Percentage of low attenuation area on computed tomography detects chronic lung allograft dysfunction, especially bronchiolitis obliterans syndrome, after bilateral lung transplantation

Running title: %LAA on CT to detect CLAD after LT

Key words: bronchiolitis obliterans syndrome, chronic lung allograft dysfunction, computed tomography, lung transplantation, restrictive allograft syndrome

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Abbreviations:

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CLT, cadaveric lung transplantation; CMV, cytomegalovirus; CT, computed tomography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HU, Hounsfield units; ISHLT, the International Society for Heart and Lung Transplantation; LAA, low attenuation area; %LAA, percentage of the low attenuation area; LAS, lung allocation score; LDLLT, living-donor lobar lung transplantation; LT, lung transplantation; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome; TLC, total lung capacity

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Abstract

Introduction: The percentage of low attenuation area (%LAA) on computed tomography (CT) is useful for evaluating lung emphysema, and higher %LAA was observed in patients with chronic lung allograft dysfunction (CLAD). This study investigated the relationship between the %LAA and the development of CLAD after bilateral lung transplantation (LT).

Methods: We conducted a single-center retrospective study of 75 recipients who underwent bilateral LT; the recipients were divided into a CLAD group (n = 30) and a non-CLAD group (n = 45). The %LAA was calculated using CT and compared between the two groups from 4 years before to 4 years after the diagnosis of CLAD. The relationships between the %LAA and the percent baseline values of the pulmonary function test parameters were also calculated.

Results: The %LAA was significantly higher in the CLAD group than in the non-CLAD group from 2 years before to 2 years after the diagnosis of CLAD ($P < 0.05$). In particular, patients with bronchiolitis obliterans syndrome (BOS) exhibited significant differences even from 4 years before to 4 years after diagnosis ($P < 0.05$). Significant negative correlations between the %LAA and the percent baseline values of the forced expiratory volume in 1 s (r = -0.36, $P = 0.0031$), the forced vital capacity (r = -0.27, $P = 0.027$), and the total lung capacity (r = -0.40, $P < 0.001$) were seen at the time of CLAD diagnosis.

Conclusion: The %LAA on CT was associated with the development of CLAD and appears to have the potential to predict CLAD, especially BOS, after bilateral LT.

Key words: bronchiolitis obliterans syndrome, chronic lung allograft dysfunction, computed tomography, lung transplantation, restrictive allograft syndrome

Introduction

Recipients of lung transplantation (LT) continue to have a worse long-term survival than heart, liver, or kidney recipients. [1-3] Long-term survival after LT is mainly hampered by chronic lung allograft dysfunction (CLAD) after both cadaveric LT (CLT) and living-donor lobar LT (LDLLT). [4] CLAD develops in approximately 50% of recipients at 5 years after LT, according to the registry of the International Society for Heart and Lung Transplantation (ISHLT). [5] CLAD is diagnosed based on the results of pulmonary function tests after LT. [6,7] CLAD is defined as a persistent decline (≥20%) in the forced expiratory volume in 1 s (FEV1) from the baseline value, which is calculated as the average of the best 2 postoperative FEV1 values obtained at least 3 weeks apart. [7] CLAD can present either as a predominantly obstructive ventilatory pattern, a restrictive pattern, or a mixed obstructive and restrictive pattern that is not explained by other conditions or as a combination of these. [7] Recently, advanced diagnostic imaging methods including lung perfusion scintigraphy, inspiratory and expiratory computed tomography (CT) volumetry, the CT-scan score, quantitative CT analysis, and machine learning CT analysis have opened more doors to diagnosing CLAD. [8-12]

In the CT analysis of lung disease, the percentage of low attenuation area (%LAA) is a useful parameter for evaluating the severity of lung emphysematous changes on CT in patients with chronic obstructive pulmonary disease (COPD). [13] The %LAA is automatically calculated using diagnostic imaging software, enabling an objective evaluation of the severity of COPD. Moreover, the %LAA is correlated with the prognosis of patients with COPD. [14] Since both COPD and CLAD patients exhibit a decline in the FEV1 with disease progression, we previously showed that patients with CLAD had a significantly higher %LAA than those without CLAD at a single time point after bilateral LT. [15] However, the relationship between the postoperative change in %LAA and the development of CLAD after bilateral LT remains

unknown. In the present study, we evaluated the usefulness of the %LAA on CT images for the diagnosis of CLAD after bilateral LT, including CLT and LDLLT.

Methods

Patients

We conducted a single-center retrospective study of 112 recipients who underwent bilateral LT at Okayama University Hospital between May 2000 and August 2015 (**Figure 1**). Thirty-six patients were excluded from this study because adequate CT data for the %LAA evaluation were unavailable. One infant patient was also excluded because the patient was expected to have a larger %LAA because of their smaller whole lung volume. Of the remaining 75 patients who underwent bilateral LDLLT (n = 37) or CLT (n = 38), 30 patients who developed CLAD were designated as the CLAD group; the remaining 45 patients who did not develop CLAD were designated as the non-CLAD group. In the CLAD group, a subgroup analysis was performed to compare the %LAA between the patients with bronchiolitis obliterans syndrome (BOS) (n = 20) and those with restrictive allograft syndrome (RAS) (n = 10). The study protocol (No. 2205-005) was approved, and individual written informed consent was waived by the institutional review board of Okayama University Hospital. All the methods were implemented in accordance with the relevant guidelines and regulations.

