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Et al.

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Abstract

Objectives: **A growing body of evidence shows that frailty and functional performance predict liver transplant outcomes. The Organ Procurement and Transplant Network uses the Karnofsky Performance Status scale to adjust for transplant center case mix in assessing quality measures. This study explores the strength of the relationship between Karnofsky Performance Status scores and objective measures of frailty.**

Materials and Methods: **This observational study includes 136 adult, first-time liver transplant recipients at UMass Memorial (2006-2015) who had 2 abdominal computed tomography scans available (at ≤ 90 days pretransplant and ≥ 7 days before that). We analyzed the relationship between Karnofsky Performance Status and muscle wasting using absolute and change in psoas muscle size and quality pretransplant.**

Results: **The mean age was 55 years, mean Model for End-Stage Liver Disease was 22, and 34% of patients were women. In the study group, 50% of patients had sarcopenia pretransplant and 71.3% demonstrated declined lean psoas area at an average rate of 11% per month. Patients who experienced muscle wasting at a rate of ≥ 1% per month had 2.83 times the risk (95% confidence interval, 1.18-6.80) of being severely impaired/disabled pretransplant. The risk increased by 2.32-fold (95% confidence interval, 1.44-3.75) for every standard deviation decrease in pretransplant lean psoas area.**

Conclusions: **Provider-assessed physical health status moderately correlates with objective measures of frailty.**

Key words: *Biostatistics, Frailty, Hepatology, Karnofsky Performance Status, United Network for Organ Sharing*

Introduction

Over the past decade, the growing shortage in organ availability in the United States has transformed practice patterns in liver transplantation.[1,2] To minimize mortality on wait lists, the current system of liver allocation was designed to prioritize the "sickest first." Patients are ranked according to the Model for End-Stage Liver Disease (MELD) score, which is calculated using 3 objective laboratory values (creatinine, bilirubin, and international normalized ratio). Although MELD is a reliable predictor of 3-month wait list mortality at the population level, it is a poor predictor of posttransplant mortality.[3-5] Recent studies have shown that MELD score underestimates the risk of wait list and postoperative mortality among liver transplant patients who are considered to be "frail."[5-7] It is hypothesized that frailty may make patients more vulnerable to stressors such as surgery due to limited physiologic reserve, leading to worse outcomes when faced with a stressor such as major abdominal surgery.[6,8]

Frailty syndrome describes a dynamic and potentially modifiable phenomenon of decreasing strength, function, and overall health status as a result of advanced age, chronic disease and malnutrition, comorbidities, and other systemic dysfunctions.[9,10] Muscle wasting, or sarcopenia, is a hallmark of end-stage liver disease and has been used as an objective measure of frailty and predictor of morbidity and mortality in this population.[11-19] However, assessment of sarcopenia or other proposed objective measures of frailty have limited clinical utility because they are

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often not practical to assess in the perioperative setting. Moreover, this measure may be too narrow to describe global physical health status[11] compared with a phenotypic, clinician-assigned score on a validated scale of frailty.[17]

Decreased muscle mass due to reductions in muscle fiber number and size and strength leads to declined functional performance.[20-22] Functional status has also been shown to independently predict liver transplant outcomes.[8,23-27] In accordance with a United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network (OPTN) mandate, functional status data have been collected from all US transplant centers using the Karnofsky Performance Status (KPS) scale for more than a decade. These data are then used to risk-adjust for center case mix in the creation of program-specific reports on outcomes. Although KPS is a widely validated tool for assessment of global physical function across many disease indications and has been used clinically and in clinical trials for over 60 years,[25,28-33] its validity in a liver transplant population remains unknown. Although analytic morphomic research has been used to identify a strong correlation between objective measures of sarcopenia and global assessments of physical health status, the study was conducted in a population of older (> 70 years) general surgery patients and not in liver transplant patients.[34] There remains a gap in the literature on defining and understanding the mechanisms underlying the frailty phenotype for liver transplant patients. This will be the first study to describe the relationship between phenotypic and physiologic signs and symptoms of frailty syndrome in a liver transplant population.

