Original Article (Clinical Original)

Impact of chronic lung allograft dysfunction, especially restrictive allograft syndrome, on the survival after living-donor lobar lung transplantation compared with cadaveric lung transplantation in adults: A single-center experience

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Abstract

Purpose: The differences in chronic lung allograft dysfunction (CLAD) between living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT) remain unclear. We conducted this study to compare the impact of CLAD on the outcomes after LDLLT vs. CLT.

Methods: We conducted a retrospective review of the data of 97 recipients of bilateral lung transplantation, including 51 recipients of LDLLT and 46 recipients of CLT.

Results: The CLAD-free survival and overall survival after LDLLT were similar to those after CLT. CLAD and restrictive allograft syndrome (RAS), but not bronchiolitis obliterans syndrome (BOS), developed significantly later after LDLLT than after CLT ($p = 0.015$ and $p = 0.035$). Consequently, patients with CLAD and RAS, but not those with BOS, after LDLLT had a significantly better overall survival than those after CLT ($p = 0.037$ and $p = 0.0006$). Furthermore, after the diagnosis of CLAD, the survival of patients with RAS after LDLLT tended to be better than that after CLT ($p = 0.083$).

Conclusion: CLAD, especially RAS, appears to develop later after LDLLT than after CLT and seems to have a lower impact on the overall survival after LDLLT than that after CLT.

Keywords: lung transplantation; chronic lung allograft dysfunction; bronchiolitis obliterans syndrome; restrictive allograft syndrome; living-donor; rejection

Introduction

Living-donor lobar lung transplantation (LDLLT) has become an established treatment for end-stage lung diseases [1-3] and has been shown to result in a similar survival to cadaveric lung transplantation (CLT) [3]. Similar to the case after CLT, chronic lung allograft dysfunction (CLAD) is a major obstacle hampering the long-term survival after LDLLT [2, 3].

In bilateral LDLLT, because the right and left lower lobes of the lungs from two different donors are implanted in the recipient in place of the entire lungs, the different immunological features between the two donor lungs may affect the characteristics of CLAD after LDLLT. Indeed, CLAD has been shown to develop predominantly on one side after bilateral LDLLT [4]. Furthermore, morphologically, size mismatch between the chest cavity of the recipient and the donor lobar lungs might also affect the development of CLAD after LDLLT [5]. It was shown more than a decade ago that the rate of freedom from bronchiolitis obliterans syndrome (BOS) did not differ markedly between LDLLT and CLT [6]; however, since the introduction of the concept of restrictive allograft syndrome (RAS) [7], little information has been obtained regarding the differences in the phenotypes of CLAD between LDLLT and CLT, especially in relation to the long-term outcomes of CLAD.

In the present study, we compared the impact of CLAD on the long-term outcomes after bilateral LDLLT vs. bilateral CLT.

Methods

Patients

This study was a retrospective review of patients who underwent bilateral lung transplantation (LT) for end-stage lung disease at Okayama University Hospital between October 1998 and August 2016. Patients undergoing lung retransplantation and patients <18 years of age were excluded from this study in order to eliminate the effect of the initial LT and the effect of physical growth on the lung function in pediatric patients. A total of 97 adult patients who underwent bilateral LT, including 51 recipients of bilateral LDLLT and 46 recipients of bilateral CLT, were included in this study. One patient underwent bilateral LDLLT sparing the native right upper lobe. We assessed the preoperative and operative patient characteristics and the postoperative outcomes. The lung allocation score (LAS) of each patient was retrospectively calculated using the LAS calculator published on the OPTN website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/las-calculator/) in November 2015 in order to establish the recipients' preoperative disease severity. The CLAD-free survival was defined as the interval from LT to the onset of CLAD, and the data were censored on the date of death. The overall survival was defined as the interval from LT to the date of death.

The study protocol (No. 1803-008) was approved by the institutional review board of Okayama University Hospital.

Donor and recipient selection and the transplantation procedures

Patients requiring CLT are registered with the Japan Organ Transplantation Network. The allocation of organs from brain-dead donors is still based mainly on the waiting time, and the LAS system has not yet been adopted in Japan. LDLLT is considered for critically ill patients who cannot afford to wait for CLT. Patients hoping for LDLLT must meet all if the

criteria for CLT. Only blood relatives within the third degree or a spouse are accepted as living donors at our institution. The size-matching protocol and transplant procedures have been described in a previous report [8]. The graft ischemic time was defined as the ischemic time to the second transplanted lung.

Postoperative care

The postoperative management of the recipients, including the immunosuppressive therapy and prescribed prophylactic therapies against fungal and viral infections, has been described elsewhere [9, 10]. The patients were assigned PGD grades according to the definition of primary graft dysfunction proposed by the International Society for Heart and Lung Transplantation (ISHLT) [11]. LT recipients received triple immunosuppressive therapy consisting of tacrolimus or cyclosporine, mycophenolate mofetil or azathioprine, and a corticosteroid. The calcineurin inhibitor was initially given by the enteric route via a nasogastric tube during the first period between 1998 and 2010 and by intravenous administration during the second period between 2011 and 2017, followed by oral administration [10]. Acute rejection episodes were treated by bolus intravenous corticosteroid therapy on three consecutive days. Pulmonary function testing, including measurement of the forced expiratory volume in 1 second (FEV1) to diagnose BOS (obstructive CLAD) [12] and that of the total lung capacity (TLC) to diagnose RAS (restrictive CLAD) [7], was performed at 3, 6, and 12 months and once every year thereafter following LT. According to the classification system proposed by the ISHLT [12], the baseline FEV1 value was calculated as the average of the two best FEV1 values obtained at least three weeks apart, and the baseline values of other parameters of