Preoperative and operative patient characteristics and postoperative outcomes were evaluated. To estimate the preoperative severity of the recipient's disease, each patient's lung allocation score (LAS) was obtained using the LAS calculator, available on the OPTN website (https://optn.transplant.hrsa.gov/data/allocation-calculators/lung-cas-calculator/). A maximum number of 12 HLA mismatches is allowed in LDLLT, since two different donors for one recipient are required.

Lung transplant procedure

Patients who require a CLT are registered with the Japan Organ Transplantation Network. The allocation of lungs from brain-dead donors is still based mainly on the waiting time, and the LAS system has not yet been introduced in Japan. LDLLT is considered for critically ill patients who cannot wait for CLT, and only patients who meet all CLT criteria are able to receive LDLLT. At our hospital, up to third-degree blood relatives or spouses are accepted as living donors. The size matching protocol and transplant procedures have been described in previous reports. [16] The graft ischemia time was defined as the ischemic time until the second lung was transplanted.

Postoperative care

The postoperative management of the recipient, including immunosuppressive and prophylactic therapies, has been described previously. [17,18] The grades of primary graft dysfunction (PGD) were assigned in accordance with the definition of PGD using the ISHLT criteria. [19] Pulmonary function tests, including the FEV1, the forced vital capacity (FVC), and the total lung capacity (TLC), were performed at 3, 6, and 12 months after LT and annually thereafter. [6,7] According to the classification system of CLAD proposed by ISHLT, CLAD was defined as a decline in the FEV1 ≥20% of the baseline value after excluding processes and diseases that may lead to chronic loss of function of the graft and are not included in the current definition of CLAD. [7] The baseline FEV1 values were calculated as the average of the two best FEV1 values obtained at least 3 weeks apart. The baseline values of other pulmonary function test parameters were obtained as the average of the values measured at the time of the best FEV1 measurements. For the classification of the CLAD phenotype, BOS was defined as a substantial and persistent decline in the FEV1 ≥20% of the baseline value without persistent radiologic pulmonary

opacities. [7] RAS was defined as a persistent ≥20% decline in FEV1 (± FVC) of the baseline value, a decrease in TLC to ≤90% compared with baseline, and the presence of persistent opacities on chest X-ray and/or CT. [7] At the same time as the pulmonary function testing, lung ventilation scintigraphy to check the washout imaging and lung perfusion scintigraphy to observe a blood flow shift to the contralateral unaffected lung were performed to detect CLAD after LT. [12,20] A blood examination, chest X-ray, chest CT scan, and electrocardiogram were simultaneously performed for the differential diagnosis of CLAD.

Evaluation of low attenuation area (LAA) in transplanted lungs

Chest CT images (5.0 mm thick) in the maximal inspiration phase were obtained and were transferred to a workstation running the Synapse Vincent imaging software program (Fujifilm Medical, Tokyo, Japan) to evaluate the severity of the emphysematous changes in transplanted lungs. Lung field areas with attenuation values less than a threshold of -950 Hounsfield units were defined as the low attenuation area (LAA). [21] The percentage of the LAA in the whole lung relative to the total lung volume was automatically calculated as the %LAA (**Figure 2**). The %LAA was compared between the CLAD group and the non-CLAD group from 4 years before to 4 years after the diagnosis of CLAD. Since the median time until the onset of CLAD after LT was 1856 (152-5833) days, or nearly 5 years after LT, in the CLAD group, the %LAA at 5 years after bilateral LT was designated as the control value in the non-CLAD group. The relationships between the %LAA and the percent baseline values of the pulmonary function test parameters, including the FEV1, the FVC, and the TLC, were calculated.

Statistical analysis

The statistical analyses were performed using GraphPad Prism 9 Software (GraphPad Software,

Inc., San Diego, CA) and R (R Foundation for Statistical Computing, Vienna, Austria). All values except for the %LAA were expressed as the mean ± standard deviation. The value of %LAA for evaluating postoperative changes was expressed as the mean ± standard error of the mean. Bivariate comparisons of continuous variables were performed using the Student *t*-test. Associations between categorical variables were examined using the Fisher exact test. Associations between the %LAA and the percent baseline values of the FEV1, the FVC, and the TLC at the diagnosis of CLAD were tested using the Pearson product-moment correlation coefficient. Differences were considered significant at $P < 0.05$.

