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Quantity and quality of antigravity muscles in patients undergoing living-donor lobar lung transplantation: 1-year longitudinal analysis using chest computed tomography images

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ABSTRACT

Background: Skeletal muscle dysfunction is a common feature in patients with severe lung diseases. Although lung transplantation aims to save these patients, the surgical procedure and disuse may cause additional deterioration and prolonged functional disability. We investigated the postoperative course of antigravity muscle condition in terms of quantity and quality using chest computed tomography.

Methods: 35 consecutive patients were investigated for 12 months after living-donor lobar lung transplantation (LDLLT). The erector spinae muscles (ESMs), which are antigravity muscles, were evaluated, and the cross-sectional area (ESM_{CSA}) and mean attenuation (ESM_{CT}) were analysed to determine the quantity and quality of ESMs. Functional capacity was evaluated by the 6-min walk distance (6MWD). Age-matched living donors with lower lobectomy were evaluated as controls.

Results: Recipient and donor ESM_{CSA} values temporarily decreased at 3 months and recovered by 12 months post-operatively. The ESM_{CSA} of recipients, but not that of donors, surpassed baseline values by 12 months post-operatively. Increased ESM_{CSA} (ratio to baseline $\geqslant 1$) may occur at 12 months in patients with a high baseline ESM_{CT}. Although the recipient ESM_{CT} may continuously decrease for 12 months, the ESM_{CT} is a major determinant, in addition to lung function, of the postoperative 6MWD at both 3 and 12 months.

Conclusion: The quantity of ESMs may increase within 12 months after LDLLT in recipients with better muscle quality at baseline. The quality of ESMs is also important for physical performance; therefore, further approaches to prevent deterioration in muscle quality are required.

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The quantity of antigravity muscles in patients undergoing lung transplantation (LTx) will increase within 1 year after LTx. The quality of muscles is important for increase of muscle quantity as well as physical performance. https://bit.ly/3bItfB9

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Introduction

Currently, more than 4000 lung transplantation (LTx) procedures per year are performed as a life-saving measure for patients with critical respiratory illnesses [1]. Poor muscle mass is common in LTx candidates [2–6] and has been identified as an important physiological factor associated with poor postoperative survival in recipients of heart [7], liver [8], and lung transplants [9, 10].

While skeletal muscle quality detected by medical imaging modalities has been reported to deteriorate in cases of chronic respiratory disease, including in lung transplant patients [11], to the best of our knowledge, there are no reports examining postoperative changes over time. Several mechanisms underlying skeletal muscle atrophy and dysfunction have been revealed [12], and LTx surgery is an invasive procedure that requires a long-term stay in an intensive care unit or hospital. Due to such temporary inactivity, patients may face additional disuse muscle atrophy, especially in antigravity muscles. Although preoperative and postoperative therapeutic approaches are available to address early morbidities and various other physical issues [13, 14], it is still not well known how muscle dysfunction changes over time after LTx. Skeletal muscle mass loss may not recover 1 year after LTx, the degree of recovery varies widely [15], and delayed recovery of skeletal muscles may lead to limited exercise performance [2, 3]. Both muscle quantity and quality may contribute to physiological performance in LTx candidates, and consequently, pre-existing conditions may affect both the postoperative course and physical performance.

Computed tomography (CT) is an established method used to quantitatively assess skeletal muscle conditions. The cross-sectional area (CSA) of the muscle is used as an index of muscle quantity [16], and poor skeletal muscle CSA is associated with a low exercise capacity in chronic obstructive pulmonary disease (COPD) patients [17], a poor prognosis [18], and prolonged hospital stays and low survival in LTx recipients [9, 19]. Moreover, muscle quality can be evaluated by radiography attenuation, which is associated with lipid content [20]. Low muscle attenuation in CT images (CT values) is associated with a low exercise capacity in COPD patients [21] and with increased mortality in patients with liver transplants [22].

We hypothesised that the preoperative and postoperative quantity and quality of skeletal muscles contribute to the clinical course of LTx patients, and that by using chest CT images, it is possible to quantitatively evaluate the quantity and quality of skeletal muscles. The specific aims of this study were to evaluate the postoperative course of skeletal muscle dysfunction in patients with LDLLT in terms of quantity and quality and to investigate what may affect the recovery of muscle dysfunction and physical performance after LTx. To this end, we quantified the erector spinae muscles (ESMs) [18, 23] using existing chest CT images because these scans are usually performed to diagnose and monitor a patient's lung condition; thus, these imaging data are readily available.

Materials and methods

Patients and study design

This study was part of our prospective cohort study on LDLLT at Kyoto University Hospital. Consecutive LDLLT recipients (⩾18 years old) were enrolled between August 2008 and July 2015. The exclusion criteria were as follows: 1) death within 12 months after LDLLT; 2) diagnosis of malignancy; 3) diagnosis of bronchiolitis obliterans syndrome (BOS) grade ⩾2 [24]; 4) diagnosis of compression fracture of the 12th thoracic vertebra; and 5) failure to undergo all chest CT analyses at baseline (within 3 months before LDLLT) and at 3 and 12 months after LDLLT. All recipients had end-stage pulmonary disease and were treated with oxygen therapy. We also investigated equivalent numbers of age-, sex- and height-matched living donors as almost-healthy controls with open lobectomy (figure 1). The ethics committee of Kyoto University approved this study (approval no. R1770), and all patients provided written informed consent prior to study participation.