pulmonary function test were taken as the average of the parameters measured at the time of the best FEV1 measurements. CLAD was defined as an irreversible decline in FEV1 to <80% of the baseline [12]. RAS was defined as CLAD with an irreversible decline in TLC to <90% of the baseline [7]. BOS was defined as CLAD without restrictive changes of RAS [7]. For a definitive diagnosis of CLAD, blood examinations, chest X-ray, computed tomography of the chest, inspiratory and expiratory computed tomography volumetry, ventilation-perfusion scanning, and electrocardiography were also performed at the same time as the pulmonary function testing. Among these, computed tomography of the chest, inspiratory and expiratory computed tomography volumetry, and ventilation-perfusion scanning were mainly used to exclude other potential causes of a reduced lung function [4, 7, 12, 13]. The six-minute walk test and echocardiography were performed at the same time during the first five years after LT.

Statistical analyses

All statistical analyses were performed using the GraphPad Prism 7.03 software program (San Diego, CA, USA). Normally distributed continuous data were expressed as the means ± standard deviations. The bivariate comparison of continuous variables was performed by Student's *t*-test. Associations between categorical variables were examined by Fisher's exact test. The postoperative survival rates were analyzed by the Kaplan–Meier method, and the log rank test was used to compare the differences between the groups. Differences were considered significant at $p < 0.05$. The results as of October 31, 2017, were analyzed.

Results

Patient characteristics

Table 1 summarizes the patients' characteristics. The proportion of female patients was significantly higher in the LDLLT group than in the CLT group ($p = 0.0007$). The LAS of the LDLLT group was significantly higher than that of the CLT group ($p < 0.0001$). In regard to the donor variables, the donor age was significantly lower in the LDLLT group than in the CLT group ($p < 0.0001$). While the total number of HLA-A, HLA-B, and HLA-DR mismatches with the bilateral donors in the LDLLT group was significantly higher than that in the CLT group ($p < 0.0001$), those of the right lung lobe donor or left lung lobe donor alone in the LDLLT group were significantly lower than in the CLT group ($p < 0.0001$). The total ischemic time in the LDLLT group was significantly shorter than that in the CLT group ($p < 0.0001$). Furthermore, the highest grade of PGD until 72 h after the LT in the LDLLT group was significantly lower than that in the CLT group ($p < 0.0001$).

Outcomes of CLAD

The CLAD-free survival after LDLLT was similar to that after CLT ($p = 0.57$) (Fig. 1), as were the BOS- and RAS-free survival. In the LDLLT group, CLAD developed predominantly in the lung of one side at disease onset in 19 of 22 patients, including 10 patients with BOS and 9 patients with RAS. The time of onset of CLAD in the LDLLT group was significantly later than that in the CLT group ($p = 0.015$) (Fig. 2a). With regard to the CLAD phenotypes, while the time of the onset of BOS was similar between the two groups, the onset of RAS in the LDLLT group occurred significantly later than that in the CLT group ($p = 0.035$) (Fig. 2b, c). One patient in the LDLLT group, who first developed the BOS

phenotype and thereafter the RAS phenotype, was treated for BOS according to the CLAD onset type. There was no significant difference in the overall survival after LT between the 2 groups (p = 0.11) (Fig. 3). However, patients who developed CLAD after LDLLT showed a significantly better overall survival than those who developed CLAD after CLT (p = 0.037) (Fig. 4a). Furthermore, while the overall survival of patients who developed BOS after LT was similar between the two groups, patients who developed RAS after LDLLT showed a significantly better overall survival than those who developed RAS after CLT (p = 0.0006) (Fig. 4b, c). There were no significant differences in the survival after the diagnosis of CLAD between the two LT groups; however, the survival of patients who developed RAS after LDLLT tended to be better than that of patients who developed RAS after CLT (p = 0.083) (Fig. 5a, b, c).

Discussion

Although the donor characteristics and the recipient characteristics were different between LDLLT and CLT, the CLAD-free survival and overall survival after bilateral LT were similar between the recipients of LDLLT and CLT. However, CLAD, especially RAS, but not BOS, after LDLLT, developed at a later time than that after CLT. Owing to the later development of CLAD or RAS after LDLLT, the recipients with CLAD or RAS after LDLLT showed a favorable overall survival compared to the recipients who developed CLAD or RAS after CLT. Furthermore, following the diagnosis of CLAD, the survival of patients who developed RAS after LDLLT tended to be better than that of patients who developed RAS after CLT. Our results suggest that CLAD after LDLLT may have a similar incidence but develop at a later time compared with CLAD occurring after CLT; in addition, CLAD

developing after LDLLT has a lower impact on the overall survival than that developing after CLT.

The differences in the characteristics of the donors and recipients reflected the differences in the procedures between LDLLT and CLT. First, LDLLT is usually performed in small adult females or pediatric patients; thus, the proportion of female recipients in the LDLLT group was significantly higher than that in the CLT group. The survival of adult primary LT recipients has been reported to be significantly better among females than among males [14]; however, the overall survival did not differ markedly between the two groups. In addition, to eliminate the influence of the effect of physical growth on the lung function in pediatric patients, pediatric patients were excluded from this study. Second, the preoperative severity of the disease, which was reflected by the LAS, was significantly greater in the LDLLT recipients than in the CLT recipients, because LDLLT is the main option for urgent LT in Japan due to the severe shortage of donor organs. As LT has been shown to provide a survival benefit even for high-LAS patients if lungs are transplanted from a low-risk donor [15], the overall survival after LDLLT was comparable to that after CLT. Third, the mean age of the healthy living donors for LDLLT was significantly lower than that of the deceased donors for CLT, and the quality of the donor lungs, as represented by the lung donor score, was significantly better in the LDLLT group than in the CLT group. Consequently, despite the smaller size of the pulmonary vascular bed in the lobar grafts, ideal grafts were implanted with a shorter ischemic time in LDLLT, which resulted in less severe PGD after LDLLT than after CLT. Because the severity of PGD has been shown to be associated with the risk of CLAD [16], the less severe PGD after LDLLT than after CLT may have contributed to the delayed development of CLAD after LDLLT

observed in this study.