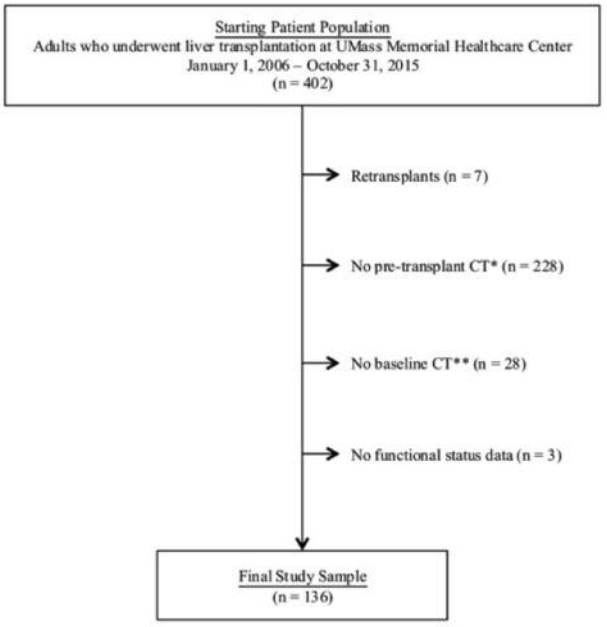
In this study, our aim was to describe the relationship between provider-assessed functional status (KPS) and objective measures of sarcopenia, collected using validated analytic morphomic methodology.

Materials and Methods

Study design and population

This retrospective cohort study included adults who underwent first-time liver transplant at UMass Memorial Healthcare Center (UMMHC) between January 1, 2006, and October 31, 2015, a 781-bed, tertiary care medical center located in Worcester, Massachusetts, USA. The UMMHC transplant program includes adult and pediatric liver, kidney, and pancreas transplants. In 2012, this center performed more liver transplants than any other program in the New England area of the United States.[35] Patients without both a "pretransplant" (≤ 90 days before transplant) abdominal computed tomography (CT) scan (n = 228) and a referent ("baseline") CT scan at least 7 days before the pretransplant CT (n = 28) or patients who were missing data on functional status at transplant (n = 3) were excluded (Figure 1). This study was approved by the UMass Medical School Institutional Review Board.

Figure 1. Study Inclusion/Exclusion Flow Chart



*Abdominal CT ≤ 90 days before transplant
**Abdominal CT at least 7 days before pre-transplant CT

CT: computed tomography abdominal scan

Data collection and variable definitions

Muscle measures

Muscle measurements were collected from CT scans performed as part of routine clinical care. Patients who are on the UMMHC liver transplant wait list undergo routine abdominal imaging at the time of candidacy evaluation and every 6 to 12 months until transplant, depending on their primary diagnosis. Baseline and pretransplant psoas muscle size (cross-sectional area, in mm^2) and quality (density, Hounsfield units [HU]), which included both left and right psoas muscles, were measured at the L4 vertebral level superior plate according to analytic

morphomic methodology.[12] All measures were collected by a UMass radiology attending physician with fellowship training in abdominal radiology (AS) using tools built into the radiology management system (General Electric Centricity Radiology Information System/Picture Archiving and Communication System).

Intrarater reliability was confirmed using test-retest methodology prior to initiation of study data collection.[36] Briefly, this approach involves re-ascertainment of the same patients, using the same tools and administered by the same research staff, ideally 2 weeks apart to prevent recall bias. We used images from patients who did not otherwise meet study inclusion criteria. We used power calculations to determine that a sample that was 5% of the target study sample (n = 125), which included 4 images per patient, would be sufficient to determine good reliability, defined as ≥ 90% correlation using Pearson correlation coefficient. Correlation between the identical images measured 2 weeks apart was found to be 97%.

