ORIGINAL ARTICLE

Thoracic muscle cross-sectional area is associated with hospital length of stay post lung transplantation: a retrospective cohort study

Dmitry Rozenberg[1,2], Sunita Mathur[3,*], Margaret Herridge[1,4], Roger Goldstein[1,5], Heidi Schmidt[6], Noori A. Chowdhury[2], Polyana Mendes[3] & Lianne G. Singer[1,2,*]

1 Department of Medicine, Respirology, University of Toronto, Toronto, ON, Canada
2 Lung Transplant Program, University Health Network, Toronto, ON, Canada
3 Department of Physical Therapy, University of Toronto, Toronto, ON, Canada
4 Critical Care, University Health Network, Toronto, ON, Canada
5 Respirology, West Park Healthcare Center, Toronto, ON, Canada
6 Department of Medical Imaging, University of Toronto, Toronto, ON, Canada

Correspondence
Dr. Lianne G. Singer, Toronto General Hospital, 585 University Avenue, 11 PMB 134, Toronto, ON M5G 2N2, Canada.
Tel.: +1 (416)-340-4996;
fax: +1 (416) 340-3609;
e-mail: Lianne.Singer@uhn.ca

*Both authors contributed equally to this manuscript.This work was in part presented at the ISHLT meeting in 2015 (Nice, France). Rozenberg D, *et al. The Journal of Heart and Lung Transplantation* 34 (4S), April 2015.

SUMMARY

Low muscle mass is common in lung transplant (LTx) candidates; however, the clinical implications have not been well described. The study aims were to compare skeletal muscle mass in LTx candidates with controls using thoracic muscle cross-sectional area (CSA) from computed tomography and assess the association with pre- and post-transplant clinical outcomes. This was a retrospective, single-center cohort study of 527 LTx candidates [median age: 55 IQR (42–62) years; 54% male]. Thoracic muscle CSA was compared to an age- and sex-matched control group. Associations between muscle CSA and pre-transplant six-minute walk distance (6MWD), health-related quality of life (HRQL), delisting/mortality, and post-transplant hospital outcomes and one-year mortality were evaluated using multivariable regression analysis. Muscle CSA for LTx candidates was about 10% lower than controls (n = 38). Muscle CSA was associated with pre-transplant 6MWD, but not HRQL, delisting or pre- or post-transplant mortality. Muscle CSA (per 10 cm^2 difference) was associated with shorter hospital stay [0.7 median days 95% CI (0.2–1.3)], independent of 6MWD. In conclusion, thoracic muscle CSA is a simple, readily available estimate of skeletal muscle mass predictive of hospital length of stay, but further study is needed to evaluate the relative contribution of muscle mass versus functional deficits in LTx candidates.

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Introduction

Lung transplantation improves health-related quality of life (HRQL) [1], exercise capacity [2], and survival [3,4] in people with advanced lung disease. However, optimal selection of lung transplant candidates is critical given the morbidity and mortality associated with transplantation. One fifth of lung transplant candidates die or are de-listed prior to receiving a transplant and the mortality rate post-transplant is almost 20% in the first year

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[5,6]. Despite improvements in medical management and surgical techniques, there is a growing need for novel assessments of physical function and body composition that could aid with risk stratification and management in this population [7].

Sarcopenia, defined as age-related loss of muscle mass and function, is related to increased physical disability, impairments in HRQL and death in older adults and is accelerated in chronic disease states [8,9]. Low muscle mass has been independently associated with reduced post-transplant survival in liver and renal transplant recipients [10,11]. In lung transplant patients, low muscle mass has been observed to be prevalent using bioelectrical impedance [12]; however, measures of muscle mass have not been routinely utilized for prognostication in lung transplantation [13].

A practical method for quantifying segmental muscle mass is computed tomography (CT), which is considered a gold-standard for muscle size measurement [14,15]. Muscle cross-sectional area (CSA) taken from a single axial slice from abdominal CT has been shown to be a good marker of total body skeletal mass [16]. In those undergoing major abdominal surgeries, low psoas muscle size from abdominal CT has been associated with increased post-operative complications, healthcare costs, and increased mortality [17–19]. In a recent systematic review of 19 studies in liver transplantation, low skeletal muscle mass quantified with abdominal CT was prevalent (range 22–70%) and associated with waiting list and post-transplant mortality [20]. Similarly, in lung transplant patients, muscle CSA from abdominal CT has been associated with post-transplant outcomes such as intensive care unit (ICU) [21] and hospital length of stay [22]. In patients with chronic obstructive pulmonary disease (COPD), muscle CSA from chest CT has been associated with disease severity [23,24], exercise capacity [23], and mortality [24]. We have recently shown that measures of thoracic muscle CSA from a single axial slice of the chest correlated well with accepted measures of muscle mass and were reproducible in lung transplant candidates [25]. Chest CT muscle CSA could prove to be a valuable marker in risk stratification given the availability of chest CT in clinical practice. To our knowledge, the clinical implications of muscle CSA with respect to pre-transplant de-listing/mortality, HRQL, and strength training volumes have not been previously described. Furthermore, the incremental utility of muscle CSA to predict post-transplant outcomes compared to established parameters such as the six-minute walk distance (6MWD) remains unknown [26,27].

