REVIEW

Clinical outcomes associated with computed tomography-based body composition measures in lung transplantation: a systematic review

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SUMMARY

Computed tomography (CT) is gaining increased recognition in the assessment of body composition in lung transplant (LTx) candidates as a prognostic marker of post-transplant outcomes. This systematic review was conducted to describe the methodology of CT measures of body composition used in LTx patients and its association with post-transplant outcomes. Six databases were searched (inception-April 2020) for studies of adult LTx patients with thoracic or abdominal CT measures [muscle cross-sectional area (CSA) and/or adiposity]. Thirteen articles were included with 1911 LTx candidates, 58% males, mean age range (48–61 years) and body mass index of 21.0–26.1 kg/m^2. Several methods were utilized using thoracic or abdominal CT scans to assess skeletal muscle (n = 11) and adiposity (n = 4) at various anatomic locations (carina, thoracic, and lumbar vertebrae), differing muscle groups, and adipose tissue compartments. Low muscle mass was associated with adverse outcomes in 6/11 studies, including longer mechanical ventilation days (n = 2), intensive care (n = 2) and hospital stay (n = 2), and mortality (n = 4). Greater subcutaneous and mediastinal fat were associated with increased risk of primary graft dysfunction (n = 2), but implications of adiposity on survival were variable across four studies. Further standardization of CT body composition assessments is needed to assess the prognostic utility of these measures on LTx outcomes.

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Introduction

Body composition (muscle and fat mass) is an important marker of overall health in people with chronic disease [1]. The presence of low muscle mass or high-fat mass has been shown to be associated with poor clinical outcomes in various chronic diseases [2,3]. In the solid organ transplant population, low muscle mass and sarcopenic obesity (combination of low muscle mass and high-fat mass) have been associated with greater

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hospital length of stay (LOS), waitlist mortality, and post-transplant survival [4–7]. Thus, the evaluation of body composition is an important part of the overall assessment of patients undergoing solid organ transplantation.

There are several standard methods of evaluating body composition, including dual X-ray absorptiometry (D-XA), bioelectrical impedance analysis (BIA), whole body computed tomography (CT), and magnetic resonance imaging (MRI) [8]. However, these methods have limited availability in the clinical setting due to the time and cost associated with these procedures. There is a growing body of literature utilizing CT scans that are collected for clinical purposes as a method of evaluating muscle cross-sectional area (CSA) and various regions of adiposity (subcutaneous and visceral adipose depots) [9,10]. Single-slice abdominal CT scans have been used widely in chronic disease populations such as cancer and liver cirrhosis to evaluate psoas muscle area, and also visceral and subcutaneous fat depots [11,12]. Abdominal CT scans have also been validated against whole body measures of body composition [13]. In people with lung disease, there is limited availability of CT scans that allow visualization of the abdominal region [14,15]. However, thoracic CT scans are routinely performed clinically in chronic lung disease patients, so methods to evaluate muscle size from thoracic CT have also been developed [16,17].

The literature on CT-based body composition in lung transplantation shows that various landmarks from thoracic and lumbar CT scans have been used to evaluate body composition. Investigators have evaluated muscle CSA of single muscles, such as the pectorals [16,18] or multiple muscles of the chest [19,20], whereas only a few studies have examined adipose depots from thoracic CT [21,22]. Also, several studies have evaluated the relationship of pretransplant muscle CSA from CT scans and their relationship with post-transplant outcomes, such as days of mechanical ventilation (MV), hospital LOS, and mortality [19,20,23]. The associations with post-transplant outcomes have been variable, which may be due to differences in methodologies applied for evaluating body composition, transplant center practices, or the variety of assessed clinical outcomes.

Given the growing body of literature using CT body composition measures in LTx patients, this systematic review was undertaken with the following two objectives: (i) To describe the methodology of CT-based measures of body composition used in LTx patients. (ii) To describe the association of CT-based measures of body composition with early and late post-transplant clinical outcomes.

Methods

Study design

This was a systematic review of studies utilizing thoracic or abdominal CT to assess skeletal muscle size or adiposity in LTx patients. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. No ethics approval was required given this was a systematic review.

Search strategy

A comprehensive search strategy was developed by a medical librarian (A.O-C), in collaboration with the team, to identify published English language literature on chronic respiratory diseases, CT, and skeletal muscle size and adiposity. The following databases were searched from inception through April 27, 2020 (last update): Ovid MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Clinical Trials, CINAHL, and PubMed for non-Medline records. The search was customized for each database and details are provided for Ovid MEDLINE (Table S1). Limits were applied for human and adult populations. Books and conference materials were excluded from EMBASE. References from included articles were also reviewed.

Eligibility criteria

Full-text articles were included of adult participants (≥18 years old) with chronic lung disease (lung parenchyma, airways, and pulmonary vasculature) that required lung transplantation. For study inclusion, participants had to have thoracic or abdominal CT body composition measure (muscle CSA or adiposity measure) pretransplant and the association of pretransplant body composition evaluated with at least one-post LTx outcome (mechanical ventilation days, intensive care unit (ICU), primary graft dysfunction (PGD), hospital LOS, discharge disposition, post-transplant exercise capacity, or survival within any time period reported). Both prospective and retrospective cohort studies, randomized and nonrandomized controlled trials were eligible for study inclusion. Case series or reports were

excluded. Full-text articles were limited to English language only.

Study selection

Two assessors (D.R. and CE.O.) independently reviewed all abstracts obtained from the search. The full text of the article was reviewed if at least one reviewer felt that the eligibility criteria was met. A third investigator (S.M.) reviewed any articles where consensus was not reached after full-text review.

Data extraction and synthesis

A standardized form was used for data extraction, which was performed independently by two reviewers (S.N. and CE.O. or K.C.). Demographic characteristics, lung function, disease severity measures and confirmation of LTx candidacy (active on the waiting list) [25] were ascertained from the articles. Details on CT measures (anatomic location, muscles and adiposity compartments, and number of axial slices) were abstracted. We abstracted the terminology and cutoffs used for low muscle mass in the papers, as we anticipated that publications may use the term "sarcopenia" to represent low muscle mass, given the definition of sarcopenia has evolved to include low muscle mass and physical function [26]. Associations with CT-based measures of body composition with early LTx outcomes such as MV days, intensive care unit (ICU), PGD, hospital LOS, discharge disposition, and late post-transplant outcomes being exercise capacity and survival were abstracted.

We determined a meta-analysis would not be feasible at the time of formal screening for article inclusion given significant heterogeneity in the methodology used to evaluate CT body composition measures. Descriptive statistics and ranges were used to describe the demographic characteristics and disease severity measures in LTx candidates across studies.

Quality assessment

Quality appraisal for the included articles was assessed using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [27]. We also utilized the RoBANS tool to assess risk of bias across six domains: participation selection, confounding, exposure, blinding of assessments, data completion, and reporting of outcomes, which has shown promising validity in its use in nonrandomized studies [28]. Two reviewers (S.N. and CE.O./K.C) independently reviewed the quality of the studies with disagreements resolved by consensus.