Individual psoas muscle measurements were combined to create the following variables: total psoas area (TPA; left + right cross-sectional area, mm^2), mean density ([left + right density]/2, HU), lean psoas area (LPA; TPA × [mean density+85]/170, mm^2), and stature-normalized.[15] We determined LPA (LPA/height^2, mm^2/m^2) for each time point. These measures were explored as follows: (1) sarcopenia pretransplant (pretransplant LPA relative to "normal"), (2) relative sarcopenia or extent of muscle wasting (relative LPA change from baseline), and (3) muscle wasting rate (rate of relative change per month). Normal sarcopenia pretransplant was defined using sex-specific LPA averages reported in a sample of over 1200 elective surgery patients[37] and assessed at a single time point (pretransplant) of sarcopenia (sarcopenic/not sarcopenic: > 1 standard deviation [SD] below average/≤ 1 SD above average, with cutoff points of 1488.4 mm^2 for men and 974.8 mm^2 for women). Cutoff points were used to facilitate comparability with other studies. Relative sarcopenia uses a patient's own "baseline" (psoas measures from earliest available abdominal CT scan) as the referent, measured as patient score pre-transplant minus baseline LPA/baseline LPA (%). Because this was a retrospective study, time between scans was not uniform among patients. We therefore standardized relative change in LPA per the number of months between CT scans (%/month). Relative change variables were explored as both continuous variables and grouped into tertiles.

Functional status

Functional status was defined using the KPS scale, which is described in Table 1. The KPS scale was designed to be assessed by providers and has been widely used and validated in many different populations, including patients with end-stage renal disease.[25,28,29,31-33,38-42] The original KPS is an 11-tiered scale, which decreases from a maximum of "100%: normal, no complaints, no evidence of disease" to "0%: dead" in 10% increments. A collapsed, 3-tiered version is also available and has high interrater reliability.[25,38,43] We assigned labels to summarize extent of functional impairment/disability in each respective category as follows: none/normal function (category A: 80%-100%), moderate limitations (category B: 50%-70%), and severely impaired disabled (category C: ≤ 40%). We explored KPS as a continuous, categorical, and binary variable.

Table 1. Karnofsky Performance Status Scale and Variable Handling

Condition	%	Rating Criteria
A ("none/normal")	100	- Normal, no complaints; no evidence of disease
• Able to carry on normal activity and to work; no special care needed	90	- Able to carry on normal activity; minor signs or symptoms of disease
	80	- Normal activity with effort; some signs or symptoms of disease
B ("moderate")	70	- Cares for self; unable to carry on normal activity or to do active work
• Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	60	- Requires occasional assistance but is able to care for most of his personal needs
	50	- Requires considerable assistance and frequent medical care
C ("severe")	40	- Disabled; requires special care and assistance.
• Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	30	- Severely disabled; hospital admission is indicated although death not imminent
	20	- Very sick; hospital admission necessary; active supportive treatment necessary
	10	- Moribund; fatal processes progressing rapidly
	0	- Dead

Abbreviations: Author-assigned variable labels are shown in parentheses.

Covariates of interest

Potential confounders of interest were selected based on literature review and a priori knowledge. Characteristics of interest included sociodemographics, body habitus, comorbidities, liver diagnoses, and illness severity (laboratory-based MELD scores, Child-Pugh scores, sequelae of liver disease, and medical condition). Because previous studies have shown substantial differences in degree and mechanism of muscle wasting in men versus women, patient sex was a key characteristic that we explored in the most depth.

These data were collected from the UMMHC transplant registry, which included variables collected and submitted by mandate to UNOS/SRTR database and other clinical and laboratory variables from patients' electronic medical records that are automatically imported into the registry in real time.

Statistical analyses

Univariate and bivariate distributions of muscle measures, functional status, and key characteristics at baseline and pretransplant were explored graphically and with contingency table analyses. For descriptive statistics of the study sample, continuous variables are described as mean and SD if normally distributed and median and interquartile range (IQR) if skewed, and categorical variables are described as proportions (%).

