Title

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Journal

Transplantation, 100(8)

ISSN

0041-1337

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Publication Date

2016-08-01

DOI

10.1097/tp.0000000000001232

Peer reviewed

HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Transplantation. 2016 August ; 100(8): 1692–1698. doi:10.1097/TP.0000000000001232.

A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results from the Functional Assessment in Liver Transplantation (FrAILT) Study

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Abstract

Background—Sarcopenia and functional impairment are common and lethal extra-hepatic manifestations of cirrhosis. We aimed to determine the association between computed-tomography (CT)-based measures of muscle mass and quality (sarcopenia) and performance-based measures of muscle function.

Methods—Adults listed for liver transplant underwent testing of muscle function [grip strength, Short Physical Performance Battery (SPPB)] within 3 months of abdominal CT. Muscle mass (cm^2/m^2) =total cross-sectional area of psoas, paraspinal, and abdominal wall muscles at L3 on CT, normalized for height. Muscle quality=mean Hounsfield units (HU) for total skeletal muscle area at L3.

Results—Among 292 candidates, median grip strength was 31kg, SPPB score was 11, muscle mass was $49cm^2/m^2$, and muscle quality was 35HU. Grip strength weakly correlated with muscle mass (ρ=0.26, p<0.001) and quality (ρ=0.27; p<0.001) in men, and muscle quality (ρ=0.23,

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Authorship Contribution: Connie W. Wang and Jennifer C. Lai contributed to study design. Connie W. Wang, Hilary Hayssen, and Li-Qin Zhou participated in data collection; all authors contributed to data analysis. Connie W. Wang, Sandy Feng, Kenneth E. Covinsky, Benjamin M. Yeh, and Jennifer C. Lai contributed to the drafting of the manuscript; all authors approved the final version.

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

Description of Supporting Information: Additional Supporting Information may be found in the online version of this article.

p=0.02), but not muscle mass, in women. SPPB correlated weakly with muscle quality in men (ρ=0.38; p<0.001) and women (ρ=0.25; p=0.02), however did not correlate with muscle mass in men or women. After adjustment for gender, MELD-Na, hepatocellular carcinoma, and BMI, grip strength (HR 0.74, 95%CI 0.59–0.92, p=0.008), SPPB (HR 0.89, 95%CI 0.82–0.97, p=0.01), and muscle quality (HR 0.77, 95%CI 0.63–0.95, p=0.02) were associated with wait-list mortality, but muscle mass was not (HR 0.91, 95%CI 0.75–1.11, p=0.35).

Conclusions—Performance-based tests of muscle function are only modestly associated with CT-based muscle measures. Given that they predict wait-list mortality and can be conducted quickly and economically, tests of muscle function may have greater clinical utility than CT-based measures of sarcopenia.

INTRODUCTION

Patients with cirrhosis, who suffer from abnormal protein synthesis and energy metabolism, are at high risk for severe muscle mass depletion, more commonly known as sarcopenia (1, 2). Sarcopenia has been linked to increased wait-list and posttransplant mortality, as well as increased infection and longer posttransplant length of stay (3–6). Reduced muscle quality, as determined by fat infiltration seen at imaging, also contributes to poor physical condition and is associated with higher mortality after living donor liver transplantation (7). However, these measures of muscle mass and muscle quality are only available on cross-sectional imaging studies, and, as a consequence, can be costly, inconvenient, and challenging to implement in the clinical setting.

The European Working Group on Sarcopenia in Older People recommended that the definition of sarcopenia should include low muscle mass *and* low muscle function (8). Unlike radiographic measures of sarcopenia and muscle quality, performance-based measures of muscle function, such as hand grip strength and the Short Physical Performance Battery (SPPB), can be conducted quickly, reliably, and economically at the bedside (9, 10). Although originally developed and validated in community-dwelling populations of adults over the age of 65 years (11–13), these measures of muscle function predict wait-list mortality – independent of liver disease severity in chronologically younger liver transplant candidates (14). The relationship between muscle function with sarcopenia and muscle quality in liver transplant patients is poorly characterized. Therefore, we designed this study to: 1) determine the association between performance-based tests of muscle function and computed tomography (CT)-based measures of muscle mass and quality in liver transplant candidates, and 2) compare the ability of these muscle measures to predict wait-list mortality.