The aims of this study were to compare thoracic muscle CSA in lung transplant candidates with controls and to assess the associations of thoracic muscle CSA with 6MWD, strength training volumes, HRQL, pre- and post-transplant clinical outcomes. The secondary aim was to evaluate the prognostic utility of muscle CSA as an adjunct to pre-transplant 6MWD in predicting early post-transplant outcomes. We hypothesized that muscle CSA would be significantly reduced in lung transplant candidates and independently associated with functional capacity, pre-transplant de-listing/death, and early post-transplant outcomes, independent of 6MWD.

Methods

Study design and participants

This was a retrospective cohort study of adult lung transplant candidates (age $\geq$ 18 years) listed at University Health Network between November 1, 2003 and May 30, 2009. This period was chosen due to an available set of exercise data from a prior study [28]. For inclusion in the current study, patients had to have a chest CT within 3 months of transplant listing. Lung transplant patients who were listed for a re-transplant during the study period were excluded. Research ethics approval was obtained from University Health Network (REB # 13-6430-BE).

The control group was comprised of 38 participants matched for age ($\geq$ 50 years old) and sex who underwent lung cancer screening with low dose CT, as part of a research study at University Health Network [29]. All participants had at least a 10 pack-year smoking history, had generally good health, and no history of malignancy. The sample size was based on the assumption that thoracic CSA would be 20% lower for lung transplant candidates than controls (effect size = 1.0, n = 17 for each sex). Previous studies have demonstrated that peripheral measures of muscle mass (i.e. quadriceps CSA) were about 20% lower in COPD patients compared with controls [30,31].

Muscle cross-sectional area assessment

Thoracic CT (1–5 mm slices) were acquired on a Toshiba Aquilion scanner as part of routine clinical evaluation for lung transplantation. The CT scan utilized for analysis was within 3 months of transplant listing. Muscle CSA of the pectoralis major and minor, intercostals, serratus anterior, paraspinal, and latissimus dorsi muscles was quantified from CT using Slice-O-

matic software (Version 5.0; Tomovision, Montreal, Canada) [32], Hounsfield unit ranges of −29 to 150, Fig. 1 [33]. The average of three slices, one at the carina level and one slice above and below, was used to quantify muscle CSA. The same technique was applied to the control group using low dose thoracic CT images (1–1.25 mm slices).

We have previously demonstrated that thoracic muscle CSA from a single axial CT slice correlates strongly with thoracic muscle volume ($r = 0.89–0.91$, $P < 0.001$) and has excellent inter-rater reliability [25]. The inter-rater reliability for this study was re-assessed in the first twenty subjects, between two observers (D.R and P.M) at the carinal level (ICC = 0.998, 95% CI 0.995–0.999). Given the high ICC values, muscle CSA for the remaining subjects was assessed by one observer (D.R).

Clinical variables

The following variables were abstracted from the medical records and Toronto Lung Transplant clinical database at the time of transplant listing: Age (years), sex, anthropometric measurements [weight (kg), height (cm), and body mass index (BMI, kg/m^2)], diagnostic indication for transplant, daily corticosteroid use, albumin (g/l), and need for bridging to lung transplantation with mechanical ventilation or extra-corporeal life support. The listing urgency status (Status 1, 2 and Rapidly deteriorating) was assessed at the time of transplant listing, which is a subjective determination of disease severity predictive of waiting list survival [34].

Exercise capacity was evaluated using the 6MWD (meters), which was routinely performed within 4 weeks of transplant listing by a physical therapist as per American Thoracic Society guidelines [35,36] and reported as percent predicted [37]. All lung transplant candidates at our center participate in a mandatory pulmonary rehabilitation program three times per week, which is initiated at the time of listing and is ongoing for the waitlist duration [28,38]. As a surrogate of muscle strength, biceps and quadriceps strength training volumes at the start of pulmonary rehabilitation (end of first week) were calculated from training logs on a subset of patients as follows: [# repetitions * weight (pounds) * # sets] [28]. Training volumes were calculated at the start of rehabilitation to reduce the influence of any training effect with rehabilitation.