The relationship between sarcopenia and functional status was assessed using correlation and logistic regression analyses. Correlations between continuous KPS and LPA rate of change were compared using Spearman rho rank correlation coefficient for ordinal data.[44]

Testing correlation assumptions revealed a parabolic relationship between variables, with an inflection point at 20% increase in LPA per month; therefore, we reported correlations for patients with values of less than +20%, which excluded 5 people (N = 131). Briefly, we assessed linear and monotonic assumptions of correlation (for Pearson and Spearman correlation) by exploring scatter plots and locally weighted scatterplot smoothing-weighted curves for 10-point KPS scale versus rate of muscle wasting (% change in LPA/month). Using locally weighted scatterplot smoothing results in which the association reverses direction past a certain (extreme) point and a potential parabolic relationship between the 2 variables occurs, we explored a squared transformation of LPA rate. A linear regression model was run with functional status as the dependent variable and LPA rate plus a squared (positive value) transformation of the LPA rate to test whether this was the case (yes if *P* value of squared variable was significant) and to quantify the point of inflection where the effect reverses. Transformation of the primary independent variable was decided against to simplify the primary variable of interest and to allow ease of interpretation from a clinician's perspective. Instead, correlations were assessed in a sample subset in which the monotonic form in the relationship between variables held (uniform direction of effect; that is, no reversal). After exploring potential explanations for the 5 unlikely values of increasing LPA at a rate of > 20%/month, we were unable to determine a definite explanation that would have otherwise been considered a conceptually important exclusion criterion.

For power calculations, we assumed normal distributions of both sarcopenia and functional status variables, a sample size of 131 patients (after applying exclusions described in the above paragraph), an alpha of 0.05, power (1-beta) of 0.80, and a null correlation of 0. Thus, the smallest correlation detectible was 0.24 for a two-tailed test (weak correlation). Given these parameter restrictions, we may not be able to detect correlations weaker than 0.24.

We evaluated unadjusted and adjusted odds of severe functional impairment (KPS of 10% to 40% versus referent [KPS of 50% to 100%]) for 3 working definitions of muscle wasting: (1) rate of muscle wasting, (2) pretransplant sarcopenia (yes/no), and (3) pretransplant LPA (per SD decrease), using logistic regression and adjusting for age (≥ 55 vs < 55 years), sex (women vs men), and race (white vs non-white ethnicity). Results are presented as odds ratios (OR) with accompanying 95% confidence intervals (CI).

Tests of statistical significance were selected as appropriate based on normality of the dependent variable. For normally distributed continuous variables, we used *t* tests, paired *t* tests (for baseline vs pretransplant comparisons), and analysis of variance. For skewed continuous variables, we used Wilcoxon rank-sum test for unmatched pairs or signed-rank test for pairs (baseline vs pretransplant psoas measures). For categorical variables, we used chi-square or Fischer exact test for cell sizes < 5.

P values ≤ .05 were considered significant. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX, USA).

Results

The final study sample included 136 patients who underwent first-time liver transplant between 2006 and 2015, with 266 patients excluded. In the included patient sample, the mean age was 55.4 years, 38% were women, the most common ethnic minority was Hispanic/Latino (14.7%), and 77.2% of patients were white, the mean age was 55.6 years and other results were 39.1%, 11.8%, and 84.4%, respectively, in the excluded group. Primary causes of liver disease included hepatitis C/viral hepatitis (47.1%), alcoholic hepatitis (24.3%), and other liver diseases (28.7%) versus 34.2%, 38.4%, and 25.9%, respectively, in the excluded group. Hepatocellular carcinoma was present in 36.0% of the included versus 16.9% of the excluded group ($P < .001$). In the included versus excluded group, the mean laboratory-calculated MELD score pretransplant was 22.3 versus 18.7 ($P < .01$), with most patients in both groups (68.4% vs 61.7; $P = .20$) categorized with Child-Pugh class C for cirrhosis severity. The median (IQR) wait list time was 3.2 months (0.8-12.4 mo) versus 3.4 months (0.9-10.1 mo) (not significant, $P = .96$).

Muscle wasting and recipient characteristics

Table 2 shows descriptive statistics of the sample according to the presence or absence of sarcopenia on pretransplant CT (in relation to sex-specific thresholds of "normal" LPA). Patients with sarcopenia were 5 years older on average, weighed an average of 20 pounds less, and were twice as likely to have been previously diagnosed with diabetes versus those who did not have sarcopenia. Alcoholic hepatitis was a more common primary cause of liver disease (29.9% versus 18.8%), and hepatocellular carcinoma was less likely among patients with sarcopenia. Patients with sarcopenia had more severe disease according to pretransplant laboratory MELD score, laboratory tests, and hospitalization status (31.3% vs 11.6% in intensive care unit); more than 75% of patients with sarcopenia were classified with Child-Pugh class C.