MATERIALS AND METHODS

Study population

The Functional Assessment in Liver Transplantation (FrAILT) Study is a prospective cohort study of all adult (≥18 years) patients with cirrhosis who are actively listed for liver transplantation at the University of California, San Francisco with a 97% recruitment rate (14). Enrollment occurred from November 1, 2011 through November 30, 2014. At

enrollment, all patients undergo testing of muscle function using grip strength and the SPPB (defined below). In order to ensure muscle function testing was representative of muscle mass and quality as measured on cross-sectional imaging, only candidates with an abdominal computed tomography (CT) scan within 3 months of muscle function testing were included. Of the available CT scans for assessment, 160 (55%) were performed for hepatocellular carcinoma (HCC) evaluation or follow-up, 64 (22%) for HCC screening, 16 (6%) for preliver transplant evaluation, 17 (6%) for portal vein evaluation, and the remaining for acute indications including abdominal pain, sepsis, incarcerated hernia evaluation, small bowel obstruction, etc. Five patients were excluded because their CT scans did not fully capture abdominal wall musculature in the anatomic scan range.

Data collection

An axial CT image at the third lumbar (L3) vertebral level was identified from each patient's scan. The surrounding skeletal muscles were identified and quantified within standard Hounsfield units (HU) thresholds of −29 to +150. All CT images were viewed and analyzed by a trained research staff member using a CT scan postprocessing workstation (Advantage Windows 2.2, Volume Viewer software, GE Healthcare, Waukesha, WI).

At the time of muscle function testing, information regarding demographics, medical comorbidities (e.g., hypertension, diabetes) noted as a problem in the past medical history, degree of ascites, and laboratory tests were collected from the patient's electronic health record. Hepatic encephalopathy was classified as none/mild, moderate, or severe based on a Numbers Connection Test time of ≤60 seconds, 60 to 120 seconds, or >120 seconds, respectively (15).

Measures of muscle function, mass, and quality

The following tests assessed:

1) Muscle function

a) Grip strength: Grip strength was measured with a handheld Jamar dynamometer in the dominant hand using the average of 3 trials for analysis and taking less than thirty seconds to perform. The Jamar dynamometer costs approximately $200 and is a 1-time cost. Weak grip was determined by reported cut-off values established in community-dwelling older adults (16) and applied in a prior study of functional impairment in liver transplant candidates (14). The cut-off values in men were: ≤29 kg if BMI was ≤24 kg/m^2, ≤30 kg if BMI was 24.1–28 kg/m^2, and ≤32 kg if BMI was >28 kg/m^2. In women: ≤17 kg if BMI was ≤23 kg/m^2, ≤17.3 kg if BMI was 23.1–26 kg/m^2, ≤18 kg if BMI was 26.1–29kg/m^2, and ≤21 kg if BMI was >29 kg/m^2.

b) Short Physical Performance Battery (SPPB): The SPPB consists of timed repeated chair stands, balance testing, and a timed 13-foot walk (9) and takes 2 to 3 minutes to complete. The scale ranges from 0 to 12 by summing the score of each component of the SPPB

based on the patient's ability to complete the test with a maximum score of 4 per component. A score of 0 indicates lowest function and 12 indicates highest function. We selected an SPPB score ≤9 to indicate “functional impairment” as this would represent at least 1-point of impairment in each of the 3 components of the SPPB, or at least 2-points of impairment in 1 of the components.