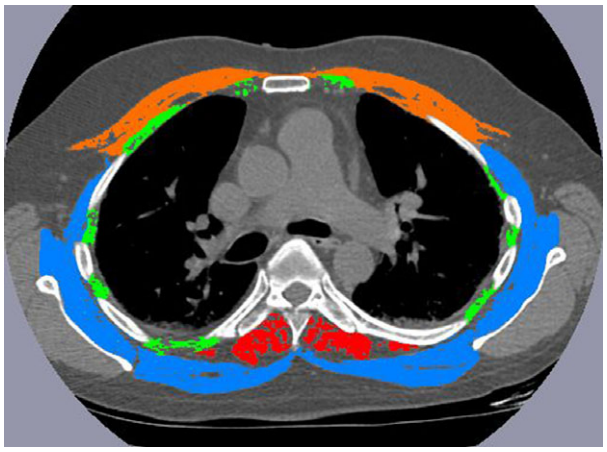

Figure 1 Representation of cross-sectional muscle area using slice-O-matic software. Thoracic muscles: Orange = pectoralis; Green = intercostal muscles; Red = para-spinal muscles; Blue = serratus anterior and latissimus dorsi muscles.

Short-Form 36 (SF-36) and St. George's Respiratory Questionnaire (SGRQ) were available in a subset of patients within 3 months of transplant listing from a completed prospective study on HRQL [1]. We included the SF-36 physical function domain, SF-36 physical component score, and the activity domain of the SGRQ given their associations with physical activity in lung transplant patients [39,40].

Pre-transplant clinical outcomes assessed were medical delisting or death. We treated these two as a composite outcome and patients were medically delisted if they were too ill to derive benefit from lung transplantation. Post-transplant outcomes included: days of mechanical ventilation, ICU days, hospital length of stay, mortality in hospital and at 1 year, and development of grade 3 primary graft dysfunction (PGD) at 72 h as per International Society of Heart-Lung Transplant consensus definition (PaO_2/FiO_2 ratio of <200 mmHg or requirement for extra-corporeal membrane oxygenation or nitric oxide) [41]. Grade 3 PGD was specifically evaluated as it is associated with post-transplant mortality [42]. Discharge disposition (home versus inpatient rehabilitation) was also documented. The standard practice at our center is for lung transplant recipients to participate in an outpatient rehabilitation program for at least 3 months post-transplant; however, recipients that are unable to meet functional requirements for safe discharge home are referred to an inpatient rehabilitation program [26]. Pre- and post-transplant outcomes were abstracted from the Toronto Lung Transplant clinical database.

Statistical analysis

Analysis was performed using GRAPH-PAD PRISM (Version 7.0) and R (Version 3.32). Continuous variables are described using mean ± standard deviation or median

[interquartile range 25–75%] with categorical variables described using frequencies. Visual inspection of scatter plots, Kolmogorov-Smirnov, and Pearson omnibus normality tests were used to assess the distribution of data. Muscle CSA of lung transplant candidates aged 50–69 years versus controls in the same age group were compared using an unpaired *t*-test with Welch's correction, stratified by sex.

Crude and adjusted associations between muscle CSA and 6MWD, strength training volumes, HRQL, and pretransplant medical delisting/death and post-transplant outcomes were assessed using linear and logistic regression analyses. Covariates were selected based on previously described associations with muscle mass [age, sex, height-squared (m^2), and diagnosis] with additional clinically relevant co-variates outlined in the results section. Logistic regression analyses examined the association of muscle CSA with the development of grade 3 PGD at 72 h and mortality on the post-transplant admission and at 1 year. After exclusion of patients who died during the hospitalization post-transplant, adjusted quantile regression was used to assess the relationship of pre-transplant muscle CSA with median time-based post-transplant outcomes (days of mechanical ventilation, ICU and hospital length of stay). Discharge disposition (home versus inpatient rehabilitation) was assessed using logistic regression. Pre-transplant 6MWD was included in post-transplant multivariable regression models to assess the incremental utility of muscle CSA in prediction of early post-transplant outcomes.

We performed model diagnostics examining plots of residuals to ensure assumptions of independence, normality and constant variation of errors were met. A P value of < 0.05 was considered significant for all analyses.

Results

Participants

There were 527 lung transplant candidates included in the study, Fig. 2. Baseline characteristics are described in Table 1. The mean muscle CSA for the lung transplant cohort was 94 ± 25 cm^2. Greater muscle CSA was associated with male sex, greater BMI, height, and a diagnosis of interstitial lung disease (ILD) or cystic fibrosis (CF), Table 1. Muscle CSA was not associated with age, daily prednisone use, albumin levels, or listing status (Table 1).