Pre- and postoperative evaluations

In all recipients and donors, noncontrast-enhanced chest CT analyses and pulmonary function tests were routinely performed before LDLLT and at 3- and 12-month follow-up evaluations to examine and confirm the lung condition. Spirometry, lung volume subdivisions, and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were measured using a Chestac-8800 (Chest MI, Inc., Tokyo, Japan). Predicted pulmonary function values were calculated based on the Japanese Respiratory Society guidelines [25]. To evaluate physical performance, the 6-min walk distance (6MWD) was measured before surgery and 3 and 12 months after LDLLT according to the American Thoracic Society standards [26].

Chest CT image acquisition and quantitative image analysis of the ESM

Chest CT scans were conducted using the same CT scanner (Aquilion 64; Toshiba Medical Systems Corp., Otawara, Tochigi, Japan) with the following settings: collimation, 1 mm; scan time, 500 ms; 120 kV peak (kVp); and auto exposure control. Routine calibration of the CT scanner was performed using air and

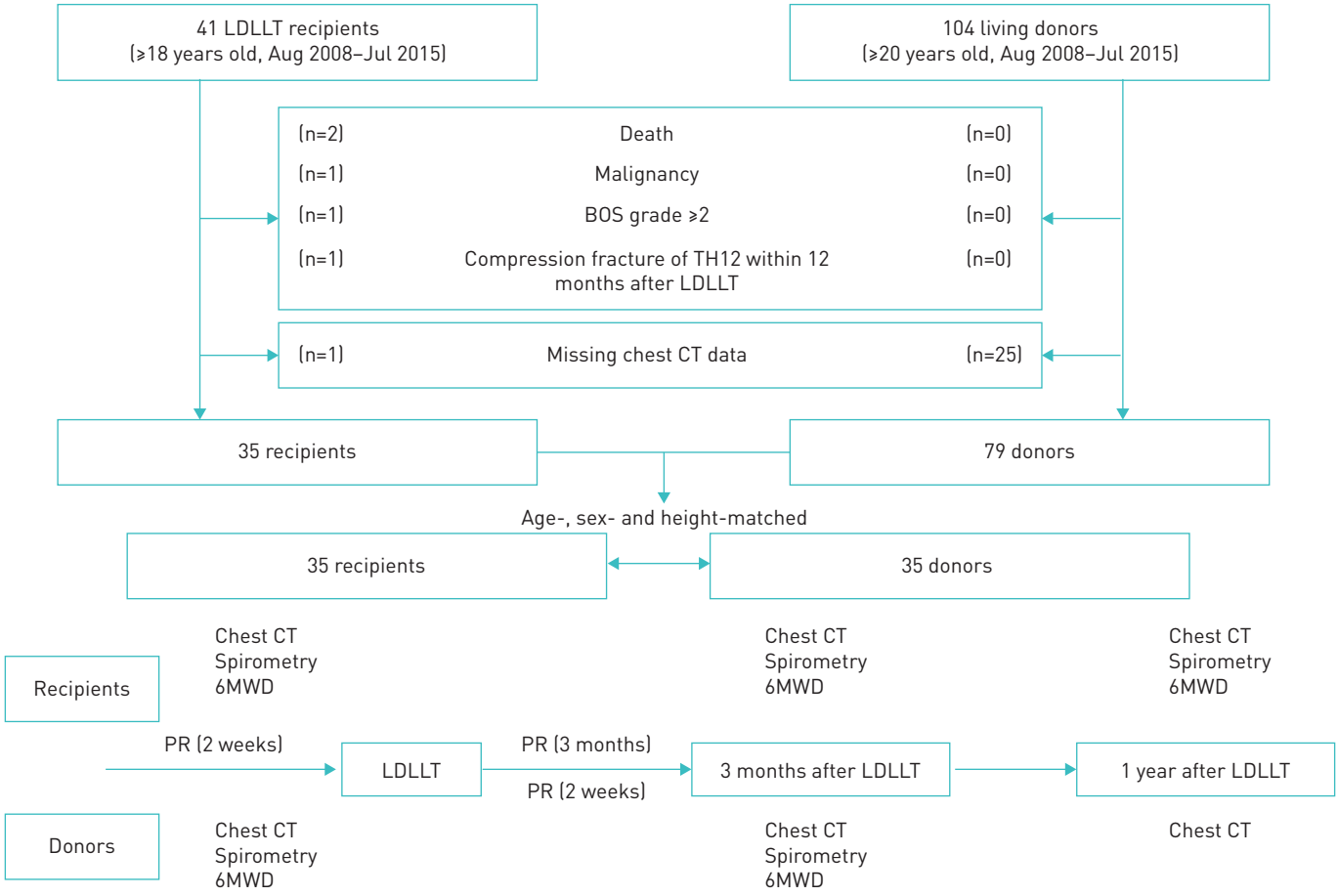

FIGURE 1 Study flowchart and scheme of our investigations and measures. BOS: bronchiolitis obliterans syndrome; LDLLT: living-donor lobar lung transplantation; CT: computed tomography; 6MWD: 6-min walk distance; PR: pulmonary rehabilitation.