2) Muscle mass

Skeletal muscle index (SMI): The total cross-sectional area (cm^2) of the psoas, paraspinal, and abdominal wall (including rectus abdominis, transverse abdominis, and internal and external obliques) muscles at L3 were semi-automatically meaured and normalized for height (cm^2/m^2) to obtain the SMI, as previously reported (17). Cut-off values for sarcopenia were derived from a CT-based study of 1,473 patients with solid tumors (18), which has been utilized previously in cirrhotic patients (6). Threshold values for sarcopenia were SMI <41 cm^2/m^2 for women, SMI <43 cm^2/m^2 for men with BMI <25 kg/m^2, and SMI <53 cm^2/m^2 for men with BMI ≥25k g/m^2.

3) Muscle quality

Skeletal muscle attenuation (SMA): SMA, which is inversely related to increased macroscopic fat infiltration of muscle, was determined by the mean CT attenuation (HU) for the entire skeletal muscle area region of interest at L3. Reduced muscle attenuation was based on published cut-off values (18) that have been previously used in patients with cirrhosis (6). Threshold values for reduced muscle attenuation were SMA <41 HU for patients with BMI <25 kg/m^2 and SMA <33 HU for patients with BMI ≥25 kg/m^2.

Statistical analysis

Differences in baseline characteristics, muscle function (by grip strength and the SPPB), muscle mass (by SMI), and muscle quality (by SMA) were compared using chi-square or Wilcoxon rank sum tests for categorical and continuous variables, respectively. Spearman's rank correlation assessed the relationships between muscle function, muscle mass, muscle quality, BMI, and laboratory tests. The Kruskal-Wallis test compared muscle function, mass, and quality by wait-list outcome.

The primary outcome was wait-list mortality, defined as death prior to liver transplantation or delisting for being too sick for transplant. Cox proportional hazards models evaluated the associations between wait-list mortality with muscle function, muscle mass, or muscle quality. Patients who were transplanted or delisted for reasons other than being too sick (e.g., substance abuse, nonadherence) were censored from the FrAILT Study at the time of wait-list removal. All covariates associated with a p-value of <0.10 in univariable analysis were evaluated in the final multivariable model. We employed backwards step-wise selection to eliminate covariates from the final multivariable model using a cut-off p-value <0.05 to determine statistical significance for inclusion. Each muscle measure was evaluated in a

separate multivariable model. Gender was forced into all multivariable models given the expected gender differences in the absolute values of the muscle measures.

The UCSF Institutional Review Board approved this study (IRB approval number 11-07513). STATA® v12 (College Station, Texas) was used for all statistical analyses.

RESULTS

Baseline characteristics

A total of 292 liver transplant wait-list candidates were included in the analyses. Baseline characteristics are shown in Table 1. Median duration of follow-up was 15 months. Women comprised 34% of the cohort. Notable characteristics include median age of 61 years, median BMI of 28 kg/m^2, and 54% were of non-Hispanic white race. The majority of patients had chronic hepatitis C (60%) as their primary liver disease etiology, no ascites (68%), and none or mild hepatic encephalopathy (83%); 46% had hepatocellular carcinoma (HCC). With respect to markers of liver disease severity, median MELD was 15, median MELD-Na was 17, median albumin was 3.0 g/dL, and the proportion of patients with Child Pugh class A, B, and C were 27%, 51%, and 22%, respectively.

Baseline measurements of muscle function, mass, and quality

Baseline measurements of muscle function, mass, and quality are shown in Table 2. Median grip strength was 31 kg; 30% of patients were functionally impaired by weak grip. On the SPPB, median score was 11, and 32% of candidates had functional impairment (by SPPB ≤9). As for the individual components of the SPPB, median gait speed was 1.2 m/sec, 74% of patients were able to complete all 3 balance tests for 10 seconds each, and median chair stands time was 12.0 sec. Median muscle mass, as determined by the skeletal muscle index, was 49 cm^2/m^2 and median muscle quality, as determined by muscle attenuation, was 35 HU. The proportion of patients with sarcopenia and poor muscle quality were 38% and 50%, respectively.