Although LDLLT provided a similar CLAD-free survival to CLT in this study, CLAD, especially RAS, developed significantly later after LDLLT than after CLT. The delayed development of RAS after LDLLT may be attributed to the morphological characteristics in LDLLT. After LDLLT, small lobar grafts gradually expand to fit the recipient's chest cavity due to the size mismatch, leading to gradual improvement of the pulmonary function parameters, especially the forced vital capacity, during the first two years after LDLLT [17]. This expansion of the lobar lungs during the first two years after LDLLT may contribute to the delayed development of RAS after LDLLT. Furthermore, CLAD developed predominantly unilaterally at the disease onset after bilateral LDLLT in this study, consistent with a previously report [4]. Because LDLLT involves 2 different donors for each recipient and the total number of HLA mismatches can be up to 12, the total number of HLA mismatches with the bilateral donors of the LDLLT group was significantly higher than with the donors of the CLT group; however, the total number of HLA mismatches with the unilateral donors alone of the LDLLT group was significantly lower than that with the donors of the CLT group. We therefore speculated that immunological similarity between the donor lungs from blood relatives and the recipients in LDLLT might contribute to the delayed development of CLAD after LDLLT [18].

The development of CLAD unilaterally after LDLLT appeared not to be related to the delayed development of CLAD after LDLLT in this study. Because CLAD developed unilaterally after bilateral LDLLT, the unaffected contralateral lung might mask the decline in the pulmonary function and delay the diagnosis of CLAD after LDLLT [4]. However, consistent with the results of a previous report [4], the decline in the pulmonary function

occurred at the same time as the diagnosis of CLAD by ventilation scintigraphy, which has been shown to be more useful for the early detection of CLAD after LT than computed tomography [19].

Regarding the survival after LT, the delayed development of CLAD and RAS, but not BOS, contributed to the better overall survival in the patients who developed CLAD after LDLLT than in those who developed CLAD after CLT. In CLT, oversized allografts have been shown to be associated with a less frequent occurrence of BOS [5] and an increased survival after LT [20]. However, in LDLLT, undersized donor grafts have been shown to expand more after LDLLT than oversized donor grafts [21]. Because smaller grafts were implanted in LDLLT than in CLT, as shown by the size matching in this study, such mismatch might affect the outcomes after LDLLT, similar to those after CLT. Further examinations will be required to investigate the association between size matching and CLAD or the survival after LDLLT. However, once the recipients were diagnosed with CLAD, the impact of CLAD developing after LDLLT on the survival after the disease onset did not markedly differ from that of CLAD developing after CLT. Thus, lung transplant physicians should be aware of the characteristics associated with the delayed development of CLAD after LDLLT for appropriate long-term management, such as drug dose reduction and withdrawal in maintenance immunosuppression, except for recipients of LDLLT from the same donor as that for the hematopoietic stem cell transplantation.

Our study had several limitations. First, this was a retrospective observational study conducted at a single transplant center. Second, although the follow-up period was more than one year in all patients in this study, this period was still intermediate in some cases, and longer follow-up periods will be required for further validation of the prognostic impact

of CLAD. Third, the follow-up period was significantly different between the two groups, and CLAD after CLT was shown to develop later in the long-term follow-up than that after LDLLT. Finally, the number of LT recipients was small, because in addition to the exclusion of pediatric patients, patients who underwent single LT were also excluded from this study in order to eliminate the effect of the native contralateral lungs on the lung function. However, considering that LDLLT is currently performed exclusively in Japan, our study provides pertinent information about the differences in the prognostic impact of CLAD developing after LDLLT versus that developing after CLT.

In conclusion, the CLAD-free survival after LDLLT was similar to that after CLT, similar to findings for the overall survival after LT. However, CLAD, especially RAS, developed at a later time after LDLLT than after CLT, leading to a better overall survival of patients with CLAD and RAS in the LDLLT group than in the CLT group.

Compliance with ethical standards

Conflict of interest: Seiichiro Sugimoto and his co-authors have no conflicts of interest.

Figure legends

Fig. 1. The CLAD-free survival after living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT). The CLAD-free survival rates were similar between the recipients of LDLLT and those of CLT (5-year CLAD-free survival rate, 74.5% vs. 65.7%; 10-year CLAD-free survival rate, 59.6% vs. 65.7%) (p = 0.79).

Fig. 2. The interval from lung transplantation to the diagnosis of chronic lung allograft dysfunction (CLAD) after living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT). (a) The CLAD onset occurred significantly later in the LDLLT group than in the CLT group (1807 ± 1402 vs. 689 ± 584 days, p = 0.015). (b) The timing of the onset of bronchiolitis obliterans syndrome (BOS) did not differ markedly between the two groups (1360 ± 1319 vs. 595 ± 643 days, p = 0.19). (c) The timing of the onset of RAS in the LDLLT group was significantly later than in the CLT group (2343 ± 1307 vs. 820 ± 460 days, p = 0.035).