Results

Study selection and patient characteristics

A total of 8589 unique abstracts were identified with 68 full-text articles reviewed for eligibility and 13 articles included in the systemic review (Fig. 1). Selected studies were published between January 2016 and January 2020. A total of 1911 participants listed for lung transplantation were included. The most common indications for transplant listing were interstitial lung disease (n = 1033, 54%), chronic obstructive pulmonary disease (n = 400, 21%), cystic fibrosis (n = 217, 11%), pulmonary arterial hypertension (n = 48, 3%), and other (n = 213, 11%). Participants in the selected studies comprised 58% males, with a mean or median age range of 49–61 years, and a mean body mass index (BMI) range of 21.0–26.1 kg/m^2 across studies. The majority of studies (n = 8) were from North America, but other included centers were Korea (n = 3), Germany (n = 1), and Spain (n = 1). In addition, LTx candidates generally had their thoracic or abdominal CT scan 3- to 12-month pretransplantation that was used for body composition evaluation (Tables 2 and 3).

Quality assessment of studies

Twelve studies were retrospective, single-center studies, whereas one study was prospective and multi-centered. The overall quality of the cohort studies had a broad range [poor (n = 2), fair (n = 5), and good (n = 6)], as shown in Table S2. Many of the studies were missing sample size justifications (n = 11), the exposure was not assessed at multiple time points (n = 12) and outcome assessors performing the image analysis were not blinded (including not reported) to the exposure status of participants (n = 6). Common strengths among all studies included a clearly stated objective, recruitment of subjects from a defined population, and the exposure of interest being measured prior to the post-transplant outcomes. Based on the RoBANS domains (Table S3), the highest risk of bias was in the selection of participants (n = 5) and lack of blinding for outcome assessments (n = 6). The bias was generally low for body composition measurements (exposure, n = 10), adjustment for confounding variables (n = 10), incomplete outcome data (n = 9), and selective outcome reporting (n = 13).

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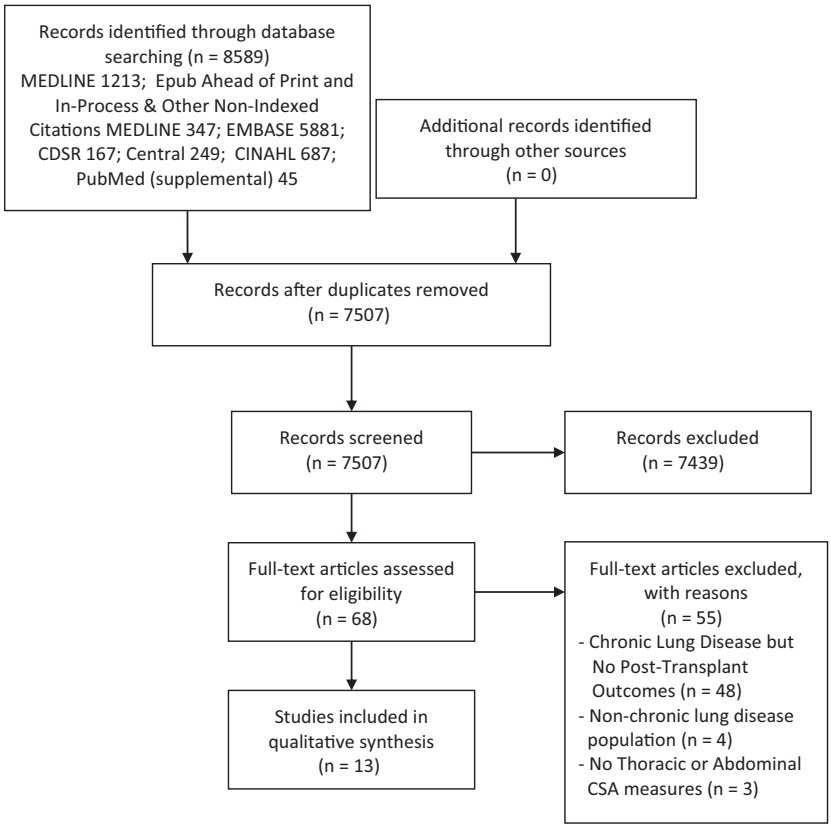

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the literature search [24].

Methodological evaluation of skeletal muscle mass

Skeletal muscle CSA with CT was evaluated in eleven studies, with most using the Slice-O-Matic ($n = 5$) software to quantify skeletal muscle tissue. Other image processing softwares were also employed, including one study that assessed psoas muscle composition using three-dimensional (3D) imaging with a Synapse visualization software [29]. Pectoralis muscle for chest CT ($n = 3$) [18–20], the psoas muscle from abdominal CT ($n = 6$) [14,15,23,29–31], and paraspinal muscles from chest or abdominal CT ($n = 5$) [19–22,31] were the most common muscles included among the selected studies, in comparison to the intercostals ($n = 3$) [19,20,22], serratus anterior ($n = 1$) [19] and latissimus dorsi muscles ($n = 2$) [19,22], as shown in Table 1. The majority of studies utilized one axial slice ($n = 7$) [18,20–23,30,31] with several studies taking the average of two to three slices [14,15,19]. Despite some similarities between studies, there was significant heterogeneity in the vertebral level analyzed and the Hounsfield Unit range for identifying skeletal muscle across the studies (Table 1). Moreover, three studies conducted reliability analysis [14,19,23], reporting excellent inter-rater agreement (>0.97) in skeletal muscle measures obtained at different vertebrae locations (Table 1).

Methodological evaluation of adiposity with computed tomography

There were four studies that assessed adiposity, Table 3 [21,22,32,33]. Pienta *et al.* [21] evaluated thoracic subcutaneous and visceral adiposity (SAT and VAT) using a single slice at the level of the ninth thoracic vertebrae (T9), whereas Anderson *et al.* [32] had quantified both SAT and VAT on chest (T7–T8) and abdominal scans (L4–L5). Cho *et al.* [22] used thoracic CT scans (at T12 level) to assess subcutaneous fat with a single slice, adjusted for several height and weight indices. Gonzalez *et al.* [33] was the only study to utilize anterior mediastinal fat (AMF) volumes. Reliability measurements of thoracic adipose tissue quantification between raters were excellent (intra-class correlation ≥0.97 for VAT and SAT) [32] and mediastinal adiposity ($r \geq 0.94$ across all axes) [33].

Table 1. Skeletal muscle mass and adiposity tissue measurements in lung transplant patients.