Muscle CSA in lung transplant candidates and healthy controls

When stratified by sex and age (50–69 years), lung transplant candidates had 10% lower muscle CSA than controls, matched for BMI (Fig. 3). Muscle CSA was as follows: [Males: LTx (n = 183): 106 ± 20 vs. Controls

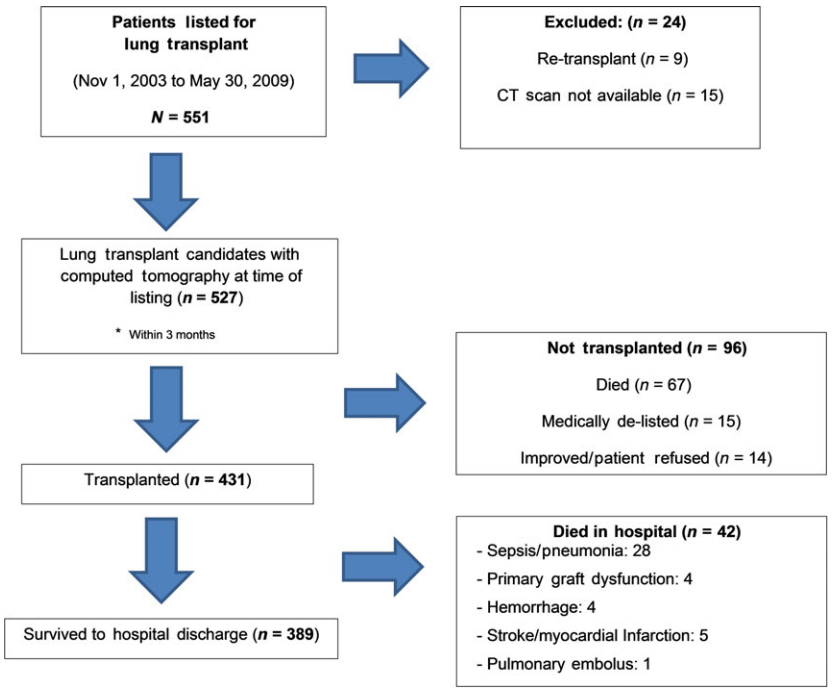

Figure 2 Flow diagram of lung transplant candidates included in the study.

(n = 19) 117 ± 12 cm^2, P = 0.002 and Females: LTx (n = 131): 72 ± 15 vs. Controls (n = 19): 80 ± 8 cm^2, P = 0.001).

Six-minute walk distance, strength training volumes, and quality of life

The lung transplant candidates had low 6MWD (46 ± 17% predicted) and HRQL [SF-36 PCS: 27 ± 8 and SGRQ Activity Domain: 92 (79–92)]. 6MWD, strength training volumes, and HRQL were associated with muscle CSA in the crude analysis (Table 2). This relationship remained significant for 6MWD and strength training volumes when adjusted for age, sex, height-squared, and diagnosis, Table 2. For instance, for every 10 cm^2 increase in muscle CSA, 6MWD increased by 9.3 m 95% CI (3.7–14.9), P = 0.001, R^2 = 0.23. The strength of the association with muscle CSA was stronger for biceps training volumes than quadriceps (R^2 0.21 vs. 0.10) after adjustment. There was no independent relationship observed between available HRQL measures and muscle CSA after adjustment for covariates (Table 2). Lung transplant candidates with available HRQL data (n = 400) compared to those without (n = 127) had greater 6MWD and were more likely to be transplanted with no difference in muscle CSA or demographics observed between the two groups (Table 3).

Pre-transplant clinical outcomes

Of the 527 lung transplant candidates, n = 15 (3%) were medically delisted, n = 67 (13%) died, and n = 14 (3%) taken off the transplant list due to clinical improvement with the remainder being transplanted. There was no relationship observed between muscle CSA and medical delisting or death (Table 2).

Post-transplant clinical outcomes

A total of 431/527 (82%) were transplanted with the majority receiving a double-lung transplantation 359 (83%). Twenty-seven of 431 (6%) lung transplant recipients required bridging with mechanical ventilation

Table 1. Patient characteristics and crude associations with muscle cross-sectional area.