Table 3 summarizes changes in psoas muscle measures by sex, with further details shown in Table 4. Most patients showed decline in either muscle size or density (86.8%), approximately three-quarters lost TPA, and slightly over one-half declined in muscle quality (55.2%). We found that 71.3% declined in LPA from baseline to pretransplant CT overall (average [IQR] time between scans of 12 mo [3.6-36.5 mo]). The mean (SD) relative change in LPA

Table 2. Pretransplant Characteristics of Patients Who Underwent Liver Transplant at UMass Memorial From 2006 to 2015, by Category of Sarcopenia Versus No Sarcopenia on Pretransplant Computed Tomography (N = 136)

Characteristic	Sarcopenia Pretransplant	
	> 1 SD Below Normal (n = 67)	Within Normal Limits (n = 69)
Age ≥ 55 years	70.2	46.4
Women	34.3	33.3
Ethnic minority	25.4	20.3
Primary insurance		
Private	43.3	34.8
Public (Medicaid)[a]	26.9	42.0
Public (Medicare)	29.9	23.2
Body mass index, kg/m^2	27.0 (5.5)	29.3 (5.6)
Weight, kg	77.6 (19.3)	86.2 (19.1)
Height, m	1.69 (0.1)	1.71 (0.1)
Diabetes (type 1, type 2, or unspecified)	34.3	14.5
Primary cause of liver disease		
Hepatitis C and similar infections	38.8	55.1
Alcoholic hepatitis	29.9	18.8
Other liver diseases	31.3	26.1
Hepatocellular carcinoma	29.9	42.0
Child-Pugh class		
A (mild)	4.5	10.1
B (moderate)	19.4	29.0
C (severe)	76.1	60.9
Wait list time, mo	2.2 (0.6-11.1)	3.6 (1.0-13.0)
Model for End-Stage Liver Disease score (laboratory)	24 (16-34)	17 (12-27)
< 15	19.4	43.5
15-29	44.8	34.8
≥ 30	35.8	21.7
Creatinine, mg/dL	2.1 (1.8)	1.5 (1.4)
Total bilirubin, mg/dL	9.4 (10.9)	8.5 (11.5)
International normalized ratio	2.0 (1.4)	2.0 (2.0)
Albumin, g/dL	3.0 (0.7)	3.0 (1.0)
Medical condition		
Hospitalized	25.4	27.5
Intensive care unit	31.3	11.6
Life support	17.9	5.8
Psoas muscle density, Hounsfield unit	36.1 (7.6)	43.4 (8.9)
Total psoas area, mm^2	1442 (376.9)	2212.3 (491.1)

Results are shown as percent, mean (standard deviation), or median (interquartile range). Lean psoas areas on pretransplant (≤ 90 days) abdominal computed tomography that are > 1 standard deviation below sex-specific averages (cutoff points of 1488.4 mm^2 for men and 974.8 mm^2 for women) were reported in a study of 1279 patients admitted for elective general surgery.[37] [a]Includes 1 person with insurance type-other.

Table 3. Changes in Psoas Muscle Measures From Baseline to Pretransplant Computed Tomography by Sex in Study Group (N = 136)

Relative Change, %	Men (n = 90)	Women (n = 46)
Total psoas area, mm^2	-11.3 (-21.1 to -0.7)	-2.9 (-16.7 to 8.9)
Density, Hounsfield unit	-1.5 (-20.2 to 12.0)	-10.0 (-24.5 to 16.6)
Lean psoas area, mm^2	-10.9 (-25.3 to -1.0)	-3.4 (-20.3 to 6.4)
Lean psoas area/month[a]	-0.5 (-1.4 to -0.1)	-0.1 (-1.6 to 0.8)

Relative percent change was calculated as (pretransplant – baseline)/baseline and shown as median (interquartile range).

[a]Per month between computed tomography scans, with median (interquartile range) value of 11.6 months (4.7-41.4 mo) for men and 13.0 months (1.4-33.7 mo) for women ($P = .30$).