Fig. 3. The overall survival after living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT). There was no significant difference in the overall survival rates between recipients of LDLLT and those of CLT (5-year survival rate, 82.0% vs. 69.6%; 10-year survival rate, 72.7% vs. 55.7%) (p = 0.10).

Fig. 4. The overall survival of patients with chronic lung allograft dysfunction (CLAD) after living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT). (a) The overall survival rates of the patients developing CLAD after LDLLT were

significantly better than those of the patients developing CLAD after CLT (5-year survival rate, 72.4% vs. 50.0%) (p = 0.037). (b) The survival of the patients who developed BOS after LT was similar between the 2 groups (p = 0.90). (c) Patients developing RAS after LDLLT had a significantly better survival than those who developed RAS after CLT (p = 0.0006).

Fig. 5. The survival after the diagnosis of chronic lung allograft dysfunction (CLAD) after living-donor lobar lung transplantation (LDLLT) and cadaveric lung transplantation (CLT). There was no significant difference in the survival after disease onset among patients who developed CLAD (p = 0.57) (a), BOS (p = 0.49) (b), and RAS (c) (p = 0.083).

References

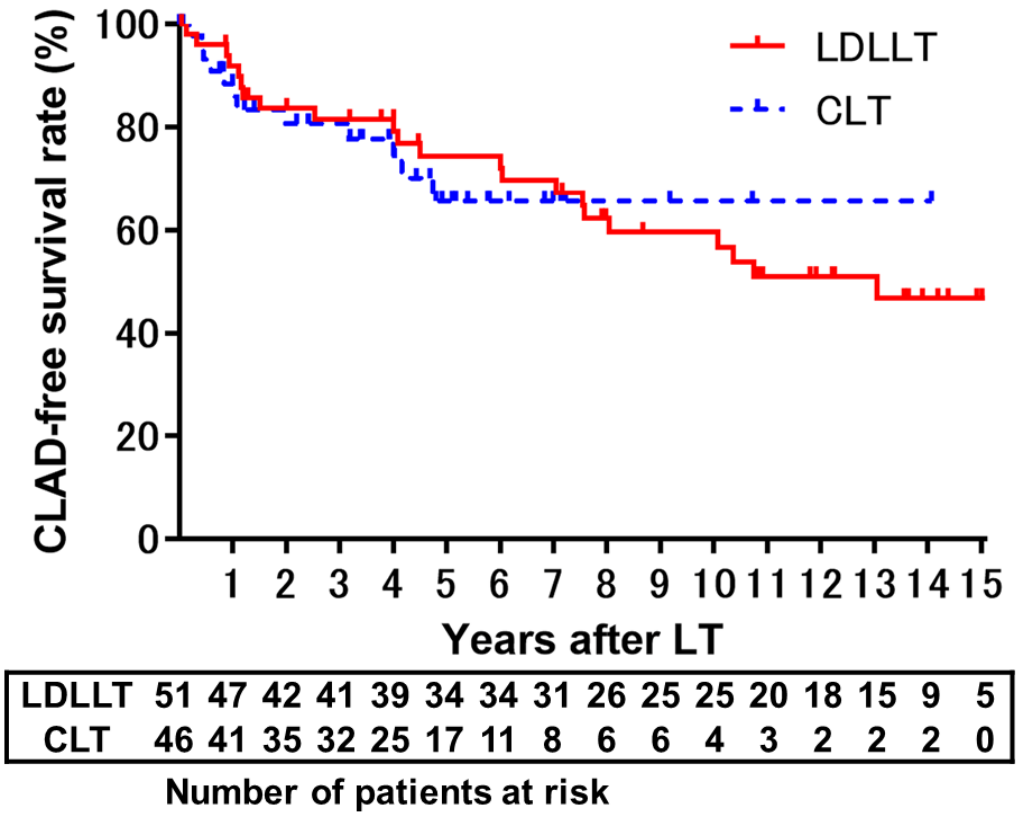
1. Starnes VA, Barr ML, Cohen RG, Hagen JA, Wells WJ, Horn MV, et al. Living-donor lobar lung transplantation experience: intermediate results. J Thorac Cardiovasc Surg 1996;112:1284-90; discussion 90-1.
2. Starnes VA, Bowdish ME, Woo MS, Barbers RG, Schenkel FA, Horn MV, et al. A decade of living lobar lung transplantation: recipient outcomes. J Thorac Cardiovasc Surg 2004;127:114-22.
3. Date H, Sato M, Aoyama A, Yamada T, Mizota T, Kinoshita H, et al. Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients. Eur J Cardiothorac Surg 2015;47:967-73.
4. Miyamoto E, Chen F, Aoyama A, Sato M, Yamada T, Date H. Unilateral chronic lung allograft dysfunction is a characteristic of bilateral living-donor lobar lung transplantation. Eur J Cardiothorac Surg 2014.
5. Eberlein M, Permutt S, Chahla MF, Bolukbas S, Nathan SD, Shlobin OA, et al. Lung size mismatch in bilateral lung transplantation is associated with allograft function and bronchiolitis obliterans syndrome. Chest 2012;141:451-60.
6. Bowdish ME, Pessotto R, Barbers RG, Schenkel FA, Starnes VA, Barr ML. Long-term pulmonary function after living-donor lobar lung transplantation in adults. Ann Thorac Surg 2005;79:418-25.
7. Sato M, Waddell TK, Wagnetz U, Roberts HC, Hwang DM, Haroon A, et al. Restrictive allograft syndrome (RAS): A novel form of chronic lung allograft dysfunction. J Heart Lung Transplant 2011;30:735-42.
8. Date H, Aoe M, Nagahiro I, Sano Y, Matsubara H, Goto K, et al. How to predict forced vital capacity after living-donor lobar-lung transplantation. J Heart Lung Transplant 2004;23:547-51.
9. Sugimoto S, Yamane M, Otani S, Kurosaki T, Okahara S, Hikasa Y, et al. Airway complications have a greater impact on the outcomes of living-donor lobar lung transplantation recipients than cadaveric lung transplantation recipients. Surg Today 2018;48:848-55.
10. Hirano Y, Sugimoto S, Mano T, Kurosaki T, Miyoshi K, Otani S, et al. Prolonged Administration of Twice-Daily Bolus Intravenous Tacrolimus in the Early Phase After Lung Transplantation. Ann Transplant 2017;22:484-92.
11. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24:1454-59.
12. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant 2014;33:127-33.
13. Saito M, Chen-Yoshikawa TF, Nakamoto Y, Kayawake H, Tokuno J, Ueda S, et al. Unilateral Chronic Lung Allograft Dysfunction Assessed by Biphasic Computed Tomographic Volumetry in Bilateral Living-donor Lobar Lung Transplantation. Transplant Direct 2018;4:e398.
14. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, et al. Antibody-mediated rejection of the lung: A consensus report of the International Society for