Parameter	Cohort summary (n = 527)	Crude mean difference in muscle CSA (95% CI)	P value
Age (per 10 years)	55 IQR [42–62]	−1.17 (−2.72 to 0.37)	0.14
Male sex	283 (54%)	33.4 (30.1 to 36.6)	<0.0001
Diagnosis			
ILD	225 (43%)	Reference	–
COPD	123 (23%)	−18.7 (−24.0 to −13.4)	<0.0001
CF	98 (19%)	−0.95 (−6.7 to 4.8)	0.74
PAH	21 (4%)	−12.3 (−23.1 to −1.5)	0.05
Other	60 (11%)	−14.9 (−21.8 to −8.1)	0.0004
Body mass index (per kg/m^2), n = 521	24.0 ± 4.4	1.77 (1.29 to 2.24)	<0.0001
BMI categories (kg/m^2)			
Normal weight: 18.5–24.9	223 (43%)	Reference	–
Underweight: <18.5	68 (13%)	−4.2 (−10.8 to 2.4)	0.28
Overweight: 25.0–29.9	188 (36%)	9.9 (5.2–14.6)	0.01
Obese: ≥30.0	42 (8%)	22.3 (14.3–30.4)	0.0004
Height (per cm), n = 527	168 ± 10	1.45 (1.27–1.64)	<0.0001
Albumin (per 1 g/l), n = 472	39 ± 6	0.06 (−0.33 to 0.45)	0.76
Daily prednisone use	192 (36%)	−2.1 (−6.6 to 2.4)	0.36
Transplant listing status			
One (standard priority)	260 (49%)	Reference	–
Two (high priority)	229 (44%)	2.8 (−1.7 to 7.3)	0.23
Rapidly deteriorating	38 (7%)	4.7 (−4.0 to 13.3)	0.29

BMI, body mass index; CI, confidence interval; CSA, cross-sectional area; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; ILD, interstitial lung disease; IQR, interquartile range; PAH, pulmonary arterial hypertension.

Data are presented as n (%), mean ± standard deviation, median [25–75% interquartile range], or mean difference (95% confidence interval).

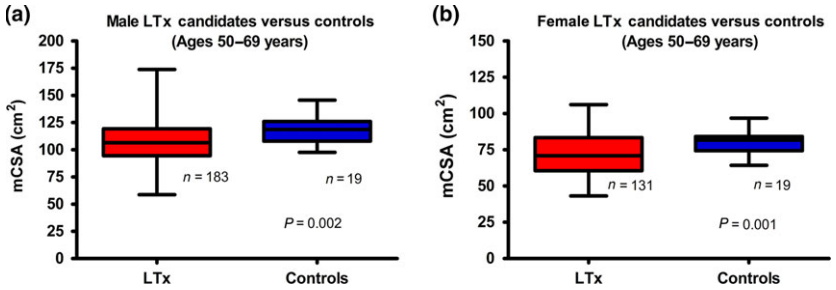

Figure 3 Muscle cross-sectional area of lung transplant candidates versus controls. Matched for age, sex, and body mass index. (a) Males: age (LTx : 60.0 ± 5.1 vs. Controls 59.6 ± 5.4 years, $P = 0.78$); BMI (LTx: 25.4 ± 4.0 kg/m^2 vs. Controls: 25.7 ± 2.5 kg/m^2, $P = 0.67$). (b) Females: age (LTx: 59.7 ± 5.1 vs. Controls: 59.5 ± 5.3 years, $P = 0.89$); BMI (LTx: 24.5 ± 4.1 kg/m^2 vs. Controls: 26.1 ± 3.8 kg/m^2, $P = 0.11$). BMI, body mass index; LTx, lung transplant; mCSA, muscle cross-sectional area.

Table 2. Associations between thoracic muscle cross-sectional area and exercise capacity, strength training volumes, quality of life, and pre-transplant outcomes.

Outcome parameters	Cohort summary	Crude Mean difference for every 10 cm^2 in mCSA (95% CI)	*P* value	Adjusted* Mean difference for every 10 cm^2 in mCSA (95% CI)	*P* value
Physical function					
Six-minute walk distance (m), *n* = 499	312 ± 123	10.9 (6.7–15.1)	<0.0001	9.3 (3.7–14.9)	0.001
Biceps training volume (reps*lbs), *n* = 258†	40 IQR [30–60]	5.7 (4.1–7.2)	<0.0001	4.6 (2.4–6.8)	<0.0001
Quadriceps training volume (reps*lbs), *n* = 252†	30 IQR [20–45]	3.0 (1.8–4.3)	<0.0001	2.3 (0.4–4.2)	0.02
Quality of life (*n* = 400)					
Short-Form 36 Physical Function Domain	15 IQR [10–32.5]	1.3 (0.6–2.0)	0.001	0.55 (−0.4 to 1.5)	0.26
Short-Form 36 Physical Component Score	27 ± 8	0.5 (0.2–0.8)	0.003	0.3 (−0.1 to 0.8)	0.17
SGRQ Activity Domain	92 IQR [79–92]	−0.8 (−1.3 to −0.3)	0.003	−0.14 (−0.9 to 0.6)	0.69
Clinical outcomes (*n* = 513)‡		Crude OR for every 10 cm^2 in mCSA (95% CI)		Adjusted OR for every 10 cm^2 in mCSA (95% CI)§	
Delisting/mortality versus transplanted	82 (16%) vs. 431 (84%)	0.91 (0.80–1.01)	0.08	0.96 (0.78–1.11)	0.60

CI, confidence interval; IQR, interquartile range; mCSA, muscle cross-sectional area; SGRQ, St. George's Respiratory Questionnaire; OR, odds ratio.