water phantoms. For quantitative analysis of the ESMs, chest CT images were reconstructed using the FC13 mediastinal reconstruction kernel. Briefly, a single axial chest CT image at the level of the lower margin of the 12th thoracic vertebra [18] was used. The left and right ESMs were subsequently identified using a predefined attenuation range of −50 to 90 HU and were manually shaded using SYNAPSE VINCENT (Fujifilm Medical Co., Ltd., Tokyo, Japan); the sum of the CSA of the right and left ESMs is presented as the ESM_{CSA}, which is considered a measure of skeletal muscle quantity (figure 2a). The mean attenuation of the ESMs, which is considered a measure of skeletal muscle quality, is presented as the ESM_{CT} (figure 2b) [20].

Patient management and medical treatments during follow-up

All recipients received postoperative immunosuppression, which consisted of triple-drug therapy with cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids for at least 12 months after LDLLT. Acute rejections were diagnosed based on radiographical and clinical findings without transbronchial lung biopsy [27], and high-dose systemic corticosteroids were then administered for 3 days. Chronic lung allograft dysfunction (CLAD) was diagnosed based on previously published criteria [28].

All recipients and donors underwent pulmonary rehabilitation (PR), including exercise training, during hospitalisation. The detailed PR programme is described in the supplemental information (see online supplemental information). Briefly, the recipients underwent five PR sessions a week, which included deep breathing, resistance training, cycling, walking and stair climbing.

Following discharge from the hospital, all recipients received standard medical treatment and PR sessions at the outpatient clinic of Kyoto University Hospital for 3 months after LDLLT. Subsequently, the recipients were usually referred to a local hospital near their hometown. All participants were instructed to maintain their physical activity and perform daily exercise training following discharge.

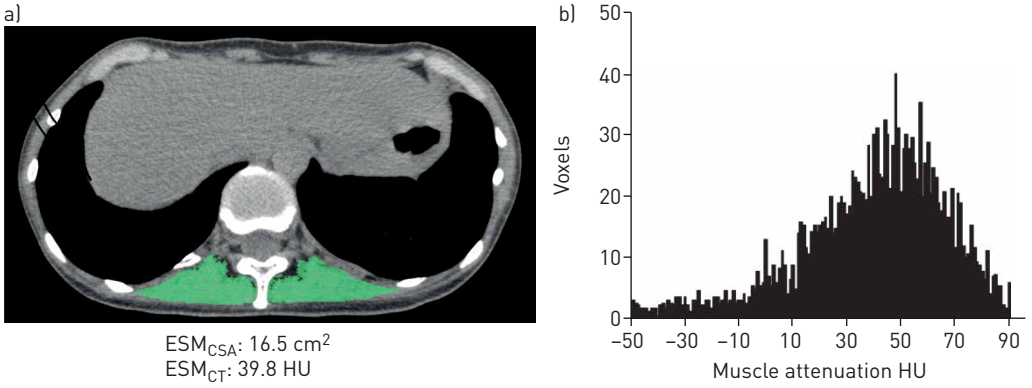

FIGURE 2 Representative computed tomography (CT) images used to measure the cross-sectional area (CSA) and attenuation of erector spinae muscles (ESMs) in recipients. Bilateral ESMs are shaded in green (a), and the frequency distribution of muscle attenuation is displayed (b). ESM_{CSA} (in cm^2) was calculated by summing the CSA of bilateral ESMs. ESM_{CT} (in Hounsfield Units (HU)) was defined by the mean ESM attenuation. Images were acquired by SYNAPSE VINCENT (FUJIFILM Medical Co., Ltd, Tokyo, Japan).

Statistical analysis

All data are shown as the mean±SD unless otherwise specified, and statistical analyses were performed using JMP 14.0 (SAS Institute, Cary, NC, USA). To analyse the time course of the postoperative changes in ESMs, we performed two-way repeated measures ANOVA, followed by *post hoc* tests. We dichotomised recipients into two groups according to the ratio of ESM_{CSA} or ESM_{CT} at 12 months after LDLLT to baseline values. The differences in clinical parameters between the two groups were analysed by a Mann–Whitney U-test for continuous variables and a Chi-squared test for categorical parameters. Logistic regression analyses were performed to identify the determinants associated with increased ESMs at 12 months. Univariate and multivariate linear regression analyses were performed to investigate the relationship between the 6MWD and clinical parameters at 3 and 12 months after LDLLT. For multiple regression analysis, the variance inflation factor was used to determine the degree of multicollinearity. Multicollinearity between variables was defined as a variance inflation factor $\geqslant$10. A p-value $<$0.05 was considered statistically significant.

Results

Study flowchart

As shown in the study flowchart (figure 1), 41 consecutive LDLLT recipients at our hospital from August 2008 to July 2015 were enrolled in this study. We excluded six recipients from the present analysis. One recipient died 3 months after LDLLT because of aspiration pneumonia, and another recipient died 10 months after LDLLT because of *Pneumocystis jirovecii* pneumonia. One recipient developed glioblastoma 5 months after LDLLT, one was diagnosed with grade 2 BOS 12 months after LDLLT, one was diagnosed with compression fracture of the 12th thoracic vertebra, and one did not undergo noncontrast-enhanced chest CT 3 months after LDLLT. Ultimately, 35 recipients were investigated successfully. There was no significant difference between the preoperative values of the 35 recipients who were included and the 6 who were excluded.