	Skeletal muscle								Adipose tissue							
Author (year)	Pectorals major and minor	Inter costals	Paraspinal	Serratus anterior	Latissimus dorsi	Trapezius	Psoas	Abdominals*	Subcutaneous	Visceral	Mediastinal	Epicardial	Landmark	Number of slices	Muscle radiodensity range (HU)	Reliability measures
Halpern (2020) [31]			X				X	X					L3	1	NR	NR
Gonzalez (2020) [33]											X		NR	NR	NR	NR
Anderson (2019) [32]									X	X			L4–L5 [Ab] T7–T8 [Chest]	1	−170 to −40	ICC = 0.98 [SAT] ICC = 0.97 [VAT]
Hsu (2019) [30]							X						L4	1	−29 to 150	NR
Suh (2019) [29]							X						NR	NR	NR	NR
Cho (2019) [22]		X	X		X			X	X				T12	1	−190 to −30	NR
Pienta (2018) [21]			X						X	X			T9	1	−29 to 150	NR
Kashani (2018) [15]							X	X†					L1–L3	2	−40 to 170	NR
Hoang (2017) [18]	X												Carina	1	−50 to 90	NR
Rozenberg (2017) [19]	X	X	X	X	X								Carina, one slice above/ below	3	−29 to 150	Inter-rater: ICC = 0.998, 95% CI (0.995–0.999)
Lee (2016) [20]	X	X	X										Carina	1	NR	NR
Weig (2016) [23]							X						L4–L5	1	10–100	Inter-rater: ICC = 0.992
Kelm (2016) [14]							X	X†					L2–L3	2	−40 to 170	Inter-rater: *r* = 0.998, 95% CI (0.997–0.999)

AB, abdominals; AT, adipose tissue; CI, confidence interval; HU, Hounsfield units; ICC, intra-class correlation coefficient; L, lumbar vertebrae; NR, not reported; *r*, correlation coefficient; SM, skeletal muscle; T, thoracic vertebrae.

*Abdominals include the following muscles: rectus abdominis, external and internal obliques, transversus abdominis.

†Abdomins plus quadratus lumborum muscle.

Table 2. Associations of low muscle mass with post-transplant outcomes.

Author	Type of LTx included	CT measure; time to LTx	Exposure measure	Statistical test used	MV days	PGD	LOS (days)	Discharge/ hospital mortality	Survival/ mortality	Summary
Halpern (2020) [31]	SLT/DBLT (n = 132)	Muscle CSA; <1 year	Sarcopenia defined based on previously established sex and BMI specific values in oncology [71]	KWT; χ^2; KM	NA	NA	ICU: NA Hospital: 13 vs. 18, P = NS*	Rehab: 20.6% vs. 21.7%, P = NS*	Survival 4-year: HR: 1.1 95% CI (0.5–2.4), P = NS†	Sarcopenia did not predict hospital outcomes or mortality
Hsu (2019) [30]	SLT/DBLT (n = 95)	Muscle CSA; <6 months [2.8 (1.3–5.3 months)]	Sarcopenia cutoff for each sex consistent with those of similar acuity patient populations [72]	KM; Cox	NA	NA	NA	NA	Lower survival 1-year: OR 8.7 P = 0.017† Lower survival 3-year: OR 13.4, P < 0.01† All-cause mortality HR 5.8, P < 0.01†	Patients with sarcopenia had decreased survival compared to those without sarcopenia
Suh (2019) [29]	DBLT (n = 107)	CT & 3D; NR	Sarcopenia was defined as ≤ lowest tercile, stratified by sex and BMI	MLR; Cox	19.2 ± 36.3 vs. 9.4 ± 13.3, P = NS*	Grade 3 at 72 h: 11.8% vs. 21.7%, P = NS*	ICU: 12.5 ± 9 vs. 9.6 ± 7.5, P = NS* Hospital: 58.1 ± 49.2 vs. 38.1 ± 33.2, P = NS*	Operative mortality: 28.6% vs. 11.1% P = 0.02*	Survival 3-year: 50.2% vs. 73.2%, P = NS*	Sarcopenia associated with increased operative mortality
Cho (2019) [22]	DBLT (n = 45)	Muscle CSA; <3 months	Sarcopenic group cutoff of 28.07 cm^2/m^2 based on statistical calculations	T-test; χ^2; Cox	35.7 ± 28 vs. 9.7 ± 9.3, P = 0.04*	NA	ICU: 43.2 ± 39.4 vs. 14.9 ± 10.5, P = 0.032* Hospital: 94.8 ± 52.5 vs. 88.0 ± 41.1, P = NS*	NA	Mortality (7–76 months) 44.4% vs. 7.4%, P = 0.005* Worse overall survival: HR, 8.6; P = 0.02†	Patients with sarcopenia had increased MV days, ICU duration and mortality rates

Table 2. Continued.

Author	Type of LTx included	CT measure; time to LTx	Exposure measure	Statistical test used	MV days	PGD	LOS (days)	Discharge/ hospital mortality	Survival/ mortality	Summary
Pienta (2018) [21]	SLT/DBLT (n = 200)	Dorsal muscle area and density	Dorsal muscle area (continuous per SD)	T-test; Poisson Kendall Corr; Cox	>48 h MV NS: data not shown	Grade 3 at 72 h: NS: data not shown	Hospital: NS; data not shown	NA	Survival 1 and 3-year NS; data not shown	No significant association with muscle area and post-transplant outcomes
Kashani (2018) [15]	SLT/ DBLT-HLT (n = 28)	Muscle CSA; <1 year [65 (−31 to 309)]	Sarcopenia index (SI): (serum creatinine value/cystatin C value) × 100	T-test; χ^2;	NS; data not shown	NA	ICU and Hospital NS; data not shown	NS; data not shown	NS; data not shown	No statistical significance was found in postoperative outcomes with SI
Hoang (2017) [18]	SLT/DBLT (n = 82)	Muscle CSA; <1 year [n = 49 at 6 months, n = 62 at 12 months]	Pectoralis muscle index (PMI) adjusted for height. "Low PMI" determined as lowest quartile, stratified by sex	ANOVA/KWT; χ^2/Fischer; Cox;	2 IQR (1,3.5) vs. 3 (2,14), P = NS*	NA	ICU: 6.5 IQR (4,13.5) vs. 14 (8,29), P = 0.02* Hospital: 15 IQR (11.5, 50) vs. 23 (15, 38), P = NS*	Discharge home: 73% vs. 69%, P = NS*	Survival 1-year: HR: 1.6 95% CI (0.7–3.9), P = NS*	Patients in the highest PMI quartile had experienced a significant increase in ICU LOS when compared to those in the lowest quartile
Rozenberg (2017) [19]	SLT/DBLT (n = 431 of 527 listed)	Muscle CSA; <3 months	Muscle CSA (per 10 cm^2 difference) analyzed as continuous variable	MLR; MLGR QR	0 95% CI (−0.18 to 0), P = NS†	Grade 3 at 72 h: OR: 0.91 95% CI (0.8–1.1), P = NS†	ICU: −0.1 95% CI (−0.3 to 0.1), P = NS† Hospital: −0.7 95% CI (−1.3 to −0.2), P = 0.04†	Rehab vs. home: OR = 0.85 95% CI (0.71–1.02), P = NS†	Mortality 1-year: OR = 0.92 95% CI (0.80–1.06), P = NS†	Thoracic muscle CSA was independently associated with hospital LOS

Table 2. Continued.