Data are presented as *n* (%), mean ± standard deviation, median [25–75% interquartile range], mean difference (95% confidence interval), or odds ratio (95% confidence interval).

*Mean difference for mCSA for physical function and quality of life outcomes: adjusted for age, sex, height (m^2), and diagnosis.

†Biceps and quadriceps training volumes taken at initiation of rehabilitation.

‡Excluded due to medical improvement pre-transplant (*n* = 14).

§Odds ratio for mCSA for delisting/mortality vsersus transplanted: adjusted for age, sex, height (m^2), diagnosis, and program transplant listing status.

Table 3. Characteristics of subjects by availability of health-related quality of life data.

Parameter	Available HRQL (n = 400)	No Available HRQL (n = 127)	P value
Age, median [IQR] years	55 IQR [43–62]	53 [40–62]	0.36
Male sex	217 (54%)	66 (52%)	0.65
Diagnosis			
Interstitial lung disease	170 (42.5%)	55 (43%)	0.17
Chronic obstructive pulmonary disease	102 (25.5%)	21 (17%)	
Cystic fibrosis	68 (17%)	30 (24%)	
Pulmonary arterial hypertension	17 (4%)	4 (3%)	
Other	43 (11%)	17 (13%)	
Muscle cross-sectional area (cm^2)	94 ± 25	93 ± 26	0.57
Six-minute walk distance (m) (n = 398/101)	322 ± 118	271 ± 133	0.01
Transplanted (n = 431)	337 (84%)	94 (74%)	0.03
Delisted/died (n = 82)	54 (14%)	28 (22%)	
Medically improved (n = 14)	9 (2%)	5 (4%)	

HRQL, health-related quality of life; IQR, interquartile range.

Data are presented as n (%), mean ± standard deviation or median [25–75% interquartile range].

(n = 19, 4%) or extra-corporeal life support (n = 8, 2%) with a median duration of 10 IQR [7–24] days in the ICU pre-transplant. No difference in muscle CSA [−5.8 cm^2 95% (−12.9 to 1.3), P = 0.11)] was observed in those requiring bridging to transplantation compared to those transplanted without bridging, adjusted for age, sex, height-squared, and diagnosis.

Three hundred and eighty-nine (90%) transplant recipients survived to hospital discharge with causes for in-hospital mortality outlined in Fig. 2. There was no observable difference in muscle CSA for hospital discharge versus death for every 10 cm^2, controlling for age, sex, height-squared, and diagnosis [OR: 1.13 95% (0.94–1.36), P = 0.20]. Hospital mortality was increased in 51 lung transplant recipients (12%) who developed grade 3 PGD [OR = 4.8 95% (2.3–9.8), P < 0.0001], but no independent association was observed between pre-transplant muscle CSA and development of Grade 3 PGD [adjusted OR = 0.91 95% (0.77–1.08), P = 0.27 for every 10 cm^2].

Of those surviving to hospital discharge, the adjusted OR of being discharged to inpatient rehab versus home was 17% lower for every 10 cm^2 increase in muscle CSA, Table 4. Muscle CSA was no longer independently associated with discharge to inpatient rehabilitation when pretransplant 6MWD was incorporated into the model (Table 4), with 6MWD associated with a reduced risk of being discharged to inpatient rehabilitation [OR = 0.74 95% (0.56–0.97), P = 0.03, n = 372, for every 100 m increase]. None of the other covariates (age, sex or height-squared) were independently associated with discharge disposition except for a diagnosis of COPD or CF, relative to ILD, who were less likely to be discharged to inpatient rehabilitation (P = 0.002).

After excluding patients who died during the transplant hospital admission, the median length of stay in the ICU and hospital was 4 days IQR [2–11] and 20 days IQR [14–35], respectively. Muscle CSA was independently associated with shorter hospital length of stay [0.7 median days 95% (0.2–1.3), P = 0.04] per 10 cm^2 muscle CSA], even after adjustment for pre-transplant 6MWD [−1.3 median days 95% (−2.8 to −0.2), P = 0.045, n = 372] per 100 m increase], Table 4. None of the other covariates were independently associated with hospital length of stay. No independent relationship was observed between muscle CSA and mechanical ventilation or ICU days post-transplant, Table 4.

A total of n = 75 (17%) recipients died within 1 year post-transplant. There was no independent association found between muscle CSA and one-year all-cause mortality [OR = 0.92 95% CI (0.80–1.06), P = 0.26 for every 10 cm^2], adjusted for age, sex, height-squared, and diagnosis.