Results

A schematic diagram of the study cohort is shown in **Figure 1**. The patient characteristics are summarized in **Table 1**. Among the known risk factors for CLAD, [22] significant differences in the number of human leukocyte antigen mismatches and the incidence of acute rejection were seen between the two groups; however, the number of cytomegalovirus mismatches, the incidence of primary graft dysfunction, and the incidence of gastroesophageal reflux disease did not differ significantly. The observation period after LT did not differ between the two groups, and the median time until the onset of CLAD after LT was 1856 (152-5833) days in this study.

As shown in **Figure 3A**, the %LAA was significantly higher in the CLAD group than in the non-CLAD group from 2 years before to 2 years after the diagnosis of CLAD. The differences in the %LAA between the two groups tended to increase over time after the diagnosis of CLAD. Notably, in the subgroup analysis, the %LAA was significantly higher in the BOS patients than in the non-CLAD patients even from 4 years before to 4 years after the diagnosis of CLAD (**Figure 3B**). In contrast, the %LAA was significantly higher in the RAS

patients than in the non-CLAD patients from the time of CLAD diagnosis until 4 years after diagnosis (**Figure 3C, D**). In addition, the values of %LAA tended to be higher in the recipients of LDLLT, compared with those of CLT, although no significant differences were seen. The postoperative changes in the %LAA were analyzed in the right and left lungs separately as shown in **Supplementary Materials**, and the results of the %LAA in the right lung were similar to those in the whole lung.

Furthermore, the %LAA was significantly and negatively correlated with the percent baseline values of the FEV1, the FVC and the TLC (FEV1, r = -0.36, $P = 0.0031$; FVC, r = -0.27, $P = 0.027$; TLC, r = -0.40, $P < 0.001$) (**Figure 4A**). Except for the TLC at 1 year after the diagnosis of CLAD, significant negative correlations were seen between the %LAA and the FEV1, the FVC and the TLC from the time of CLAD diagnosis until 4 years after diagnosis (**Figure 4B**). In contrast, prior to the onset of CLAD, a significant negative correlation was only seen between the %LAA and the TLC at 1 year before the diagnosis of CLAD.

Discussion

In this study, we found that the %LAA was significantly higher in the patients with CLAD than in those without CLAD from 2 years before to 2 years after the diagnosis of CLAD following bilateral LT. Especially, BOS patients had significant differences in %LAA even from 4 years before to 4 years after the diagnosis of CLAD, whereas RAS patients had significant differences from the time of diagnosis to 4 years after the diagnosis of CLAD. Furthermore, the %LAA was significantly and negatively correlated with the percent baseline values of FEV1, TLC and FVC from the time of CLAD diagnosis until 4 years after diagnosis, except for the TLC at 1 year after the diagnosis of CLAD. Our results suggested that the %LAA on CT could predict the development of CLAD, especially BOS, after bilateral LT. To the best of our knowledge,

this is the first report to evaluate the %LAA on CT as a potential approach for diagnosing CLAD after bilateral LT.

Consistent with previously described results, [15,23] the %LAA increased in patients with CLAD after bilateral LT in the present study. Among the patients with CLAD, the %LAA significantly increased at least 2 years before the diagnosis of CLAD, and the differences in the %LAA between the patients with CLAD and those without CLAD tended to increase over time. Different from emphysematous changes in patients with COPD, the increase of %LAA may indicate the collapse of small airways with air trapping due to the inflammation or fibrosis of small airways in patients with CLAD. Compared with the previously reported CT-based diagnostic approaches for CLAD, the %LAA was not included in the CT-scan score, which was evaluated by blinded radiologists for the evidence of consolidation, bronchiectasis, reticular change, pleural effusion, and ground-glass opacities. [9] Although a machine-learning CT analysis included hyperlucent lung, which corresponds to the %LAA in the present study, as well as ground-glass opacity, reticulation, and pulmonary vessel volume, [24] the %LAA can be obtained objectively and easily using diagnostic imaging software without requiring machine learning. Unlike a quantitative lung density analysis, [11,25] the %LAA was calculated based on lung field areas with attenuation values less than the designated threshold only, and not a lung histogram analysis. The measurement of the %LAA alone on CT may offer a novel and simple approach for the early diagnosis of CLAD after bilateral LT. Given significant correlation between the %LAA and the percent baseline values of FEV1, TLC and FVC from the time of CLAD diagnosis until 4 years after diagnosis, measuring the %LAA might contribute to the prediction of decline in these parameters of pulmonary function test.