Table 4. Frailty Measures: Sarcopenia and Functional Status by Sex in Study Group (N = 136)

Psoas Measure	Men (n = 90)	Women (n = 46)	*P* Value (men vs women)	All (N = 136)
At baseline CT scan				
Time between CT, mo	11.6 (4.7-41.4)	13.0 (1.4-33.7)	.30	12.0 (3.6-36.5)
TPA, mm^2	2344.3 (551.0)	1518.0 (437.8)	< .001	2064.8 (646.5)
Density, HU	42.7 (8.8)	41.4 (10.3)	.45	42.3 (9.3)
LPA, mm^2	1771.1 (474.4)	1131.1 (349.1)	< .001	1554.7 (530.4)
LPA (mm^2)/height $(m)^2$	582.7 (157.1)	435.4 (134.1)	< .001	532.9 (164.8)
At pretransplant CT scan				
Time from pretransplant CT to transplant, days	27 (11-47)	26 (11-60)	.89	27 (11-50.5)
TPA, mm^2	2028.9 (547.7)	1449.5 (447.7)	< .001	1832.9 (583.3)
Density, HU	41.0 (8.3)	37.3 (9.9)	.023	39.8 (9.0)
LPA, mm^2	1513.2 (451.9)	1048.6 (354.4)	< .001	1356.1 (474.5)
LPA (mm^2)/height $(m)^2$	499.2 (158.2)	403.8 (133.7)	< .001	466.9 (156.6)
Change from baseline to pretransplant CT				
Change in TPA, mm^2	-266.5 (-496.8 to -13.6)	-49.6 (-232.4 to 121.4)	.001	-167.6 (-415.3 to 11.6)
%TPA change, mm^2	-12.6 (16.4)	-3.2 (19.0)	.003	-9.5 (17.8)
Change in density, HU	-0.6 (-9.9 to 5.4)	-4.2 (-11.4 to 4.0)	.25	-1.6 (-10.6 to 5.2)
%Density change, HU	-1.5 (-20.2 to 12.0)	-10.0 (-24.5 to 16.6)	.26	-4.5 (-21.1 to 12.3)
Change in LPA, mm^2	-175.7 (-445.2 to -17.7)	-26.0 (-272.3 to 67.4)	.003	-148.2 (-377.4 to 19.1)
%LPA change, mm^2	-13.3 (18.6)	-5.7 (21.5)	.034	-10.7 (19.9)
Change in LPA/height^2	-51.6 (-145.7 to -6.1)	-10.6 (-101.4 to 28.1)	.008	-48.0 (-130.2 to 6.4)
Rate of change				
Change in LPA/height^2/mo	-3.2 (-8.8 to -0.6)	-0.5 (-7.0 to 2.8)	.031	-2.65 (-8.5 to 0.2)
%LPA change/mo	-0.5 (-1.4 to -0.1)	-0.1 (-1.6 to 0.8)	.07	-0.5 (-1.5 to 0.04)

Abbreviations: CT, computed tomography abdominal scan; HU, Hounsfield unit; LPA, lean psoas area (TPA × density adjustment factor); TPA, total psoas area (sum of left and right psoas muscles as separate measures for pretransplant and baseline CTs)

Results are shown as mean (standard deviation) or median (interquartile range). Baseline is defined as earliest available abdominal CT scan before pretransplant CT (with at least 7 days between scans). Percent change was calculated as (pretransplant LPA minus baseline LPA)/baseline LPA (note: height in the denominator cancels out).

was -10.7% (19.9%), and the average rate of relative change was -0.5% per month (-1.5% to -0.04% per month).

As shown in Table 3, although TPA and density changed significantly from baseline to pretransplant in the overall sample, women only lost a median of 2.9% of baseline TPA compared with 12.6% among men. In contrast, women significantly declined in muscle quality (-10.0%; $P = .03$), whereas men did not (-1.5%; $P = .20$). A significant difference persisted even after accounting for density in LPA. However, when we normalized relative LPA change for time (months) between CT scans, differences in muscle wasting by sex were equalized ($P = .07$).