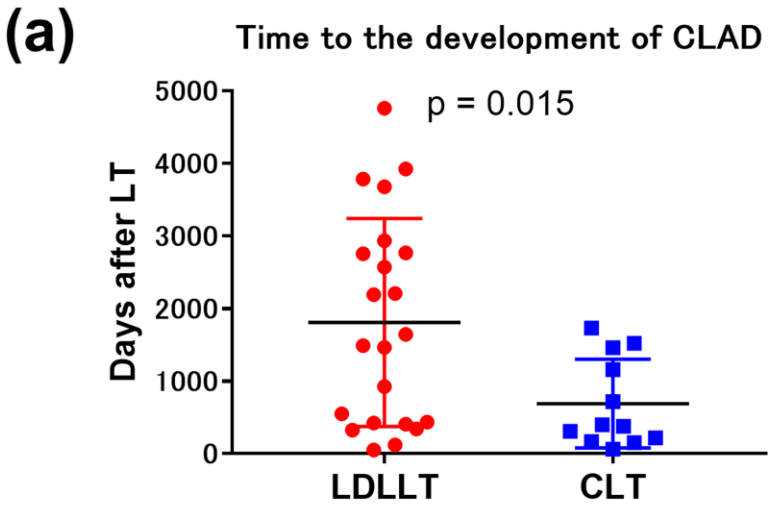
Heart and Lung Transplantation. J Heart Lung Transplant 2016;35:397-406.
15. Kurosaki T, Miyoshi K, Otani S, Imanishi K, Sugimoto S, Yamane M, et al. Low-risk donor lungs optimize the post-lung transplant outcome for high lung allocation score patients. Surg Today 2018 May 11. doi: 10.1007/s00595-018-1670-7. [Epub ahead of print].
16. Daud SA, Yusen RD, Meyers BF, Chakinala MM, Walter MJ, Aloush AA, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2007;175:507-13.
17. Yamane M, Date H, Okazaki M, Toyooka S, Aoe M, Sano Y. Long-term improvement in pulmonary function after living donor lobar lung transplantation. J Heart Lung Transplant 2007;26:687-92.
18. Yamada Y, Langner T, Inci I, Benden C, Schuurmans M, Weder W, et al. Impact of human leukocyte antigen mismatch on lung transplant outcome. Interact Cardiovasc Thorac Surg 2018;26:859-64.
19. Shinya T, Sato S, Kato K, Gobara H, Akaki S, Date H, et al. Assessment of mean transit time in the engrafted lung with 133Xe lung ventilation scintigraphy improves diagnosis of bronchiolitis obliterans syndrome in living-donor lobar lung transplant recipients. Ann Nucl Med 2008;22:31-9.
20. Eberlein M, Reed RM, Maidaa M, Bolukbas S, Arnaoutakis GJ, Orens JB, et al. Donor-recipient size matching and survival after lung transplantation. A cohort study. Ann Am Thorac Soc 2013;10:418-25.
21. Chen F, Kubo T, Yamada T, Sato M, Aoyama A, Bando T, et al. Adaptation over a wide range of donor graft lung size discrepancies in living-donor lobar lung transplantation. Am J Transplant 2013;13:1336-42.