Associations between muscle function, mass, and quality

Grip strength was moderately correlated with muscle mass (ρ=0.26, p<0.001) and muscle quality (ρ=0.27, p<0.001) in men, whereas grip strength was only moderately correlated with muscle quality (ρ=0.23, p=0.02), but not muscle mass (ρ=0.002, p=0.99), in women [Figure 1]. SPPB correlated modestly with muscle quality in both men (ρ=0.38; p<0.001) and women (ρ=0.25; p=0.002), however there was no correlation between SPPB and muscle mass in men (ρ=0.09; p=0.24) or women (ρ=0.07; p=0.50) [Figure 1]. Relationships between muscle function, mass, and quality with BMI and laboratory tests are shown in Supplemental Table 1.

Associations between muscle function, mass, and quality with wait-list outcomes

By the end of follow-up, 61/292 (21%) patients died/were delisted, 119 (41%) underwent liver transplant, 15 (5%) were removed from the wait-list for other reasons, and 97 (33%) remained on the wait-list. Table 3 compares measures of muscle function, mass, and quality by wait-list outcome. Compared to those who were transplanted, still waiting, or removed

from the wait-list for other reasons, patients who died/were delisted exhibited poor muscle function as demonstrated by the lower grip strength (p=0.049) and lower SPPB score (p=0.037). However, liver transplant candidates were similar with respect to muscle mass (p=0.81) and muscle quality (p=0.18), regardless of wait-list outcome. In gender-stratified analyses, these differences in measures of muscle function by wait-list outcome remained qualitatively similar in only men, however no longer statistically significant, whereas there was no difference in measures of muscle mass or quality by wait-list outcome in men or women.

In univariable analysis, wait-list mortality was significantly associated with grip strength (HR 0.80 per 5 kg increase; p=0.002), SPPB (HR 0.87 per point increase; p=0.001), and muscle quality (HR 0.82 per 5 HU increase; p=0.03). After adjustment for MELD-Na, gender, hepatocellular carcinoma, and BMI in multivariable models, the hazard ratios associated with grip strength (HR 0.74 per 5 kg increase; p=0.008), SPPB (HR 0.89 per point increase; p=0.01), and muscle quality (HR 0.77 per 5 HU increase; p=0.02) did not change substantially and maintained statistical significance (Table 4). Muscle mass was not predictive of wait-list mortality in uni-(HR 0.91 per 5 cm^2/m^2 increase; p=0.19) or multi-variable analyses (HR 0.91 per 5 cm^2/m^2 increase; p=0.39) [Table 4]. Other covariates that were evaluated in univariable analysis but did not meet statistical significance for inclusion in the multivariable model include: age, race, liver disease etiology, ascites, and hepatic encephalopathy.

DISCUSSION

Muscle wasting is a well-recognized and frequent complication of cirrhosis that can negatively impact a patient's function, symptoms, quality of life, and survival (19). While quantification of muscle mass with cross-sectional imaging or morphometric analysis can capture its loss (i.e., sarcopenia), it fails to evaluate these patient-centered outcomes. Furthermore, with the introduction of the MELD-based allocation system, and most recently the Share 35 policy, more liver transplant candidates are sicker at the time of transplantation (20), and likely, more severely impaired. Decreased physical function may, arguably, become more relevant to patients with end-stage liver disease who must wait longer for a transplant. It is, therefore, critically important to develop tools to quantify the effect of cirrhosis on muscle.

Our study is the largest to date to evaluate muscle function, muscle mass, and muscle quality in cirrhotics. First, we observed high rates of reduced muscle function, mass, and quality in our cohort. Second, muscle function – whether measured by grip strength or SPPB – and muscle quality predicted wait-list mortality, whereas muscle mass did not. Lastly, measures of muscle function correlated only modestly with muscle mass and quality. Our data provide a critical link between measures of muscle function and sarcopenia that had previously been lacking.