Baseline characteristics and operative procedures

As table 1 shows, more than half (60%) of recipients had indications for LTx due to interstitial lung disease, and all recipients suffered from severe breathlessness, poor pulmonary function, and malnutrition. Some recipients could not undergo examination because of their medical condition. The number of recipients in the CSAs was restricted to 25 at baseline. The reasons for inability to complete the examination were as follows: 10 recipients were unable to undergo the test for medical reasons (*e.g.* ventilator dependence, pneumothorax, extremely severe dyspnoea, severe circulatory disorder, leg amputation), and eight recipients could not perform the 6-min walk test because they were bedridden.

The baseline ESM_{CSA} of the recipients was approximately 25% lower than that of the donors; however, ESM_{CT} values were comparable (table 1). The predicted postoperative vital capacity, which was calculated from the graft-lung volume, was 61.6±15.1%; to compensate for the small graft size, six recipients underwent operations sparing the native upper lobes [29], and four underwent operations with inversion of the right and left lobes [30].

TABLE 1 Characteristics of the recipients and living donors at baseline

Variable	Recipients	Living donors	p-value[#]
Number of patients n	35	35	
Indications for lung transplantation			
Interstitial lung disease	21 (60%)	–	
Lung injury after haematopoietic stem cell transplantation	9 (26%)	–	
Idiopathic pulmonary artery hypertension	2 (6%)	–	
Bronchiectasis	2 (6%)	–	
Idiopathic pulmonary hemosiderosis	1 (3%)	–	
Smoking history (+)	15 (43%)	13 (37%)	0.63
mMRC score 0/1/2/3/4 n	0/0/0/16/19	33/2/0/0/0	<0.001
Female	19 (54%)	19 (54%)	1
Age years	46.8±13.2 (18–63)	45.1±10.9 (21–60)	0.50
Height m	1.60±0.09 (1.28–1.72)	1.63±0.06 (1.52–1.77)	0.11
Weight kg	48.0±10.8 (30.4–72.9)	60.9±9.4 (45.5–78.8)	<0.001
BMI kg·m^{-2}	18.5±3.3 (12.2–25.2)	22.6±2.8 (17.8–29.6)	<0.001
Albumin g·dL^{-1}	3.6±0.6 (2.0–5.0)	4.3±0.3 (3.7–5.2)	<0.001
VC % predicted	44.6±17.2 (16.9–88.0)[¶]	108.9±17.8 (85.1–169.8)	<0.001
FEV_1/FVC %	77.2±23.8 (21.1–100.0)[¶]	82.5±5.5 (70.8–92.8)	0.21
FEV_1 % predicted	38.9±19.0 (15.0–86.6)[¶]	104.4±13.6 (81.6–131.8)	<0.001
D_{LCO} % predicted	24.1±14.5 (7.3–63.2)[+]	92.7±10.3 (75.3–114.8)	<0.001
6MWD m	209.0±104.3 (19.0–380.0)[¶]	585.2±86.4 (400.0–736.0)[f]	<0.001
ESM_{CSA} cm^2	23.0±7.2 (11.3–39.9)	30.5±6.9 (19.7–45.8)	<0.001
ESM_{CT} HU	45.4±9.8 (13.8–59.8)	46.6±7.2 (30.9–57.6)	0.56
Quadriceps force Nm·kg^{-1}	2.11±0.71 (0.82–3.48)[§]	–	
Procedure of LDLLT			
Single/double LTx n	2/33	–	
Right/left lower lobectomy n	–	18/17	
Predicted postoperative VC % predicted	61.6±15.1 (40.3–104.8)	–	

Data are presented as n (%) or mean±SD (range), unless otherwise stated. mMRC: modified Medical Research Council; BMI: body mass index; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; ESM_{CSA}: cross-sectional area of the erector spinae muscles; ESM_{CT}: mean computed tomography values of the erector spinae muscles. [#]: Chi-squared test or t-test; [¶]: number of valid observations, 27; [+]: number of valid observations, 14; [§]: number of valid observations, 26; [f]: number of valid observations, 33.

Postoperative clinical course and pulmonary function

After LDLLT, the recipients stayed in the intensive care unit for 11.7±5.9 days and stayed in the hospital for 86.1±46.9 days. All recipients were managed as described above [27]. Twenty recipients received tacrolimus-based immunosuppression, 15 recipients received a cyclosporine-based regimen, and all received corticosteroids. Twenty-four recipients received high-dose steroid pulse therapy after LDLLT (7.8±3.9 days after LDLLT), and two recipients were diagnosed with obstructive CLAD (BOS grade 1) at 6 and 11 months after LDLLT (table 2).