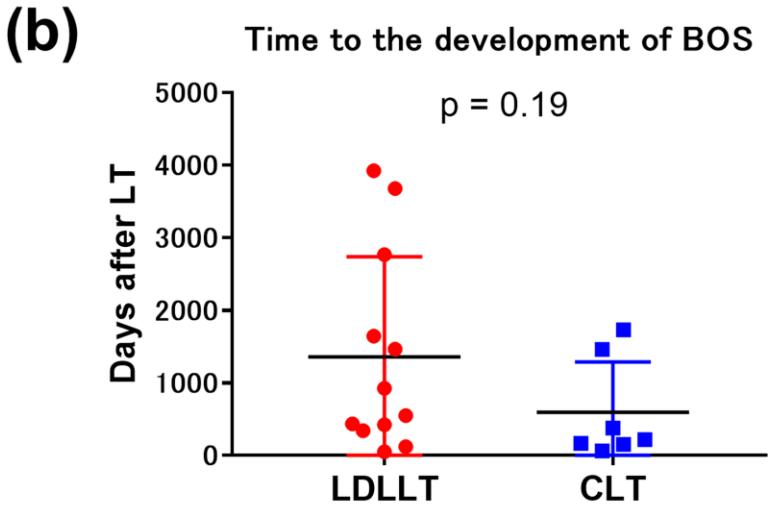
Table 1. Patient characteristics

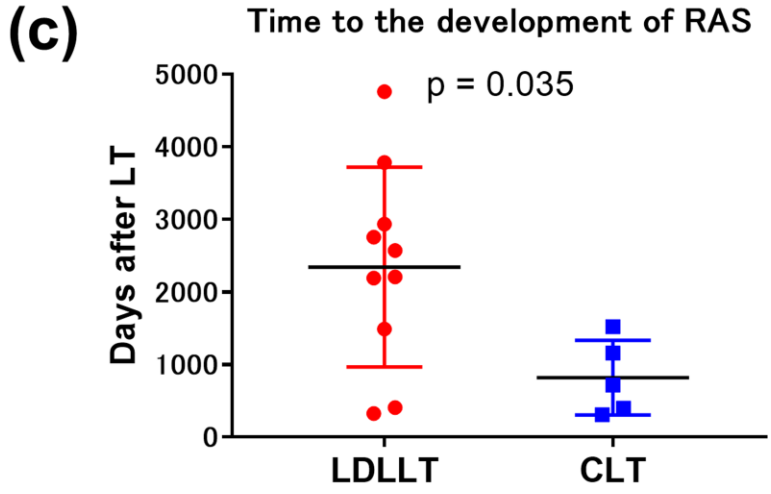
Variables	Bilateral living-donor lobar lung transplantation	Bilateral cadaveric lung transplantation	P-value
Number of patients	51	46	
Age, years	37.5 ± 11.6	37.6 ± 12.9	0.98
Gender, female	44 (86.3%)	25 (54.3%)	0.0007
Diagnoses			
Interstitial lung disease	21 (41.2%)	11 (23.9%)	0.086
Pulmonary hypertension	11 (21.6%)	13 (28.3%)	0.49
Pulmonary GVHD	7 (13.7%)	5 (10.9%)	0.76
Lymphangioleiomyomatosis	4 (7.8%)	5 (10.9%)	0.73
Bronchiectasis	3 (5.9%)	7 (15.2%)	0.18
Other diseases	5 (9.8%)	5 (10.9%)	> 0.99
Preoperative steroid use	24 (47.1%)	18 (39.1%)	0.54
Body mass index	17.9 ± 4.0	19.5 ± 4.7	0.071
Lung allocation score	50.6 ± 15.2	39.0 ± 6.5	< 0.0001
Donor variables			
Donor age	38.5 ± 11.5	47.8 ± 12.7	< 0.0001
Donor gender, female	48 (47.1%)	19 (41.3%)	0.59
CMV mismatch (recipient negative/donor positive)	4 (7.8%)	6 (0.13%)	0.51
FVC-based size matching (%)	63.0 ± 12.1	99.5 ± 16.0	< 0.0001
Total number of HLA-A, HLA-B and HLA-DR mismatches			
Bilateral donors	6.4 ± 2.1	4.8 ± 0.8	< 0.0001
Right lung donor	3.3 ± 1.4	4.8 ± 0.8	< 0.0001
Left lung donor	3.1 ± 1.3	4.8 ± 0.8	< 0.0001
Total ischemic time (min)	163.2 ± 35.4	549.9 ± 112.7	< 0.0001
Cardiopulmonary bypass use	51 (100.0%)	45 (97.8%)	0.47
Postoperative ECMO	3 (5.9%)	6 (13.0%)	0.30
Primary graft dysfunction grade	0.9 ± 1.0	1.9 ± 1.2	< 0.0001
Acute rejection, number			
First period	1.5 ± 1.1	1.0 ± 1.1	0.21
Second period	0.3 ± 0.7	0.2 ± 0.5	0.53
30-day mortality	1 (2.0%)	2 (4.4%)	0.60
Postoperative GERD	2 (3.9%)	0	0.50
CLAD	22 (43.1%)	12 (26.1%)	0.09
BOS	12 (23.5%)	7 (15.2%)	0.44
RAS	10 (19.6%)	5 (10.9%)	0.27
Time since transplant to follow-up (days)	3514 ± 1984	1601 ± 1057	< 0.0001

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; ECMO, extracorporeal membrane oxygenation; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GVHD, graft-versus-host disease; HLA, human leucocyte antigen; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome

