Original Article

Sarcopenia of thoracic muscle mass is not a risk factor for survival in lung transplant recipients

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Background: In lung transplantation (LTx), patients with thoracic muscle sarcopenia may have to require longer to recovery. We measured thoracic muscle volume by using the cross sectional area (CSA) and assessed its effect on early outcomes after LTx.

Methods: A retrospective analysis was conducted to evaluate the effect of thoracic sarcopenia in patients undergoing LTx between January 2010 and July 2015. The lowest CSA quartile (Q1) was defined as sarcopenia.

Results: In total, 109 patients were enrolled. The mean CSA was 58.24±15.82 cm^2. Patients in the highest CSA quartile were more likely to be male (92.6% *vs.* 17.9%, P<0.001), older (55.2±10.1 *vs.* 43.2±14.9 years, P=0.001), to have a higher body mass index (BMI) (22.3±4.0 *vs.* 19.4±3.7 kg/m^2, P=0.007), and to have pulmonary fibrosis (85.2% *vs.* 35.7%, P=0.003) compared with the lowest CSA quartile. Early outcomes including ventilator support duration [32.9±49.2 *vs.* 24.5±39.9 days, P= not significant (ns)], intensive care unit (ICU) stay duration (28.4±43.7 *vs.* 24.4±35.9 days, P= ns) and hospital stay duration (61.4±48.2 *vs.* 50.8±37.2 days, P= ns) tended to be longer in Q1 than Q4, but the difference was not significant. However, the 1-year survival rate was better in Q1 compared with Q4 (66.6% *vs.* 46.0%, P=0.04).

Conclusions: Although patients with thoracic sarcopenia seem to require a longer post-operative recovery time after LTx, this does not compromise their early outcomes. By contrast, patients with larger thoracic muscle volume (Q4) showed poorer survival times.

Keywords: Lung transplantation (LTx); sarcopenia; thoracic muscles; cross sectional area (CSA)

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Introduction

Lung transplantation (LTx) is the only treatment option for patients with end stage lung disease whose respiratory function is declining. Many candidates for LTx suffer from chronic disease and two thirds of them have reduced muscle mass (1). Maintaining skeletal muscle mass and strength seems to be essential for patients to recover after LTx (2-4).

Sarcopenia, which can be defined as low muscle mass and associated decreased muscle strength or function (5), leads to physical disabilities, poor quality of life, and death in older patients. Sarcopenia has also been reported to be associated with a poor survival outcome following liver (6) and renal (7) transplantation. In chronic lung disease patients, quadriceps strength (8), body composition (9), and mid-thigh cross sectional area (CSA) (10) have been reported to be related to mortality.

Several modalities have been used to assess sarcopenia.

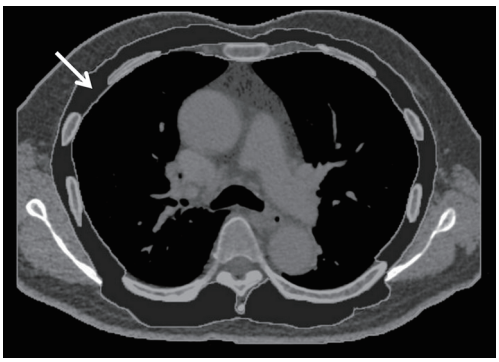

Figure 1 Thoracic muscle cross sectional area (CSA) was measured by using outline of pectoralis, intercostal and paraspinal muscles in chest computed tomography at the carina from caudal (the white arrow indicated thoracic muscles).

Computed tomography (CT) (10), magnetic resonance imaging (MRI) (11), bioelectrical impedance (BIA) (12), anthropometry (13), and dual-energy X-ray absorptiometry (DXA) (14) have been used to assess muscle mass, while handheld and computerized dynamometry have been used to measure hand grip and quadriceps strength (3,15). Short Physical Performance Battery and usual gait speed can assess functional status (16-18). The 6-minute walk test is the most commonly used modality to assess functional status but it cannot index isolated muscle function as part of the sarcopenia definition (5).