Although the %LAA did not differ between the patients with BOS and RAS over the postoperative course, the patients with BOS demonstrated significant differences in the %LAA

4 years earlier than those with RAS in the present study. Similar to the patients with lung emphysema, the early detection of BOS in our results might reflect the underlying pathology—bronchiolitis obliterans—appearing as an excess of subepithelial fibrous tissue during the early phase and with the obliteration of the lumen by fibrosis during the late phase. [7] In fact, the CT findings of BOS include air trapping in the early phase and bronchial dilatation and bronchial wall thickening in the late phase. In contrast, the pathology of RAS involves fibrotic changes in the interstitial tissue with or without pleural involvement, in addition to bronchiolitis obliterans. In the present study, the patients with RAS exhibited a surge in their %LAA after diagnosis. Thus, the measurement of %LAA might be useful for the early detection of BOS, rather than RAS, although a quantitative lung density analysis has been shown to be capable of differentiating RAS from BOS in a previous report. [25]

No significant differences in %LAA were seen between the recipients of LDLLT and CLT, although the LDLLT recipients tended to have relatively high levels of %LAA, compared with CLT recipients. Since LDLLT is still a realistic option for emergency or pediatric LT in Japan due to severe donor shortage, the rate of LDLLT was high in the present study as compared to the other countries. CLAD develops predominantly in the unilateral lung after bilateral LDLLT because of differences in the immunological features of the two donors. [4,27,28] Because the %LAA was measured as a percentage of the total volume of the bilateral lungs in the present study, a contralateral unaffected lung with CLAD after LDLLT might lead to an underestimation of the %LAA, resulting in a %LAA similar to that of CLT recipients with bilateral lungs affected by CLAD. The analysis of the %LAA in each unilateral lung showed that the results of the right lung were similar to those of the whole lung, suggesting the feasibility of the %LAA assessment in each unilateral lung after bilateral LT. Further study is required to elucidate whether the assessment of %LAA in each unilateral lung might be valuable

for the diagnosis of CLAD after bilateral LDLLT as well as CLAD after single LT in the future.

The present study had several limitations. First, the study was a retrospective cohort study conducted at a single transplant center, and the number of LT recipients were too small. A prospective multi-center trial could provide enough number of patients with CLAD for an accurate evaluation, especially according to differences in CLAD phenotypes. Second, it was difficult to obtain annual follow-up CT data from some patients with fatal CLAD, especially patients with RAS after CLT. Effective collaboration with nontransplant physicians at local hospitals might be required to maximize the amount of CT data in a further study. Third, the study included recipients who underwent either CLT or LDLLT, and a larger study would allow us to focus on the %LAA of each procedure. Fourth, negative correlation between the %LAA and the percent baseline values of FEV1, FVC and TLC at the time of CLAD diagnosis might be affected by a few measured values. Despite these limitations, the simplicity of the measurement of %LAA on CT means that our study provides practical information for the diagnosis of CLAD after bilateral LT.

In conclusion, the %LAA on CT was associated with the development of CLAD, especially BOS, and increased after the diagnosis of CLAD after bilateral LT. Moreover, the %LAA was associated with declines in the FEV1, FVC and TLC at the time of CLAD diagnosis after bilateral LT. The %LAA appears to offer the potential to predict CLAD, especially BOS, after bilateral LT, including CLT and LDLLT.

Author contributions

Corresponding author (Seiichiro Sugimoto), Yujiro Kubo and Toshio Shiotani were responsible for the study design. Yujiro Kubo and Toshio Shiotani assessed the imaging results and performed the statistical analysis. All the authors contributed to the critical appraisal and writing

of the manuscript and approved the final submission.

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Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to disclose as described by the *Clinical Transplantation*.

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Table 1. Patient characteristics

	Non-CLAD (N = 45)	CLAD (N = 30)	*P* value
Preoperative variables			
Age, years	35.1 ± 13.7	34.6 ± 14.3	0.90
Sex, female	32 (71%)	16 (53%)	0.14
Body mass index	18.1 ± 0.62	18.4 ± 0.75	0.75
Lung donor			0.35
Living	20 (44%)	17 (57%)	
Cadaveric	25 (56%)	13 (43%)	
Diagnosis			0.065
Interstitial lung disease	13 (29%)	10 (33%)	
Pulmonary hypertension	8 (18%)	8 (27%)	
Pulmonary GVHD	9 (20%)	2 (7%)	
Lymphangioleiomyomatosis	7 (16%)	0 (0%)	
Bronchiectasis	2 (4%)	4 (13%)	
Other diseases	6 (13%)	6 (20%)	
Lung allocation score	45.1 ± 1.5	45.9 ± 2.7	0.76
CMV mismatch (recipient negative/ donor positive)	5 (22%)	2 (15%)	0.98
Total number of HLA-A, HLA-B, and HLA-DR mismatches	4.8 ± 0.19	5.8 ± 0.34	0.0091
Intraoperative variables			
Operative time (min)	532 ± 16.6	526 ± 16.0	0.80
Ischemic time (min)	373 ± 29.9	343 ± 40.4	0.55
Cardiopulmonary bypass use	45 (100%)	29 (97%)	0.40
Postoperative variables			
Maximum grade of PGD (0-72h)	1.1 ± 0.16	1.2 ± 0.21	0.70
Acute rejection, yes	17 (38%)	19 (63%)	0.036
Antibody-mediated rejection	4 (9%)	4 (13%)	0.71
Postoperative GERD	1 (2%)	1 (3%)	1.0
Time since transplant to follow-up (day), median (range)	3166 (1959-6408)	3144 (380-7540)	0.60

Data are presented as n, mean ± standard deviation or n (%).