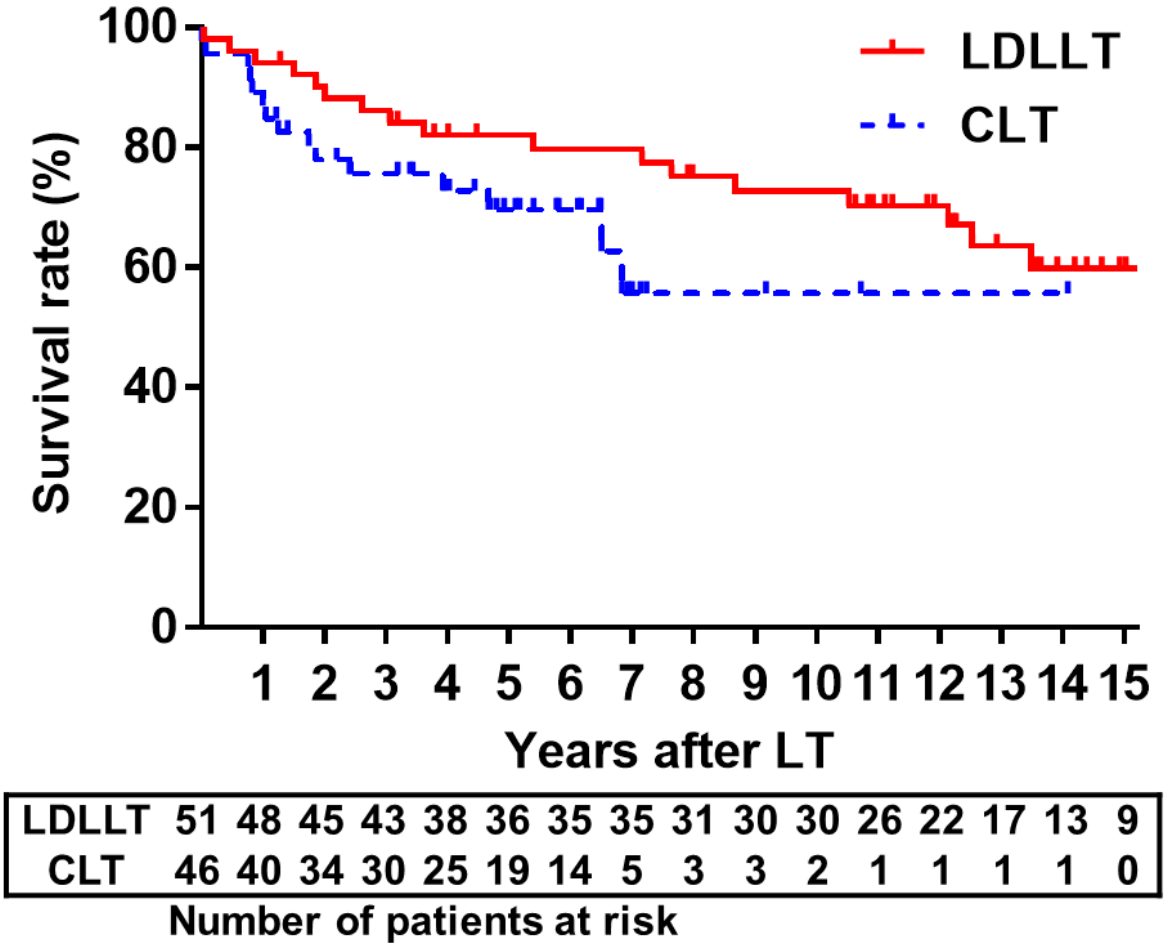

CLAD-free survival rate (%)
100
80
60
40
20
0
LDLLT
CLT
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Years after LT
LDLLT 51 47 42 41 39 34 34 31 26 25 25 20 18 15 9 5
CLT 46 41 35 32 25 17 11 8 6 6 4 3 2 2 2 0
Number of patients at risk

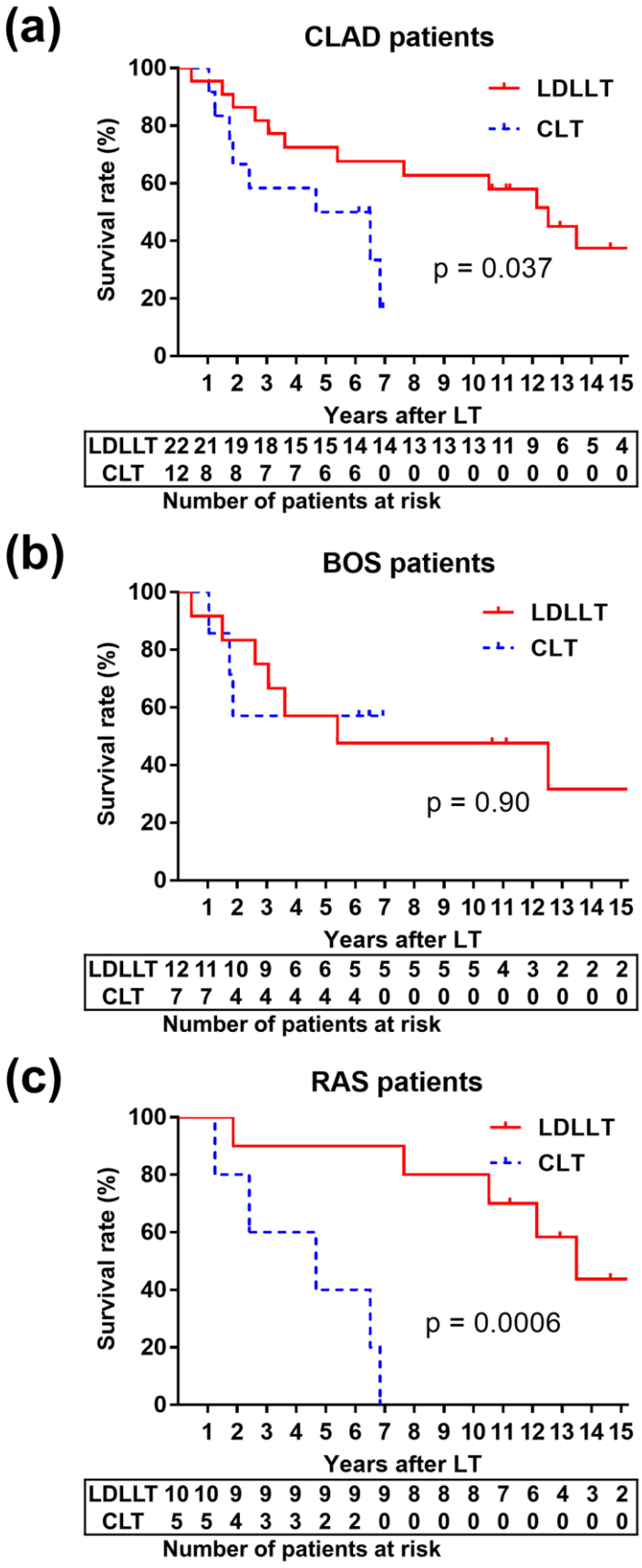

(a)
Time to the development of CLAD
p = 0.015
Days after LT
5000
4000
3000
2000
1000
0
LDLLT
CLT