Discussion

This is the first study to provide evidence that muscle CSA was significantly reduced in lung transplant candidates compared to a control group. Muscle CSA was independently associated with 6MWD, strength training volumes, and post-transplant hospital length of stay. This technique of measuring muscle CSA provides a valid surrogate for muscle mass [23,43] with no added cost or radiation exposure.

Table 4. Associations between muscle cross-sectional area and post-transplant outcomes.

Outcomes*	Transplanted cohort summary (n = 389)	Crude Median difference 10 cm^2 in mCSA (95% CI)	P	Model 1: Median difference 10 cm^2 in mCSA (95% CI)†	P	Model 2: Median difference 10 cm^2 in mCSA (95% CI)‡	P
Days of mechanical ventilation (n = 385)	2 IQR [1–6]	−0.1 (−0.14 to 0.1)	0.10	0 (−0.14 to 0)	1.0	0 (−0.18 to 0)	1.0
Days of intensive care	4 IQR [2–11]	0 (−0.3 to 0.1)	1.0	−0.1 (−0.3 to 0.1)	0.40	−0.1 (−0.3 to 0.1)	0.49
Hospital length of stay	20 IQR [14–35]	−0.8 (−1.4 to −0.1)	0.01	−0.9 (−1.4 to −0.4)	0.01	−0.7 (−1.3 to −0.2)	0.04
		Crude OR for every 10 cm^2 in mCSA (95% CI)		Model 1: OR for every 10 cm^2 in mCSA (95% CI)†		Model 2: OR for every 10 cm^2 in mCSA (95% CI)‡	
Discharge disposition		Rehab: Home		Rehab: Home		Rehab: Home	
Home	321 (83%)	0.92 (0.83–1.02)	0.11	0.83 (0.70–0.98)	0.03	0.85 (0.71–1.02)	0.07
Inpatient rehab	68 (17%)						

CI, Confidence Interval; IQR, Interquartile Range; mCSA, Muscle Cross-sectional Area; OR, Odds Ratio.

Data are presented as n (%), median [25–75% interquartile range], median difference (95% confidence interval), or odds ratio (95% confidence interval).

Adjusted median difference for mCSA on days of mechanical ventilation, intensive care, and hospital length of stay and adjusted odds ratio for mCSA on discharge disposition.

*Outcomes on n = 389 recipients; excluded those that died post-transplant in hospital.

†Model 1: adjusted for age, sex, height (m^2), and diagnosis.

‡Model 2: adjusted for age, sex, height (m^2), diagnosis, and six-minute walk distance (n = 372).

Lung transplant candidates on average had a 10% lower thoracic CSA compared to age and sex-matched healthy controls. This difference is comparable to lung transplant studies using bio-electrical impedance to characterize fat free mass [12]. Sarcopenia, specifically low muscle mass, is a marker of increased catabolic state and limited protein reserve, which is essential during periods of stress such as major surgery, hospitalization or critical illness [44]. In the present study, lower muscle CSA was independently associated with greater hospital length of stay. These findings are consistent with previous reports in patient populations undergoing major surgical procedures such as general surgery, liver and renal transplantation where core muscle size from abdominal CT was associated with longer hospital stay, higher rates of infection, and increased rates of post-transplant mortality [10,11,18,20,45]. In lung transplantation, pre-transplant abdominal muscle CSA has been shown to be associated with ICU [21] and hospital length of stay [22]. Kelm *et al.* [22] observed that muscle CSA was associated with three-year survival in a selected sample of 36 lung transplant recipients with available abdominal CT scans. This is in contrast to the present study and that of Weig *et al.* [21] where muscle CSA was not related with hospital or one-year mortality. Thus, the relationship between muscle mass and post-transplant mortality requires further study in lung transplantation.

We observed that muscle CSA was closely associated with 6MWD and accounted for 23% of the variation in 6MWD after adjustment for confounders. This is consistent with previously described relationships between 6MWD and measures of muscle mass assessed with bio-electrical impedance [46,47] and quadriceps CSA [48]. Six-minute walk distance is commonly utilized by pulmonary rehabilitation programs as an assessment of cardiopulmonary fitness [36,49]. However, the effect of exercise training on body composition parameters such

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as muscle mass is rarely evaluated due to practical limitations [50]. There is evidence from COPD patients that loss of lean muscle mass, irrespective of body weight, has significant implications on exercise capacity and muscle strength [51]. Thus, characterization of muscle CSA from available CT scans could potentially be used as a surrogate measure of muscle mass in the evaluation of patients for pulmonary rehabilitation.

Thoracic muscle CSA was also associated with biceps and quadriceps strength training volumes. The close relationship between muscle size and strength has been mainly described for the limb muscles in chronic lung disease [31,52]. However, there is growing evidence that limb muscle size is related to trunk muscle CSA [53,54]. In the present study, a stronger association between thoracic muscle CSA and biceps training volumes was observed compared to quadriceps volumes, which could partly be explained by the proximity of the upper limb (shoulder) muscles captured on the axial CT slices with the present technique. The differing relationship could also be due to the fact that upper limb and core muscles might be less prone to disuse related muscle atrophy than quadriceps muscles [55,56].