CMV cytomegalovirus, GERD gastroesophageal reflux disease, GVHD graft-versus-host disease, HLA human leukocyte antigen, PGD primary graft dysfunction.

Figure legends

Figure 1. Flow chart showing the study cohort. Among the 112 recipients of bilateral lung transplantation, 37 patients were excluded: computed tomography data required for the calculation of the percentage of the low attenuation area were unavailable for 36 patients, and one patient was an infant. Of the remaining 75 patients, 30 patients who developed chronic lung allograft dysfunction (CLAD) were designated as the CLAD group, and 45 patients who did not develop CLAD were designated as the non-CLAD group. The CLAD group was divided into patients with bronchiolitis obliterans syndrome (BOS) (n = 20) and those with restrictive allograft syndrome (RAS) (N = 10) according to the CLAD phenotype.

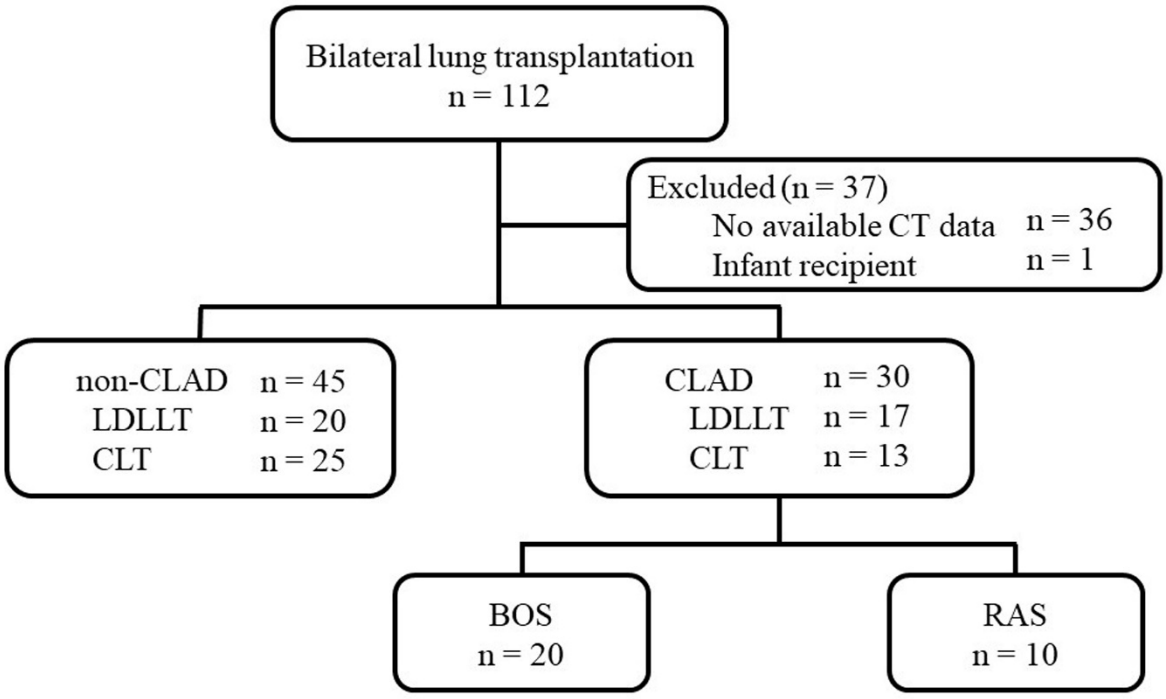
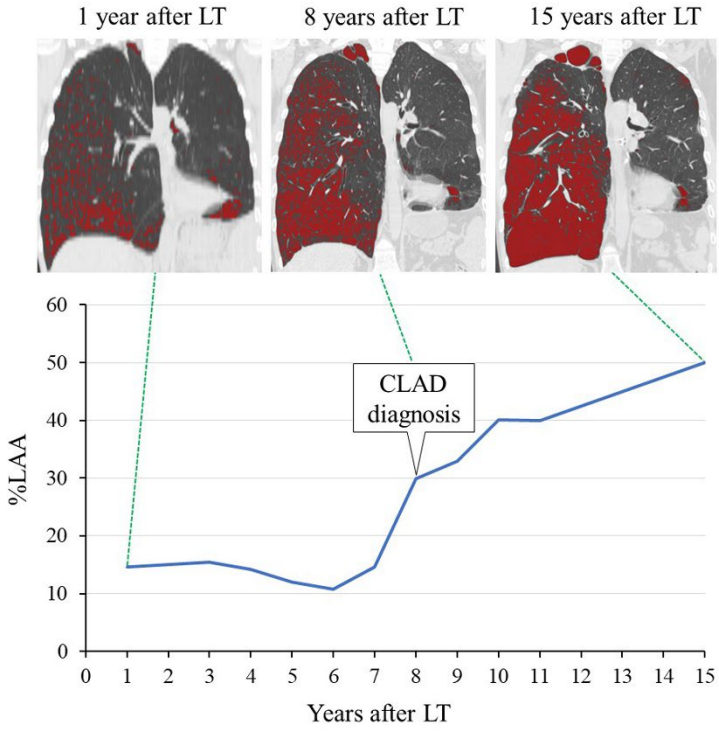