What exactly, then, do these tests of muscle function measure? In the field of geriatrics where these measures were developed, the functional property of muscle is generally defined as (21):

$$\text{muscle function} = \frac{\text{muscle strength}}{\text{unit of muscle mass}}$$

Muscle mass quantification (i.e., skeletal muscle index on cross-sectional imaging), a static measure, fails to capture the loss of muscle strength or performance that potentially occurs as a result of intramuscular fat accumulation and other biological changes in muscle structure in patients with cirrhosis (22, 23). In addition, the loss of either muscle function or strength was more strongly associated with physical disability, functional limitation, and institutionalization than muscle mass in community-dwelling older adults (10, 24, 25). Likewise, a recent study demonstrated that, for liver transplant candidates, decreased functional capacity, as determined by the 6-minute walk test, was significantly associated with increased wait-list mortality, however sarcopenia was not (26). Moreover, there was no correlation between sarcopenia and functional impairment on the 6-minute walk test. We hypothesize that muscle function can serve as a comprehensive assessment of not only the musculoskeletal system, but also the patient's global health status, overall physical condition, and, perhaps most importantly for the patient, mobility and independence.

We acknowledge several limitations to our study. The cut-off values used to define sarcopenia and reduced muscle quality were validated in a population of patients with solid tumors and obesity. To date, predefined cut-offs for sarcopenia or reduced muscle quality in cirrhotic patients are lacking. Contrary to previously published data using the same sarcopenia cut-offs, sarcopenia failed to emerge as a significant predictor of wait-list mortality in our study (4). The low rate of mortality may explain this discrepancy. More importantly, patients with cirrhosis may be physiologically different enough from patients with cancer to necessitate disease-specific cut-offs for sarcopenia. Larger or multi-center studies are necessary to more accurately define sarcopenia and determine its impact on mortality in liver transplant candidates. There is potential for selection bias of patients who received CT scans compared to those who did not, and were thus, excluded from the study. This concern provides all the more reason for the clinical utility of performance-based measures that a patient can undergo at any time, whereas it is more difficult and costly to justify repeated CT scans. The relatively small female population in our cohort limited our ability to perform gender-stratified analyses. Although the associations we identified between wait-list outcomes and muscle function, mass, and quality by gender were weaker in women than men, the interaction term was not statistically significant. Because the liver transplant candidates included in the cohort were enrolled in the outpatient setting, the median MELD score of our cohort is relatively low. Additional studies that include inpatients are necessary to evaluate the impact of functional impairment in higher MELD cohorts. Finally, this is a single-center experience and our findings need to be confirmed in other cohorts. Although there may be bias of transplanting patients with poor muscle function, the muscle function measures in this study were used for research purposes only and were not released to transplant clinicians nor had any impact on clinical decision-making.

Despite these limitations, our findings have important implications for clinical practice. First, muscle function, as assessed by grip strength and/or the SPPB, can identify liver

transplant candidates at risk of adverse wait-list outcomes. Tests of muscle function have a distinct advantage over muscle measures that must be assessed by an imaging study (i.e., skeletal muscle index and muscle attenuation) in that they can be implemented quickly and economically at the bedside, and, importantly, can be followed longitudinally. This is relevant for candidates with high MELD scores to determine who will reach transplant with enough functional reserve to undergo surgery. Equally importantly, these measures can distinguish those with low MELD scores who may be less able to withstand the stressors of acute illness on the wait-list and, therefore, most vulnerable to becoming too sick for transplant. Identifying these candidates at an *earlier* stage in the listing process (i.e. at a low MELD score) may have greater clinical utility by providing the opportunity to intervene. These interventions may include prehabilitation programs to direct care towards improving functional status and quality of life or in some cases, early referral to palliative care. Lastly, our data fill a critical gap to begin to better understand the complex relationship between functional limitation and sarcopenia. Additionally, our study provides the liver transplant community with new tools to quantify the impact of muscle function – or dysfunction - on outcomes in patients with cirrhosis. Although there is no data on posttransplant functional outcomes of candidates, we are currently conducting a prospective study to investigate the significance of pretransplant functional impairment on outcomes and recovery after liver transplantation. Our study lays the foundation for expanding the concept of sarcopenia in cirrhotics beyond simply quantifying muscle mass and quality, to developing measures of muscle function that capture meaningful and important outcomes for patients.