Table 5 shows recipient characteristics by tertiles of rate of LPA loss (% LPA lost per month between CT scans), and Table 6 shows characteristics by tertiles of relative LPA loss (%). By tertile of LPA loss rate, in order of increasing severity, the median (IQR) change in LPA was 7% (2%-13%), -14% (-26% to -6%), and -22% (-32% to -12%). Characteristics associated with more rapid rates of LPA loss included higher rate of weight loss per month on the wait list, higher laboratory MELD score at registration and pretransplant (with worse bilirubin and coagulation results), and more critical medical condition (Table 7). Patients with higher rates of muscle wasting were less likely to have hepatocellular carcinoma.

Table 5. Characteristics in Relation to Rate of Change of Lean Psoas Area (Tertiles) in Study Group (N = 136))

	Tertiles of Rates of Change (%/mo) in Lean Psoas Area Over Baseline†		
	Highest (n = 46)	Moderate) (n = 45	Minimal/No Loss (n = 45)
Median (range), %/mo	-2.75 (-57.92 to -1.02)	-0.45 (-0.95 to -0.09)	1.13 (-0.06 to 79.08)
Time between CT scans, mo	6.8 (2.7-13.0)	37.6 (16.6-64.8)	8.7 (1.8-35.2)
Characteristic			
Age ≥ 55 y	56.5	62.2	55.6
Women	30.4	20.0	51.1
Ethnic minority	17.4	26.7	24.4
Public health insurance	56.5	66.7	60.0
Body mass index, kg/m^2	24.5 (4.9)	29.0 (5.1)	28.1 (6.8)
Weight, kg	81.2 (19.1)	85.4 (16.7)	79.3 (22.5)
Height, m	1.71 (0.1)	1.71 (0.1)	1.67 (0.1)
Diabetes (type 1, type 2, or unspecified)	21.7	35.6	15.6
Primary cause of liver disease			
Hepatitis C/viral and other	45.7	53.3	42.2
Alcoholic hepatitis	23.9	24.4	24.4
Other liver diseases	30.4	22.2	33.3
Hepatocellular carcinoma	21.7	44.4	42.2
Time on wait list, mo	1.7 (0.5-6.1)	6.4 (1.5-15.5)	3.0 (0.8-13.9)
Weight loss/month on wait list			
< 0 to ≤ 5%	28.3	57.8	45.5
> 5%	26.1	8.9	25.0
Laboratory MELD at registration	22 (12-29)	14 (10-20)	15 (10-20)
Laboratory MELD pretransplant	29 (20-38)	19 (12-24)	16 (12-25)
Creatinine, mg/dL	1.4 (0.9-2.4)	1.0 (0.8-1.6)	1.1 (0.8-2.1)
Total bilirubin, mg/dL	11.1 (3.5-19)	3.0 (1.5-6.1)	3.1 (1.4-6.3)
International normalized ratio	2.0 (1.4-2.6)	1.5 (1.2-1.9)	1.4 (1.2-1.8)

Table 5. Characteristics in Relation to Rate of Change of Lean Psoas Area (Tertiles) in Study Group (N = 136))

	Tertiles of Rates of Change (%/mo) in Lean Psoas Area Over Baseline†		
	Highest (n = 46)	Moderate) (n = 45	Minimal/No Loss (n = 45)
Albumin, g/dL	2.9 (2.7-3.3)	2.8 (2.5-3.5)	3.0 (2.4-3.4)
Child-Pugh			
B	17.4	24.4	31.1
C	80.4	62.2	62.2
Portal vein thrombosis	17.4	15.6	13.3
Medical condition			
Not hospitalized	32.6	57.8	66.7
Hospitalized, not ICU	32.6	26.7	20.0
ICU	34.8	15.6	13.3
Life support	21.7	6.7	6.7

Abbreviations: CT, computed tomography; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease

Results are shown as percent, mean (standard deviation), or median (interquartile range).