Some studies of LTx patients have focused on low muscle mass and the importance of rehabilitation after LTx (3,4), but the clinical effect of sarcopenia on LTx outcome has not been studied until now. In this study, we hypothesized that thoracic skeletal muscle mass measured by analyzing the CSA from a chest CT image could be a predictor of early outcomes and survival after LTx, and can also be used to assess the suitability of lung transplant candidates.

Methods

Patients

This study was approved by the Severance Hospital Institutional Review Board (4-2016-0129). We retrospectively reviewed the medical records of 111 patients who underwent LTx at our institution between January 2010 and July 2015. Age, sex, underlying diseases, height and weight at the time of the operation, post-operative course and mortality data were collected for all patients; data on thoracic muscle CSA were available in 109 of the patients.

Measurement of thoracic skeletal muscle CSA

The thoracic muscle CSA at the level of the carina was determined based on a study performed by Rozenberg *et al.* (19). The first single slice identifying at carina level on each patient's chest CT scan was selected. We then outlined the borders of the thoracic skeletal muscle (pectoralis, intercostal and paraspinal muscles) in the CSA, and the area was measured (*Figure 1*). These steps were completed semi-automatically using Aquarius iNtuition Viewer (ver. 4.4.11, TeraRecon Inc., San Mateo, CA, USA). A radiology technician performed these steps without access to patient information.

Statistical analysis

Statistical analysis was performed using Student's *t*-test or ANOVA (two-tailed) and the chi-square test. The correlation between the CSA and body mass index (BMI) was analyzed using Pearson's correlation coefficient. Survival was analyzed with the Kaplan-Meier method. The Log-rank test was used to determine statistical significance. Multivariate analysis was performed using the Cox proportional hazards regression model to investigate the effects of several variables on survival. The criterion for statistical significance was $P<0.05$. SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, USA) was used to perform the analyses.

Results

There were 48 female and 61 male patients, with a mean age of 49.7±13.9 years (range, 16–75 years). Patient characteristics are summarized in *Table 1*. The mean CSA was 58.2±15.8 cm^2 (range, 25.4–93.3 cm^2). The median interval between the date of the CT scan and the date of LTx was 2 months (range, 0–20 months). The scatter diagram in *Figure 2* shows that the CSA and BMI were positively correlated ($r=0.367$, $P<0.001$).

We divided the patients into four groups according to CSA to visualize the effects of both the highest and lowest quartile CSA (*Table 2*). Patients in the highest CSA quartile (Q4; 79.7±6.7) were more likely to be male (92.6% *vs.* 17.9%, $P<0.001$) and older (55.2±10.1 *vs.* 43.2±14.9 years, $P=0.001$), to have a higher BMI (22.3±4.0 *vs.* 19.4±3.7 kg/m^2, $P=0.007$) and to have more pulmonary fibrosis (85.2% *vs.* 35.7%, $P=0.003$) compared with the lowest CSA quartile (Q1; 39.4±5.2) (*Table 2*).

Table 1 Recipient characteristics

Variables	Data
Age, years	49.7±13.9 (16.0–75.0)
Male	61 (56.0)
Body mass index, kg/m^2	20.6±3.9 (12.3–33.5)
Cross sectional area, cm^2	58.2±15.8 (25.4–93.3)
Disease entity	
Pulmonary fibrosis	73 (67.0)
Bronchiolitis obliterans	13 (11.9)
Bronchiectasis	10 (9.2)
Lymphangioleiomyomatosis	9 (8.3)
Other	4 (3.6)
Transplant type	
Single	10 (9.2)
Double	99 (90.8)

Data are presented as number of patients (%) or mean ± standard deviation (range).