TABLE 2 Outcome parameters for the recipients at each measurement time point

Variable	Baseline	3 months after LDLLT	12 months after LDLLT
BMI kg·m^{-2}	18.5±3.3 (12.2–25.2)	17.8±3.2 (12.0–23.3)*	19.3±3.6 (12.0–25.5)[##]
VC % predicted	44.6±17.2 (16.9–88.0)	54.0±16.8 (26.3–84.7)*	57.8±19.7 (15.6–101.0)**
D_{LCO} % predicted	24.1±14.5 (7.3–63.2)	48.4±12.9 (17.5–69.3)**	48.1±14.2 (23.7–84.6)**
Steroid use	22 (63%)	34 (97%)	34 (97%)
Average steroid dose mg·kg^{-1}·day^{-1}	0.18±0.19 (0–0.78)	0.38±0.08 (0–0.45)	0.20±0.12 (0–0.65)
Cumulative steroid dose mg·kg^{-1}	–	61.6±9.1 (39.0–82.7)	149.6±26.5 (52.0–215.8)
CLAD	–	–	2 (6%)

Data are presented as mean±SD deviation (range) or n (%). LDLLT: living-donor lobar lung transplantation; BMI: body mass index; VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; CLAD: chronic lung allograft dysfunction. *: p<0.05 compared to baseline; **: p<0.01 compared to baseline; [##]: p<0.01 compared to 3 months after LDLLT.

After LDLLT, vital capacity (VC) and D_{LCO} increased significantly at 3 months and were maintained at 12 months in recipients.

Postoperative changes

For ESM_{CSA}, there were significant main effects of both time course (p<0.0001) and group (p<0.0001), and the interaction was significant (p=0.0032) (figures 3a and c). The ESM_{CSA} of the recipients was consistently lower than that of the donors at baseline (p<0.0001), 3 months (p<0.0001) and 12 months (p=0.0003) after LDLLT. The ratio to baseline was significantly lower in the recipients than in the donors at 3 months after LDLLT (0.92±0.12 *versus* 0.96±0.05, p=0.049), but at 12 months after LDLLT, it was significantly higher in the recipients than in the donors (1.06±0.18 *versus* 0.99±0.07, p=0.024).

For ESM_{CT}, there were significant main effects of both time course (p=0.0051) and group (p=0.019), and their interaction was significant (p<0.0001, figure 3b and d). At 3 and 12 months after LDLLT, the recipient ESM_{CT} continuously deteriorated compared to baseline (p=0.0033 and p=0.0006, respectively), and the ratio to baseline was significantly lower in the recipients than in the donors at 3 months (0.94±0.15 *versus* 1.02±0.11, p=0.011) and 12 months (0.92±0.20 *versus* 1.02±0.10, p=0.0092) after LDLLT.

For the 6MWD, the recipient 6MWD was only 36% of the donor value (209±104 m *versus* 585±86 m, p<0.0001) at baseline. After LDLLT, the recipient 6MWD dramatically increased to 435±113 m at 3 months and slightly increased to 497±116 m at 12 months, reaching 85% of the donor baseline 6MWD.

Increase in the ESM_{CSA} and ESM_{CT} at 12 months after LDLLT

We dichotomised recipients into two groups according to the ratio of ESM_{CSA} or ESM_{CT} at 12 months after LDLLT to baseline; namely, ⩾1 (increase) *versus* <1 (decrease) groups were created (table 3). Low body mass index (BMI) (p=0.004), tacrolimus use (p=0.02), and high baseline ESM_{CT} were significant factors related to an increase in the ESM_{CSA} (ratio to baseline >1, n=20). In addition, a greater increase in ESM_{CSA} at 3 months after LDLLT (Δ at 3 months of ESM_{CSA}) was also associated with increased ESM_{CSA} at 12 months. Increased ESM_{CT} rarely occurred (ratio to baseline >1, n=7), and only Δ at 3 months of ESM_{CT} were a significant factor related to increased ESM_{CT} at 12 months. The multivariate analysis indicated that increased ESM_{CSA} at 12 months may occur in patients with a high baseline ESM_{CT} (p<0.001) (table 4).

