approximately 9.9% within 10 years after LT (3). In addition, CKD has been shown to be associated with a 4- to 5-fold increased risk of mortality after CLT (79). CKD can also negatively impact the management of late complications. For example, patients with CKD are unable to receive chemotherapy for the treatment of malignancy after LT.

Although little information is available about CKD after LT in Japan (83), our previous study showed that 15 (7.4%) of 204 recipients and 15 (8.1%) of 185 1-year survivors after LT developed CKD requiring chronic hemodialysis in our hospital (84). Notably, the median interval between LT and dialysis was 11.5 (4.4–17.7) years, and 7 (3.4%) of the 204 patients required chronic dialysis within 10 years after undergoing LT. Compared with the ISHLT report, the decreased incidence of dialysis patients after LT might be attributable to the fact that Asian populations have a lower risk of CKD requiring chronic dialysis or KT than Caucasian populations (79). Nine of the 15 patients requiring hemodialysis developed CLAD, and 1 patient died of CLAD. Eight patients are still alive. The main cause of death was infection in 6 patients, including sepsis (n=3), pneumonia (n=1), aspergillosis (n=1) and COVID-19 (n=1). Considering that hemodialysis patients, especially immunosuppressed transplant recipients, are susceptible to infection, KT is recommended for hemodialysis patients after LT (82). Late living-donor KT after LT has been shown to offer excellent survival in the long term as well as acceptable kidney and lung function (82). In fact, we previously described the first successful case of living-donor KT after LT in Japan in a patient who had undergone bilateral CLT in the USA 18 years earlier, before the Organ Transplant Act was established in Japan in 1997 (85). Encouraged by this case, 2 LDLLT patients have since undergone living-donor KT for CKD, 2 are preparing to undergo living-donor KT, and 1 is waiting for a deceased-donor KT in our hospital (84). Since the average waiting time for deceased-donor KT is approximately 15 years in Japan, living-donor KT should be a realistic option even for patients with CKD after LT. Since the number of long-term survivors after LT is increasing, the number of hemodialysis patients after LT is also expected to increase in Japan. Currently, Japan has the second largest prevalence of dialysis per population, according to the 2022 United States Renal Data System Annual Data Report (86). The easy access to dialysis, which is mostly covered by the Japanese

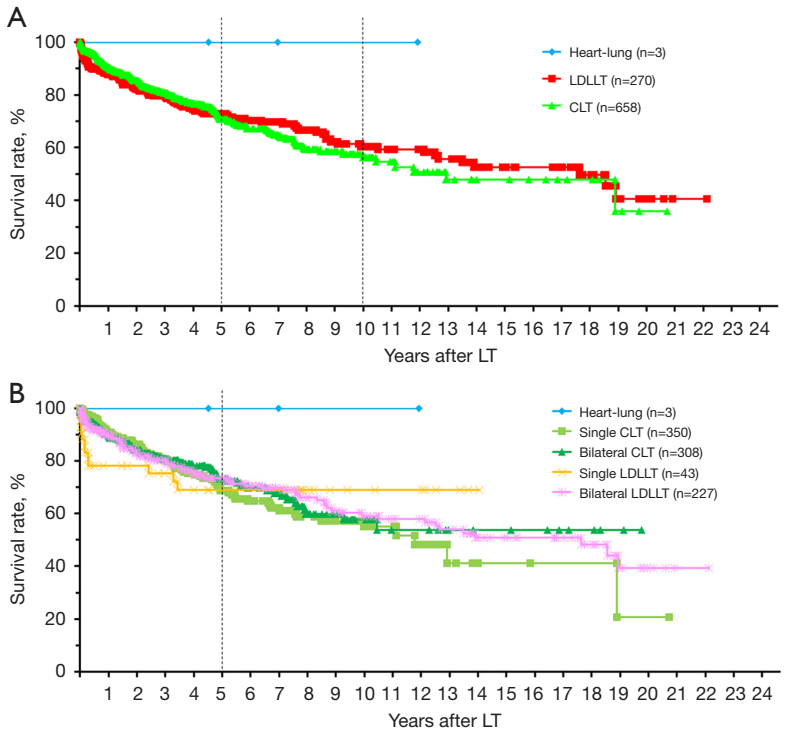

Figure 2 Overall survival after CLT (n=658), LDLLT (n=270) and heart-lung transplantation (n=3) in Japan (A). The 5- and 10-year overall survival rates were 73.72% and 61.37% after CLT, 73.84% and 62.48% after LDLLT, respectively. The 5-year overall survival was 75.69% after bilateral CLT (308 patients), 71.84% after single CLT (350 patients), 74.53% after bilateral LDLLT (227 patients), and 69.96% after single LDLLT (43 patients) (B). This figure was reproduced from reference (2) with permission from the Japanese Society of Lung and Heart-Lung Transplantation. CLT, cadaveric lung transplantation; LDLLT, living-donor lobar lung transplantation.

national health insurance program, is likely to be beneficial for long-term survivors after LT.