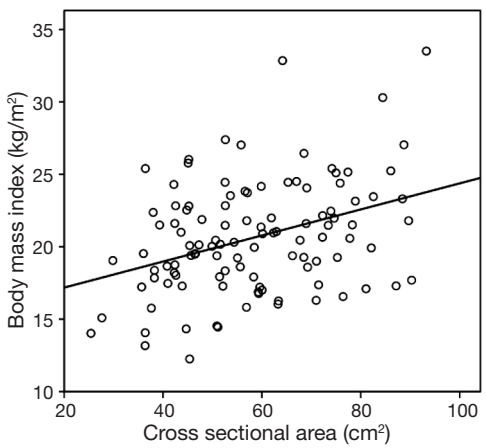

Figure 2 Scatter diagram demonstrating the correlation between thoracic muscle mass cross sectional area (cm^2) and body mass index (kg/m^2). A positive relationship is noted (r=0.367, P<0.001).

Early post-operative recovery times including ventilator support duration (32.9±49.1 *vs.* 24.5±39.5 days, P=0.488), intensive care unit (ICU) stay duration (28.4±43.7 *vs.* 24.4±35.9 days, P=0.714) and hospital stay duration (61.4±48.2 *vs.* 50.8±37.2 days, P=0.367) showed longer trends in Q1 compared with Q4, but the difference was not significant. Early (≤30 days) mortality (7.1% *vs.* 11.1%, P=0.669) and 90 days mortality (28.6% *vs.* 29.6%, P= ns) were not different between Q1 and Q4 (*Table 3*).

Survival was analyzed according to CSA quartile. The highest CSA (Q4) showed poorer survival compared to sarcopenia (Q1; P=0.044), Q2 (P=0.094) and Q3 (P=0.583). When Q4 was compared to the other groups simultaneously (Q1, Q2, Q3), poorer survival times were noted, but the difference was not statistically significant (P=0.063) (*Figure 3*). Sarcopenia (Q1) was not a risk factor for survival.

Discussion

The first human LTx was performed in 1963 (20), and the first successful LTx was reported in 1983 (21). Thereafter, the quantity of LTx operations has increased significantly, and 3,893 adult LTx procedures were performed worldwide in 2013 (22). LTx is the only therapeutic option available to patients with end-stage lung diseases of various nonmalignant etiologies in whom medical therapy has failed. Survival following LTx has steadily increased over time, and risk factors for early and late outcomes have been studied to improve survival.

Many transplant recipient factors, such as old age, type of disease, increased severity of illness (e.g., ICU stay, ventilator support), lower cardiac output and higher creatinine levels have been identified as risk factors for increased mortality in the International Society for Heart and Lung Transplantation (ISHLT) Registry (22).

BMI is considered a risk factor for death after LTx. Obesity and decreased body weight, which are defined using BMI, have been considered relative contraindications for LTx (23,24). In previous studies, obesity (BMI greater than 30 kg/m^2) was considered a relative contraindication to LTx (25), and these patients had a marked decrease in post-transplantation survival rate (26). A recent study suggested that higher levels of plasma leptin and adipose tissue were detected in patients with obesity, factors that may be associated with primary graft dysfunction (27). Therefore, obesity was associated with an increased mortality rate after LTx. However, another study suggested that obesity is not associated with 1-year mortality after LTx, and a BMI greater than 30 kg/m^2 may no longer represent a contraindication (28). Overall, controversy surrounds interpretation the relationship between obesity and survival rates in LTx patients.

In addition, the relationship between low body mass and a poor outcome after LTx has not been fully elucidated. In order to explain this problem, sarcopenia has emerged as a potential risk factor (2,23), but it is not clear whether sarcopenia is an independent risk factor for survival.