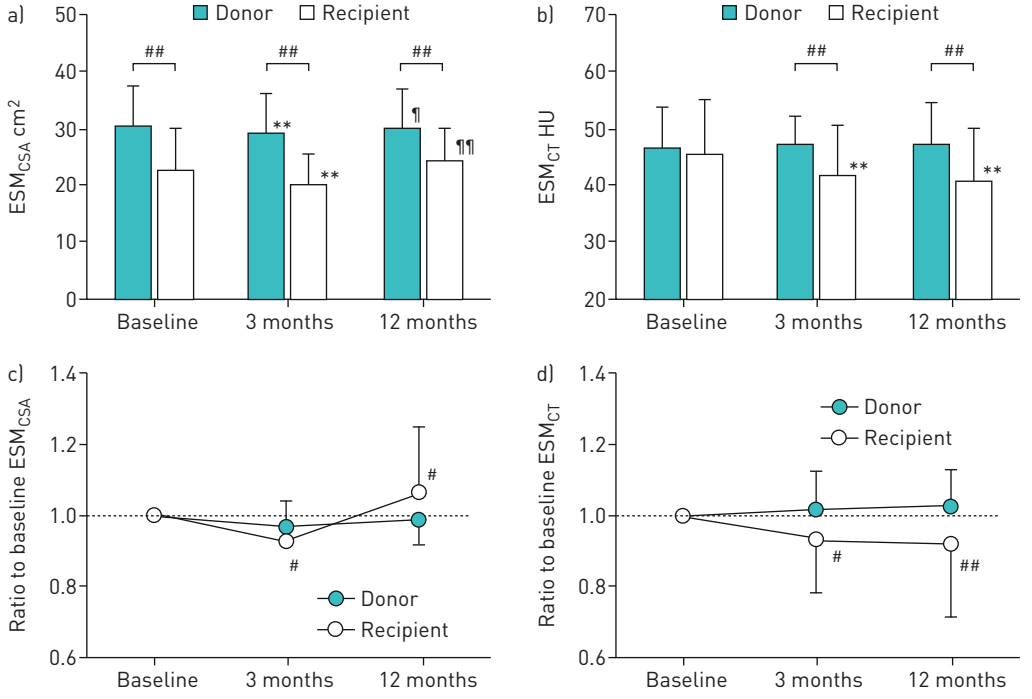

FIGURE 3 Time course of the postoperative changes in ESMs. Averages of the ESM_{CSA} (a) and ESM_{CT} (b) in the recipients (white) and donors (black) at each of the following time points: baseline, 3 months after LDLLT and 12 months after LDLLT. Ratios of the ESM_{CSA} (c) and ESM_{CT} (d) to baseline among the recipients (white) and donors (green) at each time point. **: p<0.01 compared to baseline; ¶: p<0.05, ¶¶: p<0.01 compared to 3 months; #: p<0.05, ##: p<0.01 by t-test.

TABLE 3 Differences in baseline characteristics and clinical courses between the groups with and without changes from baseline to 12 months after LDLLT in the ESM_{CSA} or ESM_{CT}

	ESM_{CSA} at 12 months after LDLLT			ESM_{CT} at 12 months after LDLLT		
	Ratio to baseline <1	Ratio to baseline ⩾1	p-value#	Ratio to baseline <1	Ratio to baseline ⩾1	p-value#
Patients n	15	20		28	7	
Female n (%)	9 (60%)	10 (50%)	0.57	15 (46%)	4 (43%)	0.87
mMRC score 0/1/2/3/4 n	0/0/0/8/7	0/0/0/8/12	0.43	0/0/0/13/15	0/0/0/3/4	0.60
Age years	49.9±11.1	44.5±14.4	0.23	46.3±13.4	48.6±12.9	0.69
BMI kg·m^{-2}	20.2±3.4	17.2±2.5	0.004	18.5±3.3	18.5±3.1	0.98
Albumin g·dL^{-1}	3.7±0.6	3.6±0.5	0.70	3.6±0.6	3.7±0.6	0.94
VC % predicted	47.3±16.8	42.1±17.7	0.44	45.4±18.2	41.8±13.8	0.66
FEV_1/FVC %	84.7±20.1	70.1±25.5	0.11	75.8±23.4	81.9±26.9	0.59
FEV_1 % predicted	47.6±18.3	30.8±16.4	0.02	38.7±19.2	39.7±19.9	0.91
D_{LCO} % predicted	21.5±16.5	28.7±9.9	0.40	25.2±15.3	17.5±7.4	0.51
6MWD m	225.7±107.9	195.6±103.0	0.47	204.5±107.7	228.6±95.5	0.65
ESM_{CSA} cm^2	26.3±8.2	20.6±5.3	0.02	23.0±7.1	23.2±8.2	0.95
ESM_{CT} HU	40.9±11.4	48.8±6.8	0.02	46.7±8.2	40.3±14.0	0.12
Predicted postoperative VC % predicted	59.0±10.8	63.6±17.6	0.37	61.5±16.4	62.3±8.5	0.65
Preoperative steroid use n (%)	8 (53%)	14 (70%)	0.33	19 (68%)	3 (43%)	0.23
Postoperative steroid pulse therapy n (%)	11 (73%)	14 (70%)	0.84	21 (75%)	4 (57%)	0.36
Postoperative cumulative steroid dose mg·kg^{-1}	148.4±30.7	150.5±23.6	0.81	147.7±26.3	157.1±28.0	0.41
Tacrolimus use n (%)	12 (80%)	8 (40%)	0.02	17 (61%)	3 (43%)	0.41
Tracheostomy n (%)	11 (73%)	9 (45%)	0.10	18 (64%)	2 (29%)	0.09
Duration of mechanical ventilation days	17.7±18.0	10.1±11.0	0.13	15.4±15.6	5.4±5.7	0.11
Initial walking, postoperative days	15.0±11.0	10.2±6.0	0.11	12.7±9.4	10.9±6.3	0.63
Intensive care unit stay days	13.5±7.8	10.4±3.5	0.12	12.5±6.0	8.4±4.1	0.10
Hospital stay days	96.9±67.3	78.0±21.0	0.24	85.2±51.6	89.6±22.1	0.83
Δ at 3 months of ESM_{CSA}, cm^2 (3 months – baseline)	−4.5±4.6	−0.6±1.8	0.001	−2.2±3.8	−2.5±4.0	0.86
Δ at 3 months of ESM_{CT}, HU (3 months – baseline)	−3.3±6.5	−3.9±5.8	0.79	−5.3±5.4	3.1±3.1	<0.001

Data are presented as mean±SD or n (%), unless otherwise stated. Δ at 3 months of ESM_{CSA} and ESM_{CT} were calculated by subtracting the values at baseline from those at 3 months (3 months – baseline). LDLLT: living-donor lobar lung transplantation; ESM_{CSA}: cross-sectional area of the erector spinae muscles; ESM_{CT}: mean computed tomography values of the erector spinae muscles; mMRC: modified Medical Research Council; BMI: body mass index; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance. #: Chi-squared test or t-test.