Author	Type of LTx included	CT measure; time to LTx	Exposure measure	Statistical test used	MV days	PGD	LOS (days)	Discharge/ hospital mortality	Survival/ mortality	Summary
Lee (2016) [20]	SLT/DBLT (n = 109)	Muscle CSA; 2 months [0–20]	Quartiles based on CSA; lowest quartile was defined as sarcopenia	ANOVA; χ^2; Cox	33 ± 49 vs. 25 ± 40, P = NS*	NA	ICU: 28 ± 44 vs. 24 ± 36, P = NS* Hospital: 61 ± 48 vs. 51 ± 3, P = NS*	Mortality (≤30 days); 7% vs. 11%, P = NS* Mortality (≤90 days); 29% vs. 30%, P = NS*	Survival 1-year: Q1: 67 % vs. Q4. 46%, P = 0.04*, but P = NS (all data)	No significant associations were found between postoperative outcomes and CSA quartiles
Weig (2016) [23]	SLT/DBLT (n = 103)	Muscle CSA; NR	Lean psoas area (LPA) based on quartiles; low LPA ≤ lowest tercile	Fisher; MLR; LR	OR: 0.65 95% CI (0.44–0.96), P = 0.03†	NA	ICU: OR: 0.75 95% CI (0.59–0.95) P = 0.02† Hospital: NA	Mortality ICU: *Male*: 10% vs. 3%, P = NS* *Female*: 11% vs. 7%, P = NS*	Mortality 1-year: *Male*: 19.0% vs. 17.5%, P = NS* *Female*: 7% vs. 11%, P = NS*	LPA was inversely associated with length of mechanical ventilation, and ICU LOS
Kelm (2016) [14]	SLT/DBLT-HLT (n = 36)	Muscle CSA; <6 months	Low skeletal muscle index (SMI) ≤ lowest quartile stratified by sex	Fisher; KWT; Cox	2 IQR (2–2) vs. 2 (1–3.5), P = NS†	Grade 3 at 72 h: NS†	ICU: 4 IQR (3–6) vs. 4 (3–5), P = NS† Hospital: 19.5 IQR (15–22) vs. 12 (9–17), P = 0.01†	NA	Mortality 1-year: HR: 3.8 95% CI (1.4–10.3); P = 0.01† Mortality 3-year: HR: 3.1 95% CI (1.0–9.2), P = 0.04†	Increased hospital LOS and mortality in the lowest quartile group compared to those with higher SMI

Cox, Cox's proportional hazard; CSA, cross-sectional area; CT, computed tomography; DBLT, double-lung transplantation; HLT, heart–lung transplantation; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; KM, Kaplan–Meier survival analysis; KWT, Kruskal–Wallis test; LOS, length of stay; LPA, lean psoas area; LR, linear regression; MLGR, multivariable logistic regression; MLR, multivariable linear regression; MV, mechanical ventilation; NA, not available; NR, not reported; NS, not significant (P> 0.05); OR, odds ratio; PGD, primary graft dysfunction; Q, quartile; QR, quantile regression; SLT, single-lung transplantation; Tx, transplanted; χ^2, Chi-square test.

Data are shown for groups with lower muscle mass levels versus increased levels, unless indicated otherwise.

*Unadjusted for confounding variables.

†Adjusted for confounding variables.

Table 3. Associations of high adiposity with post-transplant outcomes.

Author	Type of transplant	CT measure and time to transplant	Exposure measure	Stats test used	MV days	PGD	LOS (days)	Discharge/ hospital mortality	Survival/ mortality	Summary
González (2020) [33]	SLT (n = 92)	CT – mediastinal dimensions NR	According to the radiological AMF dimensions, low-AMF (<20 cm^3)	T-test; LR; Cox	NA	Grades 2–3 at 72 h: 23% vs. 11% P = 0.03*	ICU: 10 ± 11 vs. 10 ± 15, P = NS*	Mortality (≤30 days): 32% vs. 11% P = 0.01*	Survival 1-year: 55% vs. 85%, P < 0.001* Survival 3-year: 40% vs. 81% P < 0.001* Overall Survival (low vs. high AMF): HR = 1.02 95% CI (1.01–1.04), P < 0.001†	Elevated volumes of AMF associated with increased risk of postoperative complications and decreased survival
Anderson (2019) [32]	SLT/DBLT (n = 355)	VAT/SAT CSA; Abdomen: 182 IQR (83–397) days Chest: 150 IQR (79 –294) days	SAT and VAT CSA indexed to height-squared (m^2) as continuous variable	LR; Cox	NA	Grade 3 at 48 or 72 h: *Abdominal SAT:* OR per doubling = 1.9 95% CI (1.1–3.4), P = 0.03† *Chest SAT:* OR per doubling = 1.1 95% CI (0.8–1.5), P = 0.63 † *Abdominal and thoracic VAT:* Data not shown, P = NS†	NA	NA	Survival (median 2.7-year) *SAT abdomen* HR per doubling = 0.9 95% (0.6–1.3), P = NS† *VAT abdomen* HR per doubling = 0.9 95% CI (0.6–1.2), P = NS† *SAT thoracic* HR per doubling = 1.1 95% CI (0.8–1.4), P = NS† *VAT thoracic* HR per doubling = 1.1 95% CI (0.9–1.4), P = NS†	Abdominal SAT is associated with an increased risk of PGD

Table 3. Continued.

Author	Type of transplant	CT measure and time to transplant	Exposure measure	Stats test used	MV days	PGD	LOS (days)	Discharge/ hospital mortality	Survival/ mortality	Summary
Cho (2019) [22]	DBLT (n = 45)	Fat indices <3 months	Fat-height index (FHI) and fat-weight index (FWI) in cm^2/kg as continuous variable	PC; *T*-test	[FHI]: R = 0.18, P = NS* [FWI]: R = 0.17, P = NS*	NA	ICU: [FHI]: R = 0.29, P = NS* [FWI]: R = 0.46, P = NS*	NA	Deceased vs. alive: *FHI*: 28.8 ± 9.2 vs. 23.1 ± 11.2, P = NS* *FWI*: 1.2 ± 0.7. vs. 1.0 ± 0.5, P = NS*	No significant associations found between adiposity and clinical outcomes
Pienta (2018) [21]	SLT/DBLT (n = 200)	SAT and VAT CSA <1 year [156 days]	SAT and VAT/total body area per 1 SD	*T*-test; Poisson Kendall CorrCox	>48 h MV Mediastinal fat per 1 SD (OR = 0.64, P = 0.02)	Grade 3 at 72 h: SAT and VAT/ total body area P = NS*	ICU: NA hospital: Body CSA: Kendall = −0.2, P < 0.001	NA	Overall Survival: SAT/total body area HR = 0.60 95% (0.5–0.8), P = 0.001†	SAT/total body area significant predictor of survival

AMF, anterior mediastinal fat; Cox, Cox's proportional hazard; CSA, cross-sectional area; CT, computed tomography; DBLT, double-lung transplantation; ICU, intensive care unit; LOS, length of stay; LR, linear regression; MV, mechanical ventilation; NA, not applicable; NR, not reported; NS, not significant (P> 0.05); PC, pearson correlation coefficient; Poisson, Poisson regression; SAT, subcutaneous adipose tissue; SLT, single-lung transplantation; VAT, visceral adipose tissue.