Supplemental Tables

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was funded by an American College of Gastroenterology Junior Faculty Development Award, UCSF Older Americans Independence Center (P30AG044281), NIA Grants for Early Medical and Surgical Subspecialists' Transition to Aging Research (R03AG045072), UCSF Liver Center (P30 DK026743), NIA Paul B. Beeson Career Development Award in Aging (K23AG048337), and the UCSF Research Evaluation and Allocation Committee.

Abbreviations

CT	computed tomography
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
HU	Hounsfield units
IQR	interquartile range
MELD	model for end-stage liver disease
NAFLD	nonalcoholic fatty liver disease

SPPB	Short Physical Performance Battery
SMI	Skeletal muscle index
SMA	Skeletal muscle attenuation

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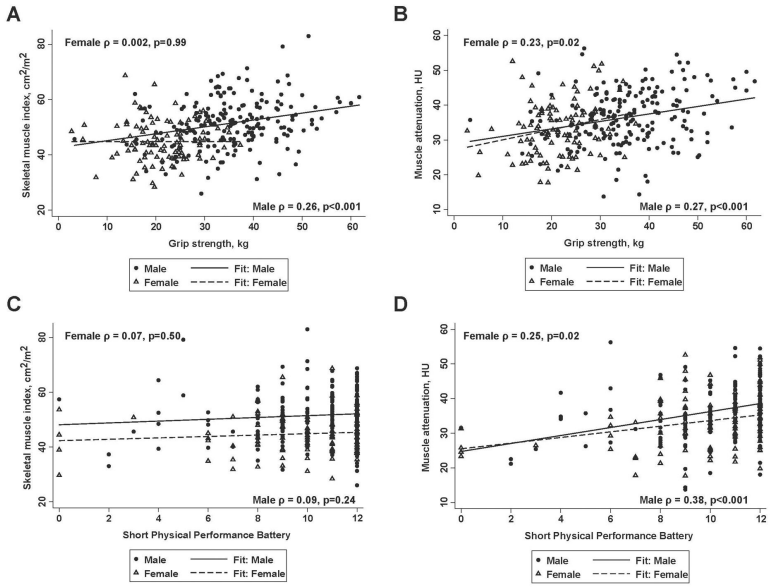

Figure 1.

Scatter plots depicting gender-specific correlations between grip strength with skeletal muscle index (A), muscle attenuation (B), and the Short Physical Performance Battery with skeletal muscle index (C), muscle attenuation (D).

Table 1

Baseline characteristics of 292 liver transplant candidates.

Characteristic*		
Follow-up time, months		15 (9–23)
Age, years		61 (55–65)
Female		34%
Race/ethnicity	**Non-Hispanic white**	55%
	Black	5%
	Hispanic	26%
	Asian	8%
	Other	6%
Etiology of liver disease	**HCV**	60%
	Alcohol	11%
	NAFLD	8%
	Cholestatic	10%
	Other	12%
Hepatocellular carcinoma		46%
BMI, kg/m^2		28 (24–32)
Medical comorbidities		
Hypertension		44%
Diabetes		34%
Laboratory tests		
Laboratory MELD		15 (12–18)
MELD-Na		17 (14–22)
Total bilirubin, mg/dL		2.3 (1.5–3.8)
INR		1.4 (1.2–1.6)
Creatinine, mg/dL		0.9 (0.7–1.2)
Sodium, mEq/L		136 (134–139)
Albumin, g/dL		3.0 (2.6–3.4)
Ascites	**Absent**	68%
	Mild-moderate	30%
	Severe	2%
Hepatic encephalopathy †	**None/mild**	83%
	Moderate	13%
	Severe	4%
Child Pugh Score	**A**	27%
	B	51%
	C	22%
Wait-list outcome	**Waiting**	33%

Characteristic*		
	Died/Delisted	21%
	Transplanted	41%
	Other	5%

*Median (interquartile range) or %.

†None/mild hepatic encephalopathy was defined as a Numbers Connection Test time ≤60 seconds, moderate hepatic encephalopathy was defined as 60–120 seconds, and severe hepatic encephalopathy was defined as >120 seconds.