Table 2 Characteristics according to cross sectional area (CSA)

Variables	Q1 (n=28)	Q2 (n=27)	Q3 (n=27)	Q4 (n=27)	P value (Q1 *vs*. Q4)
Age, years	43.2±14.9	46.3±15.3	54.3±10.9	55.2±10.1	0.001
Male	5 (17.9)	9 (33.3)	22 (81.5)	25 (92.6)	<0.001
Body mass index, kg/m^2	19.4±3.7	20.0±3.5	20.8±3.8	22.3±4.0	0.007
CSA, cm^2	39.4±5.2	51.3±3.5	63.3±6.7	79.7±6.7	<0.001
Disease entity					0.003
Pulmonary fibrosis	10 (35.7)	18 (66.7)	22 (81.5)	23 (85.2)	
Bronchiolitis obliterans	5 (17.9)	4 (14.8)	2 (7.4)	2 (7.4)	
Bronchiectasis	6 (21.4)	0	3 (11.1)	1 (3.7)	
Lymphangioleiomyomatosis	5 (17.9)	4 (14.8)	0	0	
Other	2 (7.1)	1 (3.7)	0	1 (3.7)	
Transplant type					ns
Single	2 (7.1)	1 (3.7)	6 (22.2)	1 (3.7)	
Double	26 (92.9)	26 (96.3)	21 (77.8)	25 (92.6)	

Data are presented as number of patients (%) or mean ± standard deviation (range). Q, quartile; ns, not significant.

Table 3 Intraoperative data and early outcomes

Variables	Q1 (n=28)	Q2 (n=27)	Q3 (n=27)	Q4 (n=27)	P value (Q1 *vs*. Q4)
Pre-operative support					
ECMO	7 (25.0)	4 (14.8)	4 (14.8)	4 (14.8)	0.503
Ventilator	12 (42.9)	6 (22.2)	7 (25.9)	8 (29.6)	0.582
Intra-operative ECLS support					0.135
CPS	5 (17.9)	6 (22.2)	7 (25.9)	7 (25.9)	
ECMO	17 (60.7)	20 (74.1)	17 (63.0)	19 (70.4)	
Ischemic time before 1st graft, min	227.1±64.8	225.4±82.3	231.7±79.6	247.1±111.3	0.416
Post-operative support					
ECMO	8 (28.6)	13 (48.1)	8 (29.6)	12 (44.4)	0.269
Ventilator, day	32.9±49.1	12.1±13.9	18.3±25.0	24.5±39.5	0.488
Intensive care unit stay, day	28.4±43.7	13.9±13.2	21.9±21.4	24.4±35.9	0.714
Hospital stay, day	61.4±48.2	50.1±49.9	45.9±35.1	50.8±37.2	0.367
30 days mortality	2 (7.1)	4 (14.8)	6 (22.2)	3 (11.1)	0.669

Data are presented as number of patients (%) or mean ± standard deviation. Q, quartile; ECMO, extracorporeal membrane oxygenator; ECLS, extracorporeal life support; CPS, cardiopulmonary support.

Sarcopenia has been defined as decreased muscle mass and peripheral muscle strength or function (5). However, exact definition of sarcopenia and standardized measurement techniques have not yet been established in LTx patients (2). Several methods of measuring sarcopenia have been used to assess muscle mass (quadriceps, triceps), muscle strength (quadriceps strength, hand-grip strength) and muscle function in patients with lung disease (5,29). In this study, sarcopenia of thoracic skeletal muscles was assessed by analyzing a CSA from chest CT images and defined as the lowest quartile of CSA (Q1).

Sarcopenia (quadriceps strength) is a risk factor for survival in patients with chronic obstructive pulmonary disease (COPD) (8), and patients treated with LTx showed similar changes in muscle mass and strength to patients with COPD (11). Furthermore, sarcopenia has been associated