Long-term survival

As a result of the careful management of late complications after LT, long-term survival after LT has been favorable in Japan. According to a Japanese registry report for LT that contained 931 recipients as of December 31, 2021, the 5-year survival rate was 73.84% after LDLLT and 73.72% after CLT, respectively; the 10-year survival rate was 62.48% after LDLLT and 61.37% after CLT, respectively (*Figure 2A*) (2). The survival rate after LT in Japan appears to be better than that of the registry report from the ISHLT despite the limited number of LT in Japan (3). Notably, unlike the registry report from the ISHLT (3), the 5-year survival rate after single CLT (71.84%) was comparable to that after bilateral CLT (75.69%) in Japan (*Figure 2B*) (2). Consistent with the registry report of LT in Japan, single CLT and LDLLT performed at our hospital provided long-term survival outcomes that were similar to those for bilateral CLT, contributing to the improved survival that was observed after all LT procedures (*Figure 3A,3B*).

Conclusions

In conclusion, meticulous management for late complications, including CLAD, malignancy, infection, and CKD, is an essential component of long-term care after LT. Careful attention should be paid to the CLAD phenotype and the differences in CLAD after CLT and after LDLLT, as well as the timing of lung re-transplantation for advanced CLAD, especially after single CLT. Infection monitoring for infection-related malignancies, including PTLD, and appropriate screening are important for the early diagnosis and prompt treatment of malignancy, even after LT. The management of infection including community-acquired bacteria, *Aspergillus*, and CMV, is also important during the

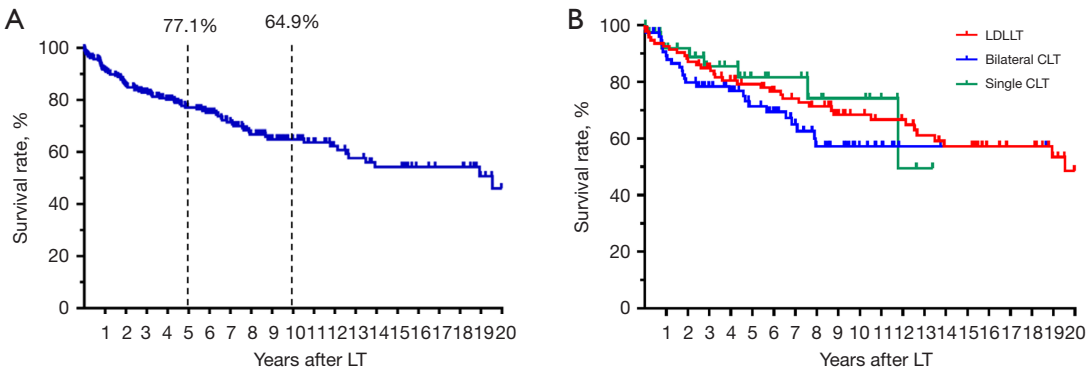

Figure 3 Overall survival after LT (n=213) in our hospital, including CLT (n=116), LDLLT (n=95), and hybrid LT combining CLT and LDLLT (n=2) (87). The 5- and 10-year overall survival rates after LT were 77.1% and 64.9%, respectively (A). Overall survival after LDLLT (n=95) and bilateral (n=76) and single CLT (n=40) in our hospital. No significant differences in overall survival according to LT procedure were seen at our hospital (P=0.37) (B). LT, lung transplantation; CLT, cadaveric LT; LDLLT, living-donor lobar lung transplantation.

chronic phase. Physicians should be aware of CKD and the timing of renal replacement therapy for patients with severe CKD in the long term after LT. Single CLT and LDLLT provide similar long-term survival outcomes to bilateral CLT, contributing to improved long-term survival after LT in Japan. Transplant physicians at LT centers should collaborate effectively with nontransplant physicians at local hospitals to achieve improved long-term outcome (5). In Japan, lung transplant surgeons have mainly followed the limited number of LT patients throughout their clinical course; however, with the further increases in the number of CLT recipients that are anticipated in the near future, we hope that more pulmonologists will become involved in long-term management after LT.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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