TABLE 4 Multivariate logistic regression analysis for increased ESM_{CSA} or ESM_{CT} from baseline to 12 months after LDLLT

Variable	Increased ESM_{CSA} at 12 months (ratio to baseline >1)			Increased ESM_{CT} at 12 months (ratio to baseline >1)		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
BMI kg·m^{-2}	0.88	0.61–1.25	0.48	–	–	–
ESM_{CT} HU	1.20	1.06–1.248	0.001	1.00	0.83–1.01	0.92
Tacrolimus use n	0.23	0.03–1.53	0.13	–	–	–
Tracheostomy n	–	–	–	0.40	0.032–4.05	0.44
Δ at 3 months of ESM_{CSA}, cm^2 (3 months – baseline)	2.54	1.31–7.22	0.002	–	–	–
Δ at 3 months of ΔESM_{CT}, HU (3 months – baseline)	–	–	–	1.60	1.17–2.62	0.001
R^2		**0.54**			**0.46**	

Increased ESM_{CSA} and increased ESM_{CT} at 3 months were calculated by subtracting the values at baseline from those at 3 months. ESM_{CSA}: cross-sectional area of the erector spinae muscles; ESM_{CT}: mean computed tomography values of the erector spinae muscles; LDLLT: living-donor lobar lung transplantation; BMI: body mass index; CI: confidence interval; R^2: coefficient of determination.

CSA of factors associated with exercise capacity after LDLLT

To evaluate the importance of ESMs for physical functional capacity (6MWD), cross-sectional univariate analyses were performed. The 6MWD was consistently associated with %VC, ESM_{CSA} and ESM_{CT} at each postoperative time point (table 5) in the univariate analysis. In the multivariate regression analysis, at 3 months after LDLLT, statistically significant contributing factors for the 6MWD were male sex, %VC, and ESM_{CT}, which had 60% explanatory power ($p<0.0001$); at 12 months after LDLLT, the significant contributing factors were ESM_{CT}, %VC, male sex, and age, which had 65% explanatory power ($p<0.0001$).

Discussion

In the present study, we focused on ESMs because they may reflect prognosis in patients with lung diseases such as COPD [18] or lung cancer resection [31]. We successfully revealed significant changes in the mass and quality of ESMs (ESM_{CSA} and ESM_{CT}) in patients after LDLLT. Although temporary decreases in ESM_{CSA} at 3 months were observed even in living donors, decreases were more apparent in LDLLT recipients than in living donors (−8% *versus* −4%). These temporary decreases were associated with delayed recovery at 12 months and were significant determinants of recovery independent of pulmonary function (%VC). In addition, both ESM_{CSA} and ESM_{CT} have significant impacts on exercise capacity in LDLLT recipients, and ESM_{CT} may have the more important role of the two. As a consequence, persistent decreases in ESM_{CT} may occur due to prolonged inactivity and medication, including systemic steroids. These findings have devastating and meaningful implications for the care of LDLLT recipients.

Although several reports have shown the time course of muscle mass before and after LTx [6, 15], the present report is the first to show the time course of both muscle quality and muscle quantity and the

TABLE 5 Univariate and multivariate analyses of factors associated with the 6MWD at 3 and 12 months after LDLLT

Variable	3 months				12 months			
	Univariate		Multivariate		Univariate		Multivariate	
	r	p	β	p	r	p	β	p
Age years	0.10	0.58	−0.19	0.20	−0.12	0.50	−0.28	0.030
Sex female=1	−0.52	0.002	−0.49	0.003	−0.36	0.04	−0.41	0.016
VC % predicted	0.59	0.004	0.55	0.006	0.61	<0.001	0.54	0.005
ESM_{CSA} cm^2	0.59	<0.001	−0.12	0.56	0.59	<0.001	−0.17	0.47
ESM_{CT} HU	0.54	0.001	0.29	0.037	0.65	<0.001	0.47	<0.001
R^2	–		0.60		–		0.65	

6MWD: 6-min walk distance; LDLLT: living-donor lobar lung transplantation; VC: vital capacity; ESM_{CSA}: cross-sectional area of the erector spinae muscles; ESM_{CT}: mean computed tomography values of the erector spinae muscles; HU: Hounsfield Units; r: Pearson's correlation coefficient; β: standardised coefficient; R^2: coefficient of determination.

significant impacts on exercise capacity after LDLLT. Our additional important findings are the temporary decreases in and later recovery of antigravity muscle mass after LDLLT. As we expected, surgery had a slight but significant impact on ESM_{CSA} in both the recipient and the living donor. Fortunately, living donors soon recovered their ESM_{CSA}, and ESM_{CT} did not change. In contrast, the recipients recovered their ESM_{CSA} and even surpassed baseline levels, but their temporal decrease was significantly greater than that of donors after 3 months. This difference in recovery may be partly because the recipients underwent a more invasive operation and required longer bed rest in the intensive care unit than the living donors. Although this decrease in ESM_{CSA} may be temporary and may even show promising recovery at the 12-month time point, decreased muscle mass may be an unfavourable sign in recipients and may lead to poor physical performance during postoperative periods. Short-term (3-month) changes in the ESM_{CSA} had a significant positive impact on long-term (12-month) increases in the ESM_{CSA} (table 4).