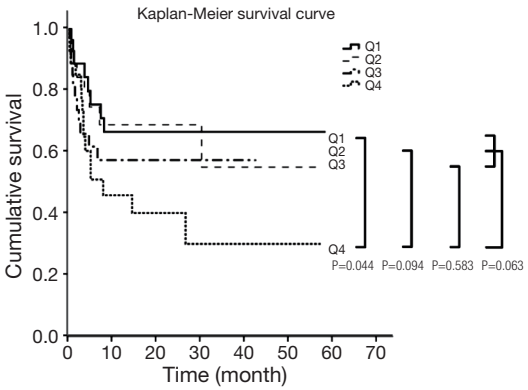

Figure 3 Kaplan-Meier curve shows that highest cross sectional area (CSA) Q4 showed poorer survival compared to Q1 (P=0.044) and Q2 (P=0.094) and Q3 (P=0.583). Also, Q4 had poorer survival than other groups together, but not statistically significant (Q4 *vs.* Q1 + Q2 + Q3, P=0.063).

with poor post-transplantation outcomes in liver and renal transplant recipients (6,7), therefore, we hypothesize that it may negatively impact survival following LTx.

Previous studies on sarcopenia have focused on physical activity and rehabilitation in LTx patients, and the quadriceps muscle is mainly used in the context of skeletal muscle assessment (3,30-32). Thoracic muscles and major respiratory muscles have been surgically dissected; nevertheless, sarcopenia of thoracic muscles in LTx patients has not been fully evaluated. Recently, Rozenberg *et al.* (19) suggested that the thoracic muscle CSA is related to physical activity, quadriceps volume, and health-related quality of life after LTx, but survival was not assessed. Therefore, the present study was designed to investigate the relationship between thoracic sarcopenia and survival after LTx.

When we began our study, we assumed that thoracic sarcopenia was related to BMI, which would negatively affect the early outcomes (ventilator support, ICU stay, and hospital stay) and early survival. Like other muscles (quadriceps, triceps) (33), respiratory muscles have been correlated with BMI, as shown in *Figure 2*. Early survival tended to be longer in sarcopenia (Q1), but the difference was not statistically significant (*Table 3*). Also, the survival of LTx patients was not affected by sarcopenia (Q1); by contrast, Q1 was associated with better survival than Q4 (*Figure 3*).

The increased survival of Q1 compared with Q4 after LTx may be explained as follows. The first possible explanation is that sarcopenia of the thoracic muscles may not be a modifiable risk factor. Quadriceps muscle atrophy can be caused by medications (corticosteroids or immunosuppressants) or inactivity after LTx (11,34), and rehabilitation leads to recovery of skeletal muscle function (3). Pinet *et al.* (34) reported that the diaphragm and abdominal respiratory muscle volume are preserved, but the quadriceps can atrophy, after transplantation (12 patients; 5 of whom underwent heart-LTx and 7 who underwent LTx). Thoracic muscles are constantly exercised by respiratory movements even on mechanical ventilation, and thus thoracic muscles may not atrophy similarly like the diaphragm or abdominal respiratory muscles. Therefore, we suggest that it may be more accurate to assess the quadriceps rather than the thoracic muscle to analyze survival in LTx patients.

Second, Q4 may be related to a high BMI. The thoracic muscle CSA showed a linear correlation with BMI (*Figure 2*), and a high BMI was a risk factor for LTx, although reports were controversial. Third, these results may be due to the heterogeneity of the patient population used in this study. In Q4, patients tended to be older males with pulmonary fibrosis (*Table 2*). However, these factors (age, sex, and diagnosis) were not independent risk factors for survival in subgroup multivariate analysis (data not shown). Lastly, there is no standard definition of sarcopenia, although in this study we defined it as Q1. Considering these possible causes, more studies are required to better understand sarcopenia of thoracic muscles in patients undergoing LTx.

The limitations of this study include its retrospective, single-center design and clinically heterogeneous patient population. These limitations notwithstanding, it is important to note that the present study attempted to analyze the association between thoracic sarcopenia and outcome after LTx.

In conclusion, sarcopenia of thoracic muscle mass did not compromise either the early outcome or 1-year survival in LTx patients. More studies are needed to clarify the relationship between thoracic sarcopenia and outcomes in LTx patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Severance Hospital Institutional Review Board (4-2016-0129).

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