Data are shown for groups with higher adiposity levels versus increased levels, unless indicated otherwise.

*Unadjusted for confounding variables.

†Adjusted for confounding variables.

Associations of skeletal muscle mass with clinical outcomes

Mechanical ventilation and intensive care unit course

Nine studies described the association between pretransplant skeletal muscle mass and MV days post-transplant (Table 2) [14,15,18–20,21,22,23,29]. Weig *et al.* [23] observed that in 103 consecutive LTx patients, lean psoas area had an independent, inverse association with MV days [$\beta = 0.65$; 95% CI (0.44–0.96); $P = 0.03$], per 1 standard deviation (SD) in lean psoas area. Cho *et al.* [22], observed a similar outcome in their study, as the muscle-height index and muscle-weight index was shown to have a negative correlation with MV duration ($r = -0.33$, $P = 0.021$ and $r = -0.54$, $P < 0.001$), respectively. However, the majority of studies (7 out of 9) demonstrated no association between skeletal muscle CSA and days of MV [14,15,18–20,29].

Eight studies evaluated the relationship between skeletal muscle CSA and ICU LOS post-transplantation [14,15,18–20,22,23,29]. A lower skeletal muscle CSA was associated with a longer ICU LOS observed in two of the studies [22,23]. Weig *et al.* had shown that in addition to MV days, ICU LOS was longer as well [$\beta = 0.75$; 95% CI (0.59–0.95) days; $P = 0.02$, per 1 SD reduction in lean psoas muscle area]. Cho *et al.* [22] reported similar findings in those with low muscle area at the lumbar level having a longer ICU LOS compared to those with normal muscle area (43.2 ± 39.4 vs. 14.9 ± 10.5 days, $P = 0.03$). However, Hoang *et al.* [18] observed that ICU LOS was shorter in those with low pectoralis muscle index stratified by sex compared to those with a high muscle index [Q1 = 6.5 IQR (4–13.5) vs. Q4 = 14 (8–29) days, $P = 0.02$], contrary to other studies.

Primary graft dysfunction at 72 h

Primary Graft Dysfunction (PGD) at 72-h post-transplant was evaluated in four studies [14,19,21,29], with no significant association observed between CT muscle mass measures and PGD.

Hospital length of stay and discharge disposition

Hospital LOS was evaluated in nine studies [14,15,18–22,29,31], but only two studies reported having significant inverse associations between pretransplant muscle CSA and post-transplant hospital LOS [14,19]. Rozenberg *et al.* [19] evaluated total muscle CSA at the level of the carina and reported that greater muscle CSA was associated with decreased hospital LOS [$\beta = -0.7$; 95% (0.2–1.3) median days per 10 cm^2 of muscle CSA; $P = 0.04$], independent of age, sex, height-squared, and six-minute walking distance (6MWD). Similarly, Kelm *et al.* [14] observed a longer hospital LOS by 7.2 days ($P = 0.01$) in those with low muscle index (lowest 25th percentile) at the L2–L3 interspace, adjusted for age and sex, compared to those with a higher muscle index.

The association of skeletal muscle mass with discharge disposition was described in only two studies [19,31]. Rozenberg *et al.* [19] showed that an increase in muscle CSA (for every 10 cm^2) was associated with a 17% lower chance in discharge to inpatient rehabilitation versus home ($P = 0.03$), adjusted for age, sex, and diagnosis, but this relationship was no longer significant after adjustment for pretransplant exercise capacity ($P = 0.07$). Halpern *et al.* [31] observed no association between muscle mass and discharge to rehabilitation facility post-transplant ($P = 0.89$).

Post-transplant exercise capacity

One study examined the relationship between muscle CSA and post-transplant exercise capacity [23]. Weig *et al.* [23] observed that greater lean psoas muscle area pretransplantation was associated with greater improvement in 6MWD post-transplant with pulmonary rehabilitation. For every SD in lean psoas muscle area, the 6MWD increased by 43 m [95% CI (7–79)], adjusted for age, sex, diagnosis, transplant type and peri-operative course, and independent of pulmonary rehabilitation duration.

Overall survival

Survival outcomes were commonly measured at 1-year post-transplant [14,15,18–23,29] with several studies reporting survival up to 3-year [14,21,29,30] and 4-year post-transplant [31], and another study evaluating survival 7- to 76-month post-transplant [22]. Kelm *et al.* [14], reported that LTx recipients with low muscle index (lowest 25th percentile) had increased risk of mortality [HR = 3.1, 95% CI (1.0–9.2), $P = 0.04$] by 3 years. Similarly, Hsu *et al.* [30] observed that survival was lower by 3-year post-transplant for those with sarcopenia (35.9%) versus those without sarcopenia (76.8%), $P < 0.01$. Cho *et al.* [22] observed that LTx recipients who died (median follow-up of 32 months) were more likely to have a lower muscle-height index (26.0 ± 5.1 vs. 30.1 ± 4.9 cm^2/m^2, $P = 0.042$) than

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those who survived. However, the majority of studies did not observe a significant association with post-transplant survival (Table 2) [15,18–21,23,29,31]. Risk factors for mortality were generally not described except for one study [30]. Hsu *et al.* [30] reported that the risk of graft failure (comprised of re-transplantation or death as a result of PGD, acute rejection, chronic rejection, or respiratory failure) was much greater in those with low psoas muscle CSA [HR 12.8; 95% CI (3.3–48.8); $P = 0.01$] compared to those without low CSA.

Associations of adiposity with clinical outcomes

Four studies evaluated associations with regional adiposity using CT and post-transplant outcomes (Table 3) [21,22,32,33]. Increased SAT and AMF volume were shown to be associated with PGD [32,33]. Pienta *et al.* [21] observed that increased SAT on chest CT (vertebral level T9) was associated with improved survival up to three-year postlung transplantation [HR = 0.60; 95% CI (0.45–0.81); $P = 0.001$]. This is in contrast with Gonzalez *et al.* [33] who observed a worse 3-year survival with high AMF. No association was observed with CT adiposity measures and post-transplant survival in the other two studies [22,32].

Considerations of CT muscle mass and adiposity measures with post-transplant outcomes

As shown in Tables 2 and 3, there was significant variability in the statistical analysis performed for post-transplant hospital-based outcomes and survival. The measure of exposure for muscle mass and adiposity was different across all 13 studies including timing of CT scans pretransplant, adjustment for important confounders not performed in 3 (23%) of studies, and timing of CT scans relative to post-transplant outcomes was not factored into the statistical analysis. Transplant type was only considered in the multivariable modelling in only 5/10 (50%) of studies that had included both single and double LTx recipients [18,21,23,31,32]. In three of the studies reporting associations with transplant procedure and post-transplant outcomes, single LTx was associated with shorter MV and ICU days [23], hospital LOS [21], but not with survival [21,31].