We hypothesized that greater muscle CSA, a surrogate marker of muscle mass and therefore overall physical fitness [47], would be associated with improved HRQL. Studies in patients with moderate COPD have described the relationship between muscle mass and HRQL to be mediated through levels of dyspnea [57] and physical activity [58]. However, we did not observe an independent association between muscle CSA and HRQL physical domains. This could possibly be explained by the fact that this relationship is mainly mediated by daily activity levels, one of the main determinants of HRQL in lung transplant candidates [38,59]. It is also possible that those patients without available HRQL might have demonstrated a differing relationship with muscle CSA, as this group was observed to have a lower exercise capacity and higher likelihood of medical delisting or mortality pre-transplant.

Measurement of thoracic muscle CSA as a marker of muscle mass is an attractive method given that sarcopenia is being recognized as an important prognostic and modifiable determinant in advanced lung disease [7,60]. However, thoracic muscle CSA might be better incorporated as part of a sarcopenia evaluation that includes both muscle mass and functional deficits (muscle strength and physical function) [61] given increasing evidence demonstrating that these functional deficits have important clinical implications in advanced lung disease. Quadriceps strength has been shown to be a significant predictor of mortality in patients with COPD [62]. Low physical function assessed with the Short Physical Performance Battery has been associated with pre-transplant delisting and mortality [63]. In the present study, we compared the utility of skeletal muscle mass to the 6MWT which is the most common measure of cardiorespiratory fitness in advanced lung disease [64] and has been shown to be a strong prognostic marker of post-transplant outcomes [26] [27]. Skeletal muscle mass and 6MWD were both independently associated with hospital length of stay; however, 6MWD was a stronger predictor of discharge disposition. This is not entirely surprising as the 6MWT captures limitations in the cardio-respiratory and musculo-skeletal systems, whereas skeletal muscle mass characterizes only one element of the sarcopenia definition [61]. Given the complex interaction between muscle mass, strength, and physical function [9,65], future studies should aim to understand the contribution of all three musculoskeletal measures pre-transplant, which may further help with prognostication and planning of post-transplant rehabilitation requirements.

We acknowledge several limitations in the present study. This was a single-center retrospective study with muscle CSA measured at the time of transplant listing. Muscle size could potentially change while on the transplant list; however, previous studies using BIA have described no significant change in muscle mass in the pre-transplant period [66]. It also remains unknown whether thoracic muscle CSA would change during an ICU admission pre-transplant; a setting where the measurement of skeletal muscle mass remains a logistical challenge [67]. Secondly, we did not have direct measures of muscle strength in this group of patients, which did not allow us to assess the added prognostic utility of muscle CSA relative to muscular functional deficits, which may have an important effect on post-transplant outcomes. Thirdly, our control group was obtained from a cohort undergoing lung cancer screening who were $\geq$ 50 years old and had at least a 10 pack-year smoking history. One can argue whether this is an appropriate control group; however, the muscle CSA difference would likely be even greater compared to control subjects without a history of smoking which is known to be a risk factor for muscle atrophy [68,69]. Additionally, most cystic fibrosis patients were not age-matched with this older control group. Also, it is unknown whether severe lung disease alters the geometry of the thoracic cavity, which could lead to differences in thoracic muscle CSA attributable to variation in the distribution of the thoracic muscles rather than

muscle atrophy [23,24]. However, in a previous study, we observed that a single thoracic axial CT slice was closely associated with thoracic muscle volume obtained from several slices in lung transplant candidates [25]. Furthermore, we did not observe an association between muscle CSA and transplant listing urgency. Unfortunately, we are unable to comment on the relationship between muscle CSA and Lung Allocation Score from the present study. Finally, all lung transplant patients at our center participate in a structured rehabilitation program, which could have an impact on the pre- and post-transplant clinical outcomes.

In conclusion, thoracic muscle CSA can be applied as a novel, simple measure of skeletal muscle mass and is independently associated with 6MWD, strength training volumes and post-transplant hospital length of stay. Further study is needed to assess the contribution of muscle functional deficits in addition to muscle mass in the evaluation of lung transplant candidates.

Authorship

DR, LGS, MH, RG and SM: made substantial contributions to the conception and design of the work. DR: wrote the first draft of the manuscript. LGS, MH, RG, HS, NAC, PM and SM: revised the manuscript for important intellectual content. All authors made substantial contributions to the analysis or interpretation of data. All authors approved the manuscript and agree to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Conflicts of interest

There are no conflicts that exist for any of the authors.

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