(b)
Time to the development of BOS
p = 0.19
Days after LT
5000
4000
3000
2000
1000
0
LDLLT
CLT

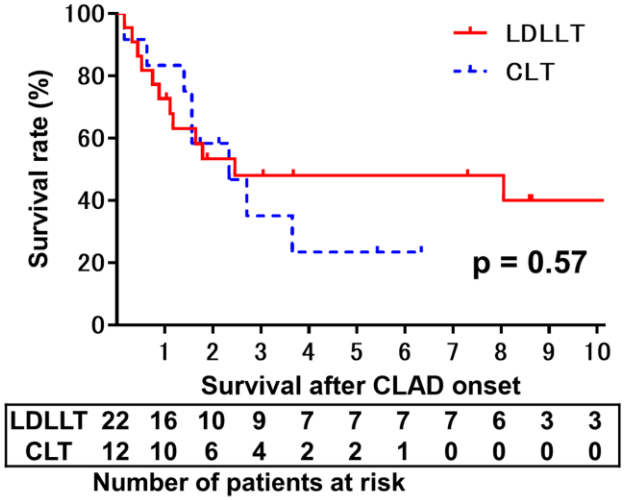

(c)
Time to the development of RAS
p = 0.035
Days after LT
5000
4000
3000
2000
1000
0
LDLLT
CLT

1


100
80
60
40
20
0
Survival rate (%)
LDLLT
CLT
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Years after LT
LDLLT 51 48 45 43 38 36 35 35 31 30 30 26 22 17 13 9
CLT 46 40 34 30 25 19 14 5 3 3 2 1 1 1 1 0
Number of patients at risk


(a)
CLAD patients
LDLLT
CLT
Survival rate (%)
p = 0.037
Years after LT
LDLLT 22 21 19 18 15 15 14 14 13 13 13 11 9 6 5 4
CLT 12 8 8 7 7 6 6 0 0 0 0 0 0 0 0 0
Number of patients at risk
(b)
BOS patients
LDLLT
CLT
Survival rate (%)
p = 0.90
Years after LT
LDLLT 12 11 10 9 6 6 5 5 5 5 4 3 2 2 2
CLT 7 7 4 4 4 4 4 0 0 0 0 0 0 0 0 0
Number of patients at risk
(c)
RAS patients
LDLLT
CLT
Survival rate (%)
p = 0.0006
Years after LT
LDLLT 10 10 9 9 9 9 9 9 8 8 8 7 6 4 3 2
CLT 5 5 4 3 3 2 2 0 0 0 0 0 0 0 0 0
Number of patients at risk

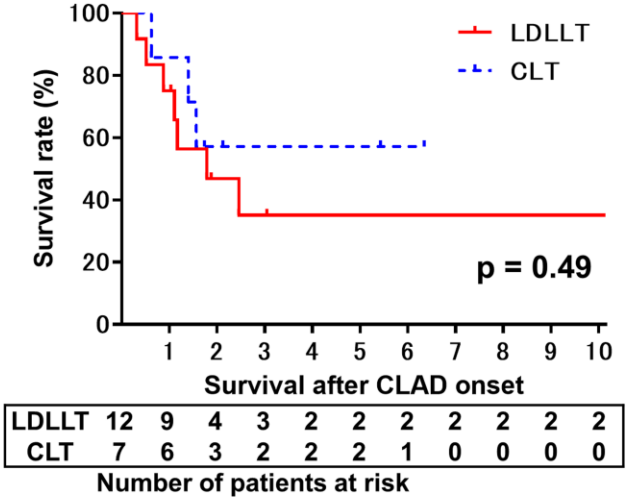
(a)



LDLLT	22	16	10	9	7	7	7	7	6	3	3
CLT	12	10	6	4	2	2	1	0	0	0	0

Number of patients at risk

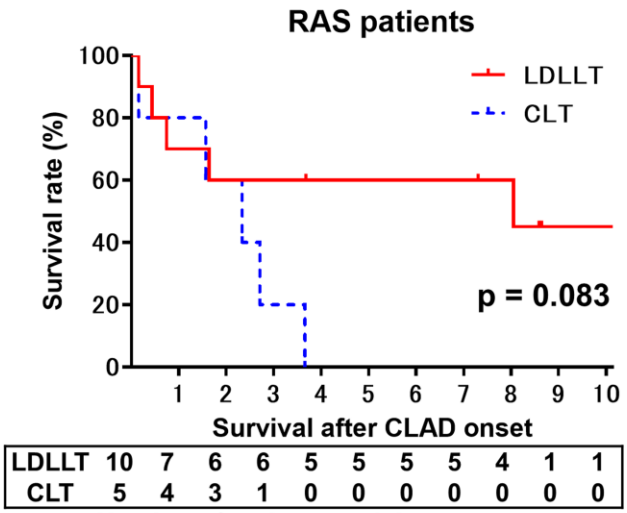
(b)



LDLLT	12	9	4	3	2	2	2	2	2	2	2
CLT	7	6	3	2	2	2	1	0	0	0	0

Number of patients at risk

(c)



LDLLT	10	7	6	6	5	5	5	5	4	1	1
CLT	5	4	3	1	0	0	0	0	0	0	0

Number of patients at risk

1