Discussion

This systematic review of CT body composition measures highlights the methodological variability of muscle mass and adiposity measures in LTx patients using both thoracic and abdominal CT. In approximately 1,900 LTx candidates, skeletal muscle mass was more commonly evaluated compared to adiposity measures using varying anatomic locations, muscle groups, and adipose tissue compartments. Despite heterogeneity in CT measures, low muscle mass was associated with at least one adverse early or late post-transplant outcome in over one-half of the studies. The implications of CT adiposity were variable across the four studies with respect to post-transplant survival. Further standardization of CT body composition is needed to assess the clinical utility of these measures on LTx outcomes.

Low muscle mass was associated with adverse LTx outcomes in six of the eleven studies. This is consistent with other major surgical procedures and transplant populations, including liver and renal transplant, that have highlighted adverse postoperative outcomes with low muscle mass [34–37]. This can be partly explained by the fact that low muscle mass represents a state of catabolism with diminished physiological reserve, which is important in order to combat critical illness and infection [38,39]. However, there was substantial variability with respect to significant associations of low muscle mass with MV days ($n = 2$), ICU ($n = 3$), hospital LOS ($n = 2$), and survival ($n = 4$) across studies. In fact, Hoang *et al.* [18] observed that LTx patients with the highest muscle pectoralis CSA pretransplant had experienced the longest ICU LOS unadjusted for age or diagnosis, which was contrary to findings from other studies. The differences in study cohorts, transplant center experience, skeletal muscles measures, timing of CT scans pretransplant, and variable approaches to statistical analysis may have contributed to some of the heterogeneity observed across the studies. The main source of heterogeneity in post-transplant outcomes could have arisen from the fact that all studies defined low muscle mass differently, driven by lack of established cutoffs for low muscle mass in this population using CT-based methods.

CT muscle mass may provide complementary information to the assessment of physiological reserve (i.e. frailty), in the evaluation of LTx candidates. Frailty is a complex geriatric syndrome that is associated with adverse pre and post-transplant LTx outcomes [40–42], highlighting the importance of biologic over chronologic age. Sarcopenia, defined as loss of muscle mass and function [26], is an important element of frailty. Even though CT muscle mass captures only one aspect of the sarcopenia definition (low muscle mass), it embodies several underlying mechanisms incorporating elements such as protein catabolism, nutritional

deficiencies, chronic inflammation (Interleukin-6, Tumor Necrosis Factor-alpha), cell senescence, and decreased physical function [43,44]. In addition, the relationship between CT thorax and abdominal measures have shown moderate-strong correlations with quadriceps size and strength [17], hand-grip strength [45], and exercise capacity [16,19], which are known to be important prognostic markers in advanced lung disease and transplantation [46–48]. Thus, CT muscle mass allows for an opportunity to indirectly quantify one aspect of biologic aging. Future studies exploring other established measures of biologic aging such as telomere shortening [49,50], increased markers of inflammation [40,51,52], and immune cell senescence [53] may provide valuable insight into the relative contribution of each of these measures to prognosis.

The analysis of CT morphometrics beyond muscle mass measurements is gaining increased recognition, as obesity has been shown to be associated with increased levels of inflammation, adipokines, and cellular senescence [54–56]. In the present review, four studies evaluated the association of adiposity tissue with post-transplant survival with heterogeneous results. Pienta *et al.* [21] observed that increased SAT from a single thoracic axial slice was associated with improved post-transplant three-year survival, whereas Gonzalez et al observed a lower three-year survival with increased mediastinal fat volume, and no association was seen in the other two studies evaluating SAT and VAT [22,56]. In two of the studies, increased SAT on abdominal CT and increased mediastinal fat volumes were associated with a higher risk of developing PGD [33,56]. This supports the notion that abdominal SAT and mediastinal adipose tissue is associated with an increased inflammatory milieu [57] characterized by increased reactive oxygen species and decreased clearance of circulating fatty acids, both risk factors for accumulation of ectopic adiposity and PGD [58,59]. However, our understanding of the adipose tissue stores is evolving as abdominal VAT has been conceptualized as the more metabolically active tissue previously associated with increased cardiometabolic risk factors [60,61], increased frailty in LTx candidates [56], and increased limb muscle adiposity [62,63]. This accumulation of adiposity in the limb muscles may result in diminished protein synthesis, regenerative capacity, and decreased function [64–66]. Thus, a potential advantage of the CT morphometric technique over whole body composition measures (BIA or DXA) is their ability to quantify regional adiposity compartments (SAT and VAT) [67], which may help advance our understanding of the differing mechanisms underlying adiposity tissue stores and their effects on pre and post-transplant LTx outcomes.

Presently, it is not possible to make a recommendation as to the optimal CT measurement technique to apply for evaluation of low muscle mass and adiposity. There remains lack of methodological standardization across CT body composition assessments with most studies using individual chest or abdominal axial slices in LTx candidates at various anatomic locations, even though these individual axial slices have shown strong correlation with CT thoracic-abdominal muscle and adiposity volumes [68,69], and with whole body composition measures (DXA, BIA) [70]. The CT body composition assessment seems to be driven by center experience and the availability of abdominal or chest scans given thoracic scans are more likely to be the standard of care at most LTx centers [18–22]. Thus, to allow for comparison between centers it would be helpful to establish CT normative values that could be applied in the assessment of low muscle mass or adiposity in this population. One consideration may be to utilize an automated software for assessment of 3D imaging as shown by Suh *et al.* [29] to help quantify CT muscle and adiposity volumes to further establish normative values. This may reduce some of the technical heterogeneity between patients and centers that may be present using a single cross-sectional axial slice.

There are several limitations in this systematic review that need to be highlighted. Firstly, there was significant heterogeneity in CT muscle CSA and adiposity measurements across studies, which prevented pooling of data to perform a meta-analysis. Despite the heterogeneity across the included studies, this was the first comprehensive review and descriptive synthesis of CT body composition measures in LTx patients performed in accordance with the PRISMA guidelines [24]. Secondly, the studies included were all retrospective, single-center studies with CT performed for clinical purposes, with the exception of one prospective multi-centered study [56]. Thirdly, it is difficult to extrapolate some of these techniques across all pretransplant diagnoses as transplant indications such as cystic fibrosis or pulmonary hypertension were underrepresented across studies. In addition, all studies reported associations of CT body composition with post-transplant outcomes, but no studies adjusted for timing of CT scan to transplantation in their multivariable modelling and only five studies factored in type of transplant, which may have influenced early and late post-transplant outcomes. Future work will need to explore whether CT body composition measures changes in the pretransplant

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period as this was not reported in any of the studies. Furthermore, it is important to highlight that CT body composition measures are surrogate markers of whole body composition shown to be stronger prognostic markers than BMI [14,23], which is known for its poor discriminatory ability for muscle mass or adiposity measures. However, it is important to highlight that CT body composition measures may be relatively preserved compared to the dynamic nature of lower extremity limb muscle size or function [46,70] and may have a differential effect on post-transplant outcomes. Future study exploring associations of body composition with functional measures, plasma biomarkers, and rehabilitation response may provider greater insight into the clinical utility of these body composition measures in lung transplantation.