Figure 2. Representative course of the percentage of the low attenuation area (%LAA) in a patient with chronic lung allograft dysfunction (CLAD) after bilateral lung transplantation (LT). The low attenuation area (LAA) was automatically indicated by the red area on the computed tomography (CT) image, as shown in the upper part of the figure, and the %LAA was automatically calculated, as shown in the lower part of the figure. In this patient, the %LAA remained at a plateau for 6 years and then increased beginning at 7 years after LT and thereafter. The patient was diagnosed as having CLAD based on a pulmonary function test performed 8 years after bilateral LT.

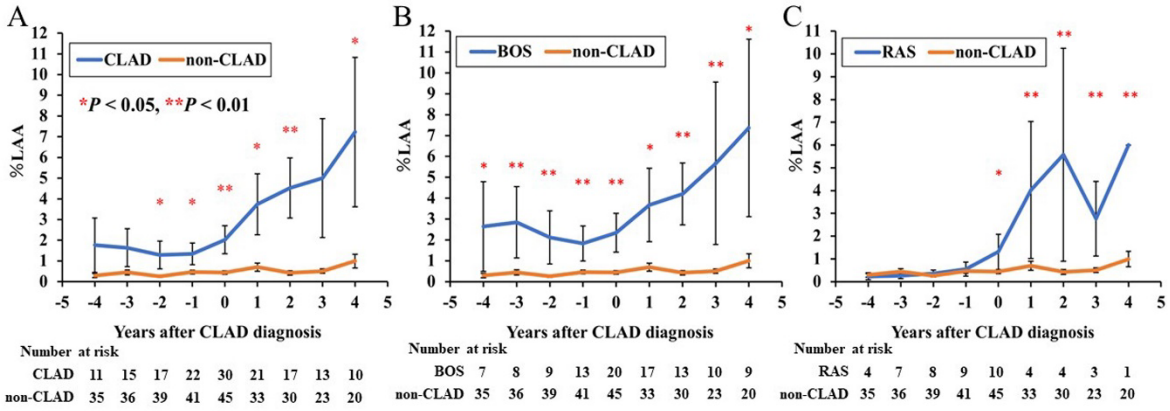


Measurement value list

Segment	Volume(ml)	LAA%	Mean
Both lungs	6512.8	33.7	-889.7
Right lung	4413.2	41.6	-914.9
Right upper lobe	1299.4	25.0	-900.8
Right middle lobe	20.5	22.5	-869.7
Right lower lobe	3093.4	48.7	-921.1
Left lung	2099.5	17.0	-836.6
Left upper lobe	963.2	0.7	-823.3
Left lower lobe	1136.3	30.9	-847.9

8 years after LT

Figure 3. Postoperative changes in the percentage of the low attenuation area (%LAA) after bilateral lung transplantation (LT). (A) The %LAA was significantly higher in the chronic lung allograft dysfunction (CLAD) group than in the non-CLAD group from 2 years before to 2 years after the diagnosis of CLAD. (B) The %LAA was significantly higher in the patients with bronchiolitis obliterans syndrome (BOS) than in the non-CLAD group from 4 years before to 4 years after the diagnosis of CLAD. (C) The %LAA was significantly higher in the patients with restrictive allograft syndrome (RAS) than in the non-CLAD group from the time of CLAD diagnosis until 4 years after diagnosis. (D) The *P* value is for comparisons between groups at each year before and after the onset of CLAD.