Table 2

Measures of muscle function, mass, and quality.

Measure*	
Muscle Function	
Grip Strength, kg	31 (23–39)
Weak grip †	30%
Short Physical Performance Battery (SPPB) Summary Score	11 (9–12)
SPPB ≤9 ‡	32%
Individual SPPB Components	
Walk speed, m/sec	1.2 (1.0–1.5)
Balance, sec	30 (30–30)
Chair stands, sec	12.0 (9.2–16.5)
Muscle Mass	
Skeletal muscle index, cm^2/m^2	49 (43–54)
Sarcopenia §	38%
Muscle Quality	
Muscle Attenuation, HU	35 (30–41)
Poor muscle quality ∥	50%

*Median (interquartile range) or %.

†For men: ≤29kg with BMI ≤24kg/m^2, ≤30kg with BMI 24.1–28kg/m^2, and ≤32kg with BMI >28kg/m^2. For women: ≤17kg with BMI ≤23kg/m^2, ≤17.3kg with BMI 23.1–26kg/m^2, ≤18kg with BMI 26.1–29kg/m^2, and ≤21kg with BMI >29kg/m^2.

‡Represents at least 1-point of impairment in each of the three components of the Short Physical Performance Battery or at least 2-points of impairment in 1 of the components.

§For men: ≤43cm^2/m^2 with BMI <25kg/m^2 and ≤53cm^2/m^2 with BMI ≥25kg/m^2. For women: ≤41cm^2/m^2 with any BMI.

∥<41HU for patients with BMI <25kg/m^2 and <33HU for patients with BMI ≥25kg/m^2.

Table 3

Measures of muscle function, mass, and quality of the entire cohort, categorized by wait-list outcome.

Measure*	Died/delisted n = 61 (21%)	Transplanted n = 119 (41%)	Waiting n = 97 (33%)	Other† n = 15 (5%)	p-value‡
Muscle Function					
Grip Strength, kg	26 (19–33)	33 (23–38)	32 (25–40)	30 (23–38)	0.049
SPPB Summary Score	10 (8–12)	11 (9–12)	11 (10–12)	11 (9–12)	0.04
Muscle Mass					
Skeletal muscle index, cm^2/m^2	48 (42–55)	49 (43–53)	50 (43–56)	46 (43–54)	0.81
Muscle Quality					
Muscle Attenuation, HU	34 (29–38)	36 (29–41)	37 (31–43)	35 (31–38)	0.18

*Median (interquartile range).

†Removed from wait-list for reasons other than death, transplant, or being too sick for transplant (i.e. substance abuse, medica nonadherence).

‡By the Kruskal-Wallis test.

Transplantation. Author manuscript; available in PMC 2017 August 01.

Table 4

Associations of muscle function, mass, and quality with wait-list mortality.

Model	Hazard Ratio (95% CI) p-value			
	Grip strength (per 5 kg increase)	SPPB (per point increase)*	Muscle mass (per 5 cm^2/m^2 increase)	Muscle quality (per 5 HU increase)
Univariable	***0.80 (0.69–0.92)***	***0.87 (0.80–0.95)***	0.91 (0.78–1.05)	***0.82 (0.68–0.98)***
	0.002	***0.001***	0.19	***0.03***
Multivariable †	***0.74 (0.59–0.92)***	***0.89 (0.82–0.97)***	0.91 (0.75–1.11)	***0.77 (0.63–0.95)***
	0.008	***0.01***	0.35	***0.02***

*Performance-based instrument that consists of three tests: repeated chair stands, balance testing, and gait speed. Range 0 (lowest function) to 12 (highest function).

†All covariates that were associated with the outcome with a p-value <0.10 in univariable analysis were evaluated for inclusion in the multivariable model. Each muscle measure was evaluated in a separate multivariable analysis adiusted for MELD-Na, gender, HCC, and BMI. Gender was forced into the model given the significant gender differences in muscle measures. Other covariates that were evaluated but not included in the final model: age, race, liver disease etiology, ascites, and hepatic encephalopathy.