In conclusion, CT morphometric analysis evaluating muscle mass and adiposity is an evolving measurement modality that has shown heterogeneity in its association with post-transplant outcomes (MV days, ICU and hospital LOS, and survival). However, its important to highlight the variability in body composition measures, timing of CT scans, and statistical analysis may have accounted for some of this heterogeneity. The optimal CT measurement landmark (thoracic or abdominal) remains unclear, and it may be reasonable to utilize either landmark in the LTx population depending on availability of scans at the transplant center. Furthermore, the assessment of adiposity has only been evaluated in a few studies to date, and its clinical utility requires further exploration. Thus, CT morphometrics is emerging as a potential surrogate measure of body composition and physiological reserve, but further standardization of CT body composition assessments is needed to assess the prognostic utility of these measures on LTx outcomes.

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Conflicts of interest

There are no conflicts that exist for any of the authors. This work was in part presented at the American Thoracic Meeting meeting in 2019 (Dallas, U.S.A.). Rozenberg *et al.* [73].

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy used for MEDLINE.

Table S2. NIH quality assessment tool for observational cohort and cross-sectional studies.

Table S3. RoBANS: risk of bias assessment tool for nonrandomized studies.

REFERENCES

1. Stephen WC, Janssen I. Sarcopenic-obesity and cardiovascular disease risk in the elderly. *J Nutr Health Aging* 2009; **13**: 460.
2. Joppa P, Tkacova R, Franssen FM, *et al.* Sarcopenic obesity, functional outcomes, and systemic inflammation in patients with chronic obstructive pulmonary disease. *J Am Med Dir Assoc* 2016; **17**: 712.
3. Carbone S, Billingsley HE, Rodriguez-Miguelez P, *et al.* Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity, and cachexia. *Curr Probl Cardiol* 2020; **45**: 100417.
4. Lederer DJ, Wilt JS, D'Ovidio F, *et al.* Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med* 2009; **180**: 887.
5. Terjimanian MN, Harbaugh CM, Hussain A, *et al.* Abdominal adiposity, body composition and survival after liver transplantation. *Clin Transplant* 2016; **30**: 289.
6. Kamo N, Kaido T, Hamaguchi Y, *et al.* Impact of sarcopenic obesity on outcomes in patients undergoing living donor liver transplantation. *Clin Nutr* 2019; **38**: 2202.
7. Chan W, Chin SH, Whittaker AC, *et al.* The associations of muscle strength, muscle mass, and adiposity with clinical outcomes and quality of life in prevalent kidney transplant recipients. *J Ren Nutr* 2019; **29**: 536.
8. Fosbol MO, Zerahn B. Contemporary methods of body composition measurement. *Clin Physiol Funct Imaging* 2015; **35**: 81.
9. Peterson SJ, Braunschweig CA. Prevalence of sarcopenia and associated outcomes in the clinical setting. *Nutr Clin Pract* 2016; **31**: 40.
10. Troschel AS, Troschel FM, Best TD, *et al.* Computed tomography-based body composition analysis and its role in lung cancer care. *J Thorac Imaging* 2020; **35**: 91.
11. Hsu CS, Kao JH. Sarcopenia and chronic liver diseases. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 1229.

12. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. *Curr Opin Support Palliat Care* 2009; **3**: 269.
13. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; **33**: 997.
14. Kelm DJ, Bonnes SL, Jensen MD, *et al*. Pre-transplant wasting (as measured by muscle index) is a novel prognostic indicator in lung transplantation. *Clin Transplant* 2016; **30**: 247.
15. Kashani K, Sarvottam K, Pereira NL, Barreto EF, Kennedy CC. The sarcopenia index: a novel measure of muscle mass in lung transplant candidates. *Clin Transplant* 2018; **32**: e13182.
16. McDonald ML, Diaz AA, Ross JC, *et al*. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. a cross-sectional study. *Ann Am Thorac Soc* 2014; **11**: 326.
17. Mathur S, Rodrigues N, Mendes P, *et al*. Computed tomography-derived thoracic muscle size as an indicator of sarcopenia in people with advanced lung disease. *Cardiopulm Phys Ther J* 2017; **28**: 99.
18. Hoang V, Li GW, Kao CC, Dronavalli G, Parulekar AD. Determinants of pre-transplantation pectoralis muscle area (PMA) and post-transplantation change in PMA in lung transplant recipients. *Clin Transplant* 2017; **31**: e12897.
19. Rozenberg D, Mathur S, Herridge M, *et al*. Thoracic muscle cross-sectional area is associated with hospital length of stay post lung transplantation: a retrospective cohort study. *Transplant Int* 2017; **30**: 713.
20. Lee S, Paik HC, Haam SJ, *et al*. Sarcopenia of thoracic muscle mass is not a risk factor for survival in lung transplant recipients. *J Thorac Dis* 2016; **8**: 2011.
21. Pienta MJ, Zhang P, Derstine BA, *et al*. Analytic morphomics predict outcomes after lung transplantation. *Ann Thorac Surg* 2018; **105**: 399.
22. Cho YH, Do KH, Chae EJ, *et al*. Association of chest CT-based quantitative measures of muscle and fat with post-lung transplant survival and morbidity: a single institutional retrospective cohort study in Korean population. *Korean J Radiol* 2019; **20**: 522.
23. Weig T, Milger K, Langhans B, *et al*. Core muscle size predicts postoperative outcome in lung transplant candidates. *Ann Thorac Surg* 2016; **101**: 1318.
24. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**: W65.
25. Weill D, Benden C, Corris PA, *et al*. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; **34**: 1.
26. Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16.
27. NIH Quality assessment tool for observational cohort and cross-sectional studies. In Systematic Evidence Reviews and Clinical Practice Guidelines. National Heart, Lung and Blood Institute 2014. Website: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Last Accessed March 31, 2020).
28. Kim SY, Park JE, Lee YJ, *et al*. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013; **66**: 408.
29. Suh JW, Paik HC, Yu WS, *et al*. Effect of sarcopenic overweight on lung transplant based in three-dimensional reconstructed psoas muscle mass. *Ann Thorac Surg* 2019; **107**: 1626.
30. Hsu J, Krishnan A, Lin CT, *et al*. Sarcopenia of the psoas muscles is associated with poor outcomes following lung transplantation. *Ann Thorac Surg* 2019; **107**: 1082.
31. Halpern AL, Boshier PR, White AM, *et al*. A comparison of frailty measures at listing to predict outcomes after lung transplantation. *Ann Thorac Surg* 2020; **109**: 233.
32. Anderson MR, Udupa JK, Edwin E, *et al*. Adipose tissue quantification and primary graft dysfunction after lung transplantation: the lung transplant body composition study. *J Heart Lung Transplant* 2019; **38**: 1246.
33. Gonzalez FJ, Alvarez A, Cantador B, *et al*. Relationship among radiological measurements of anterior mediastinal fat and outcomes of lung transplantation in fibrotic patients. *Arch Bronconeumol* 2020 **19**: 30605. https://doi.org/10.1016/j.arbres.2019.12.002
34. Englesbe MJ, Patel SP, He K, *et al*. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg* 2010; **211**: 271.
35. Streja E, Molnar MZ, Kovesdy CP, *et al*. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. *Clin J Am Soc Nephrol* 2011; **6**: 1463.
36. Sheetz KH, Waits SA, Terjimanian MN, *et al*. Cost of major surgery in the sarcopenic patient. *J Am Coll Surg* 2013; **217**: 813.
37. van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JNM. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. *Am J Transplantat* 2016; **16**: 2277.
38. Kotler DP. Cachexia. *Ann Intern Med* 2000; **133**: 622.
39. Singer JP, Lederer DJ, Baldwin MR. Frailty in pulmonary and critical care medicine. *Ann Am Thorac Soc* 2016; **13**: 1394.
40. Singer JP, Diamond JM, Gries CJ, *et al*. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med* 2015; **192**: 1325.
41. Singer JP, Diamond JM, Anderson MR, *et al*. Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. *Am J Transplant* 2018; **18**: 1995.
42. Wilson ME, Vakil AP, Kandel P, Undavalli C, Dunlay SM, Kennedy CC. Pretransplant frailty is associated with decreased survival after lung transplantation. *J Heart Lung Transplant* 2016; **35**: 173.
43. Morley JE, Malmstrom TK. Frailty, sarcopenia, and hormones. *Endocrinol Metab Clin North Am* 2013; **42**: 391.
44. Koons B, Greenland JR, Diamond JM, Singer JP. Pathobiology of frailty in lung disease. *Transl Res* 2020; **221**: 1.
45. Martinez CH, Diaz AA, Meldrum CA, *et al*. Handgrip strength in chronic obstructive pulmonary disease. associations with acute exacerbations and body composition. *Ann Am Thorac Soc* 2017; **14**: 1638.
46. Rozenberg D, Singer LG, Herridge M, *et al*. Evaluation of skeletal muscle function in lung transplant candidates. *Transplantation* 2017; **101**: 2183.
47. Swallow EB, Reyes D, Hopkinson NS, *et al*. Quadriceps strength predicts mortality in patients with moderate to