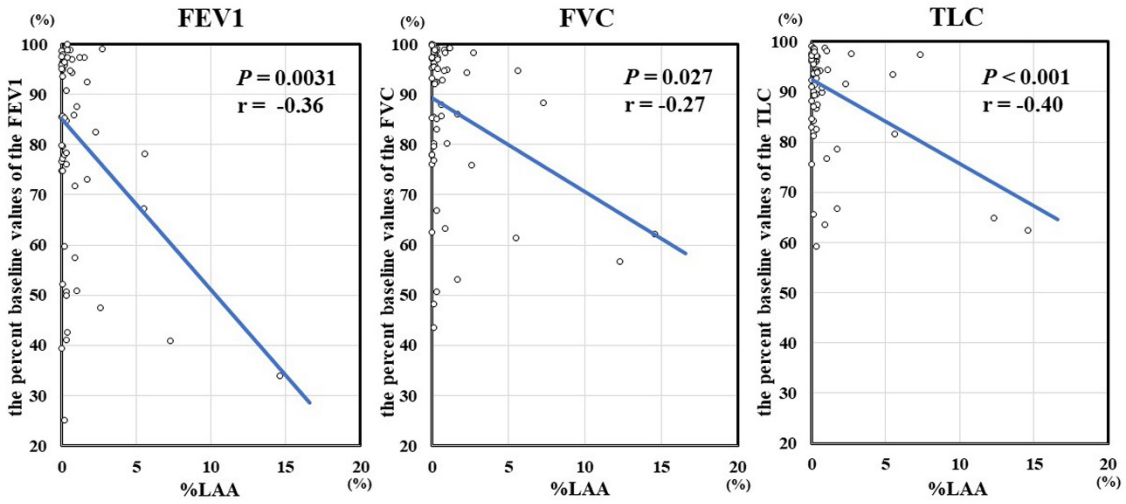


D

		P value								
	Years after CLAD diagnosis	-4	-3	-2	-1	0	+1	+2	+3	+4
A	non-CLAD vs CLAD	0.065	0.066	0.029	0.045	0.0076	0.016	0.00072	0.052	0.028
B, C	BOS vs RAS	0.43	0.18	0.22	0.26	0.50	0.93	0.71	0.70	0.92
	non-CLAD vs BOS	0.017	0.0053	0.0033	0.0077	0.0037	0.025	0.00038	0.049	0.033
	non-CLAD vs RAS	0.82	0.51	0.47	0.73	0.028	0.0045	0.0023	0.00078	0.0050
	non-CLAD vs BOS vs RAS	0.041	0.0087	0.0063	0.018	0.013	0.056	0.0028	0.12	0.091

Figure 4. (A) Correlation between the %LAA and the percent baseline values of the forced expiratory volume in 1 s (FEV1), the forced vital capacity (FVC), and the total lung capacity (TLC) at the diagnosis of CLAD. (B) The probability (*P*) values and correlation coefficient (r) values are shown from 4 years before to 4 years after the diagnosis of CLAD.

A



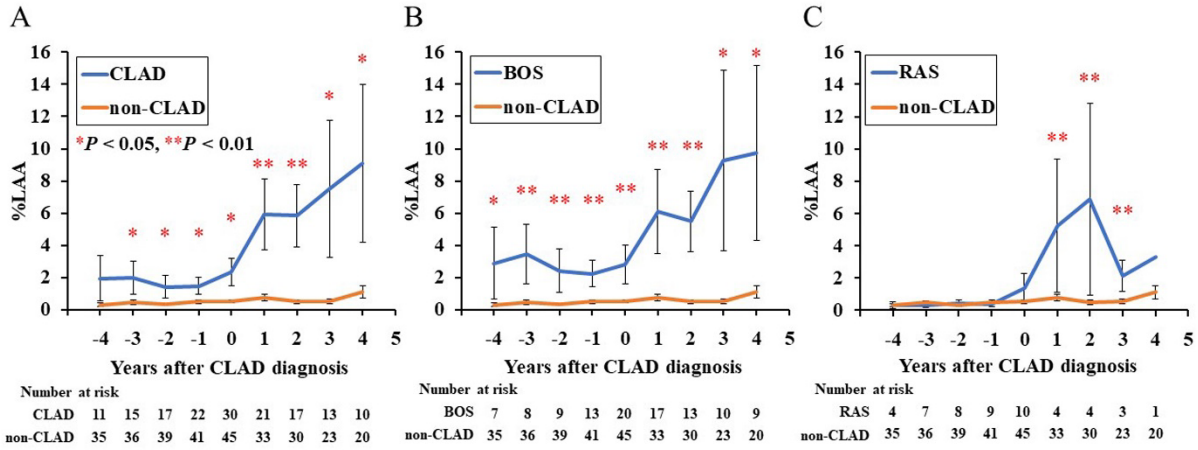
B

	Years after CLAD diagnosis								
	-4	-3	-2	-1	0	+1	+2	+3	+4
FEV1	*P* = 0.70	*P* = 0.96	*P* = 0.77	*P* = 0.81	*P* = 0.0031	*P* = 0.0041	*P* < 0.001	*P* < 0.001	*P* = 0.0012
	r = 0.58	r = 0.0075	r = 0.040	r = -0.031	r = -0.36	r = -0.40	r = -0.67	r = -0.57	r = -0.60
FVC	*P* = 0.54	*P* = 0.25	*P* = 0.84	*P* = 0.68	*P* = 0.027	*P* < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001
	r = 0.094	r = 0.163	r = 0.028	r = -0.054	r = -0.27	r = -0.47	r = -0.52	r = -0.62	r = -0.89
TLC	*P* = 0.62	*P* = 0.20	*P* = 0.33	*P* < 0.001	*P* < 0.001	*P* = 0.85	*P* = 0.009	*P* = 0.024	*P* < 0.001
	r = -0.15	r = -0.19	r = -0.14	r = -0.479	r = -0.40	r = -0.029	r = -0.40	r = -0.41	r = -0.67