Compared with age-matched living donors, the recipients showed a 25% loss of ESM_{CSA} at baseline. This finding is consistent with, but much worse than, a previous report, which showed an almost 10% decrease in thoracic muscle mass [19]. It is possible that ESMs, which are antigravity muscles [23], may decrease more than other muscles in inactive subjects [32]. Compared to other muscles, ESMs might well reflect physical performance after LTx. Moreover, because of long waiting periods, LDLLT is performed in patients who are unable to wait for deceased-donor lungs, especially in Japan [27]. Therefore, LDLLT recipients may have more severe diseases and be more likely to be in an inactive state than candidates for dead-donor lung transplantation (DDLT).

The most important and significant findings of the present study were the time course and clinical impacts of ESM_{CT}. In contrast to ESM_{CSA}, the mean ESM_{CT} continuously decreased over the 12-month period (table 2, figure 3), and increases in ESM_{CT} rarely occurred (20%, n=7). Several medications, such as systemic steroids, may cause a loss of muscle quality after LDLLT [33, 34]. Almost all the recipients in this study had received systemic steroids, and more than half of the recipients received high-dose steroid pulse therapy during the acute phase after LDLLT. Although there was no significant correlation between cumulative steroid dose and loss of ESM_{CT} at any of the examined time points (data not shown), the paradoxical course of ESM_{CSA} and ESM_{CT} may be affected by the course of each recipient's medical treatment. Other explanations include inflammation [35], physical inactivity [32, 36], and malnutrition [37]. No cases showed remarkably high inflammation during this survey, except during the perioperative period. We were not able to consider the effects of the other factors, and these factors may have affected the loss of ESM. Nevertheless, we confirmed a significant relationship between short- and long-term changes in the ESM_{CSA} and ESM_{CT} (figure S1), and Δ at 3 months of ESM_{CT} (changes during 3 months after LDLLT) were a significant determinant of increased ESM_{CT} at 12 months (table 4). In future research, we need to investigate the causes of skeletal muscle loss within 3 months after surgery, and approaches to prevent the short-term deterioration of muscle quantity and quality must be considered.

Another important finding is the importance of muscle quality rather than muscle quantity. The longitudinal benefits for physical functional capacity (6MWD) in the recipient after LDLLT may be due to VC recovery; however, the quality of the antigravity muscles (ESM_{CT}) is also noteworthy. In the multiple regression analysis, the ESM_{CT} had a close correlation with the 6MWD and was a consistent predictor thereof. Skeletal muscle attenuation, as measured by CT, is associated with skeletal muscle lipid content [20], and muscle lipid content may result in insulin resistance, metabolic activity and poor oxygen uptake [38], leading to low muscle performance [21]. Moreover, notably, the ESM_{CT} at baseline may predict an increase in muscle quantity after LDLLT, suggesting that muscle quality is important to the future recovery of muscle function. Taaffe *et al.* [39] reported that 12 weeks of high-intensity resistance training improved thigh muscle CT attenuation by approximately 5% in older adults. Physical training may be applicable to patients with chronic respiratory disease or lung transplant recipients.

This study has several limitations. First, the small sample size is a critical limitation. The sample size was restricted partly because we enrolled only LDLLT recipients. Since we intended to evaluate the time course before and after LTx, we needed to evaluate recipients immediately before LTx. Due to time limitations and long waiting times, it is difficult to examine DDLT recipients immediately before LTx. Second, we included both males and females but did not analyse them separately. Sex-based differences should be considered, but sex-based differences in the 6MWD, at least, were captured in the regression analysis. We definitely need to evaluate larger samples of LTx recipients as well as DDLT recipients. Third, there are several concerns regarding methods for quantifying skeletal muscle quality using CT images. In fact, other imaging modalities, such as magnetic resonance imaging and spectroscopy, may provide more precise evaluations [40]; however, it is difficult to conduct such imaging studies in clinical settings. Finally, we could not identify the mechanisms underlying the changes in ESM_{CSA} and ESM_{CT}. We speculate that systemic steroids and persistent inactivity may increase the lipid content of skeletal muscles. To achieve better prognosis for LDLLT recipients, increased physical activity and comprehensive long-term

interventions are needed. Further analysis is required to confirm this speculation and should include chest CT evaluations of whole muscles and their heterogeneity.

In conclusion, this study is the first to demonstrate the time course of postoperative changes in both the quantity and quality of skeletal muscle in lung transplant recipients. Skeletal muscle quality determined by chest CT imaging was a dominant factor contributing to exercise capacity in LDLLT recipients and future postoperative recovery of muscle quantity after LDLLT. Approaches to prevent deterioration of muscle quality should be considered both before and after LDLLT.

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