severe chronic obstructive pulmonary disease. *Thorax* 2007; **62**: 115.
48. Castleberry AW, Englum BR, Snyder LD, *et al*. The utility of preoperative six-minute-walk distance in lung transplantation. *Am J Respir Crit Care Med* 2015; **192**: 843.
49. Faust HE, Golden JA, Rajalingam R, *et al*. Short lung transplant donor telomere length is associated with decreased CLAD-free survival. *Thorax* 2017; **72**: 1052.
50. Everaerts S, Lammertyn EJ, Martens DS, *et al*. The aging lung: tissue telomere shortening in health and disease. *Respir Res* 2018; **19**: 95.
51. Verleden SE, Martens A, Ordies S, *et al*. Immediate post-operative broncho-alveolar lavage IL-6 and IL-8 are associated with early outcomes after lung transplantation. *Clin Transplant* 2018; **32**: e13219.
52. Diamond JM, Meyer NJ, Feng R, *et al*. Variation in PTX3 is associated with primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2012; **186**: 546.
53. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. *EBioMedicine* 2017; **21**: 21.
54. Sugimoto S. Can pretransplant computed-tomographic assessment predict outcomes after lung transplantation? *J Thorac Dis* 2018; **10**: 5652.
55. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006; **54**: 743.
56. Anderson MR, Kolaitis NA, Gao Y, *et al*. A nonlinear relationship between visceral adipose tissue and frailty in adult lung transplant candidates. *Am J Transplant* 2019; **19**: 3155.
57. Wu H, Ghosh S, Perrard XD, *et al*. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007; **115**: 1029.
58. Diamond JM, Porteous MK, Roberts LJ 2nd, *et al*. The relationship between plasma lipid peroxidation products and primary graft dysfunction after lung transplantation is modified by donor smoking and reperfusion hyperoxia. *J Heart Lung Transplant* 2016; **35**: 500.
59. Grenier-Larouche T, Galinier A, Casteilla L, Carpentier AC, Tchernof A. Omental adipocyte hypertrophy relates to coenzyme Q10 redox state and lipid peroxidation in obese women. *J Lipid Res* 2015; **56**: 1985.
60. Fox CS, Massaro JM, Hoffmann U, *et al*. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007; **116**: 39.
61. Coats V, Despres JP, Almeras N, *et al*. Ectopic adiposity and cardiometabolic health in COPD. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 3331.
62. Dube MC, Lemieux S, Piche ME, *et al*. The contribution of visceral adiposity and mid-thigh fat-rich muscle to the metabolic profile in postmenopausal women. *Obesity* 2011; **19**: 953.
63. Boettcher M, Machann J, Stefan N, *et al*. Intermuscular adipose tissue (IMAT): association with other adipose tissue compartments and insulin sensitivity. *J Magn Reson Imaging* 2009; **29**: 1340.
64. Justice JN, Gregory H, Tchkonia T, *et al*. Cellular senescence biomarker p16INK4a+ cell burden in thigh adipose is associated with poor physical function in older women. *J Gerontol A Biol Sci Med Sci* 2018; **73**: 939.
65. Maddocks M, Shrikrishna D, Vitoriano S, *et al*. Skeletal muscle adiposity is associated with physical activity, exercise capacity and fibre shift in COPD. *Eur Respir J* 2014; **44**: 1188.
66. Anderson MR, Easthausen I, Gallagher G, *et al*. Skeletal muscle adiposity and outcomes in candidates for lung transplantation: a lung transplant body composition cohort study. *Thorax* 2020; **75**: 801. https://doi.org/10.1136/thoraxjnl-2019-214461
67. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. *Proc Nutr Soc* 2015; **74**: 355.
68. Tong Y, Udupa JK, Torigian DA, *et al*. Chest fat quantification via CT based on standardized anatomy space in adult lung transplant candidates. *PLoS One* 2017; **12**: e0168932.
69. Tong Y, Udupa JK, Torigian DA. Optimization of abdominal fat quantification on CT imaging through use of standardized anatomic space: a novel approach. *Med Phys* 2014; **41**: 063501.
70. Mathur S, Rozenberg D, Verweel L, Orsso CE, Singer LG. Chest computed tomography is a valid measure of body composition in individuals with advanced lung disease. *Clin Physiol Funct Imaging* 2020; **40**: 360.
71. Martin L, Birdsell L, Macdonald N, *et al*. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; **31**: 1539.
72. Prado CM, Lieffers JR, McCargar LJ, *et al*. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**: 629.
73. Rozenberg D, Orsso, CE, & Chohan, K, *et al* Utility of computed tomography body composition measures in chronic lung disease: systematic review. *Am J Respir Crit Care Med* 2019; **199**: A6891.