Supplementary Materials

Supplementary Figures and Figure Legends

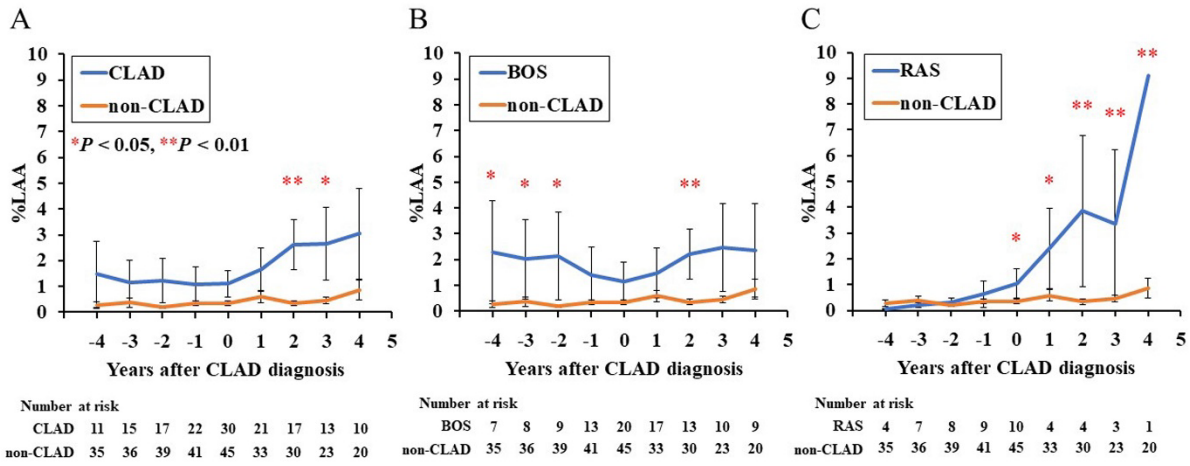
Figure S1. Postoperative changes in the percentage of the low attenuation area (%LAA) in the right lung after bilateral lung transplantation (LT). (A) The %LAA was significantly higher in the chronic lung allograft dysfunction (CLAD) group than in the non-CLAD group from 3 years before to 4 years after the diagnosis of CLAD. (B) The %LAA was significantly higher in the patients with bronchiolitis obliterans syndrome (BOS) than in the non-CLAD group from 4 years before to 4 years after the diagnosis of CLAD. (C) The %LAA was significantly higher in the patients with restrictive allograft syndrome (RAS) than in the non-CLAD group from 1 to 3 years after the diagnosis of CLAD. (D) The *P* value is for comparisons between groups at each year before and after the onset of CLAD.



D

		P value								
	Years after CLAD diagnosis	-4	-3	-2	-1	0	+1	+2	+3	+4
A	non-CLAD vs CLAD	0.050	0.032	0.024	0.024	0.012	0.0045	0.00045	0.029	0.028
B, C	BOS vs RAS	0.42	0.14	0.17	0.079	0.44	0.88	0.77	0.50	0.72
	non-CLAD vs BOS	0.013	0.0014	0.0014	0.0011	0.0063	0.0056	0.00014	0.017	0.024
	non-CLAD vs RAS	0.96	0.62	0.69	0.55	0.070	0.0034	0.0028	0.0043	0.24
	non-CLAD vs BOS vs RAS	0.033	0.0022	0.0025	0.0014	0.021	0.018	0.0020	0.044	0.074

Figure S2. Postoperative changes in the percentage of the low attenuation area (%LAA) in the left lung after bilateral lung transplantation (LT). (A) The %LAA was significantly higher in the chronic lung allograft dysfunction (CLAD) group than in the non-CLAD group from 2 to 3 years after the diagnosis of CLAD. (B) The %LAA was significantly higher in the patients with bronchiolitis obliterans syndrome (BOS) than in the non-CLAD group from 4 to 2 years before and 2 years after the diagnosis of CLAD. (C) The %LAA was significantly higher in the patients with restrictive allograft syndrome (RAS) than in the non-CLAD group from the time of CLAD diagnosis until 4 years after diagnosis. (D) The *P* value is for comparisons between groups at each year before and after the onset of CLAD.



D

		P value								
	Years after CLAD diagnosis	-4	-3	-2	-1	0	+1	+2	+3	+4
A	non-CLAD vs CLAD	0.11	0.19	0.060	0.15	0.093	0.14	0.0038	0.046	0.12
B, C	BOS vs RAS	0.43	0.29	0.30	0.58	0.93	0.68	0.50	0.80	0.28
	non-CLAD vs BOS	0.032	0.045	0.011	0.095	0.13	0.24	0.0062	0.083	0.27
	non-CLAD vs RAS	0.53	0.65	0.22	0.34	0.033	0.029	0.0014	0.0050	0.00017
	non-CLAD vs BOS vs RAS	0.072	0.082	0.023	0.23	0.24	0.27	0.0081	0.13	0.051