Table 6. Characteristics of Liver Transplant Recipients (N = 136) in Relation to Change in Lean Psoas Area Relative to Baseline (Tertiles)

	Tertiles of Relative Change in Lean Psoas Area		
	Severe Loss of LPA (n = 46)	Moderate) Loss of LPA (n = 45	Minimal/No Loss of LPA (n = 45
Median change in LPA (range	-30.1 (-64.5 to -19.0)	-9.1 (-1.0 to 46.1)	7.4 (-1.0 to 46.1)
Median months CT (IQR)	19.7 (8.7-54.9)	9.8 (4.0-31.7)	8.1 (1.8-31.9)
Characteristic			
Age ≥ 55 y	65.2	53.3	55.6
Women	26.1	26.7	48.9
Ethnic minority	10.9	33.3	24.4
Public health insurance	54.4	71.1	57.8
Body mass index, kg/m2	27.4 (4.8)	29.1 (5.3)	28.1 (6.7)
Weight, kg	82.6 (18.6)	83.4 (18.2)	79.8 (22.0)
Height, m	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Diabetes (type 1, type 2, or unspecified)	30.4	26.7	15.6
Primary cause of liver disease			
Hepatitis C/viral or other	50.0	46.7	44.4
Alcoholic hepatitis	21.7	26.7	24.4
Other liver diseases	28.3	26.7	31.1
Hepatocellular c arcinoma	32.6	31.1	44.4
Time on wait list, mo	2.2 (0.7-11.1)	4.6 (1.5-13.0)	3.0 (0.8-9.1)
Weight loss per month on wait list			
< 0 to ≤ 5%	41.3	44.4	45.5
> 5%	21.7	13.3	25.0
Laboratory MELD at registration	20.5 (11-26)	15 (10-22)	15 (10-20)
Laboratory MELD pretransplant	25.5 (16-36)	22 (12-30)	16 (12-24)
Creatinine, mg/dL	1.3 (0.9-2.5)	1.0 (0.8-1.6)	1.1 (0.8-1.8)
Total bilirubin, mg/dL	6.4 (2.8-19)	5.0 (1.7-12.5)	2.9 (1.4-6.1)
International normalized ratio	1.7 (1.3-2.2)	1.7 (1.3-2.3)	1.4 (1.1-1.8)
Albumin, g/dL	3.0 (2.5-3.4)	2.8 (2.5-3.5)	3.0 (2.4-3.3)
Child-Pugh			
B	19.6	22.2	31.1
C	78.3	66.7	60.0
Portal vein thrombosis	15.2	17.8	13.3
Medical condition			
Not hospitalized	41.3	46.7	68.9
Hospitalized, not ICU	26.1	35.6	17.8
ICU	32.6	17.8	13.3
Life support	19.6	8.9	6.7

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MELD, Model for End-Stage Liver Disease

Results are shown as percent, mean (standard deviation), or median (interquartile range).

Table 7. Characteristics of Liver Transplant Recipients (N = 136) in Relation to Functional Status

	Functional Impairment/Disability		
	Severe (n = 62)	Moderate (n = 55)	None/Normal (n = 19)
Median %LPA change (range	-13.1 (-33.3 to -1.3)	-9.5 (-20.9 to 4.0)	-2.2 (-8.2 to 0.95)
Median months on wait list (IQR)	1.7 (0.39-8.7)	4.3 (1.3-13.0)	3.8 (1.2-13.9)
Median months between CT scans (IQR)	10.4 (2.7-43.0)	15.0 (4.8-35.4)	16.9 (6.1-35.2)
Characteristic			
Age ≥ 55 y	56.5	60.0	57.9
Women	33.9	33.2	21.1
Ethnic minority	27.4	18.2	21.1
Public health insurance	66.1	61.8	42.1
Body mass index, kg/m^2	27.9 (5.6)	29.4 (5.8)	25.6 (4.2)
Weight, kg	80.8 (20.0)	85.9 (20.0)	74.2 (14.4)
Height, m	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Diabetes (type 1, type 2, or unspecified)	27.4	23.6	15.8
Primary cause of liver disease			
Hepatitis C/viral or other	43.6	49.1	52.6
Alcoholic hepatitis	29.0	25.5	5.3
Other liver diseases	27.4	25.5	42.1
Hepatocellular carcinoma	13.4	40.0	79.0
Weight loss per month on wait list			
< 0 to ≤ 5%	26.2	16.4	10.5
> 5%	37.7	43.6	63.2
Laboratory MELD at registration	21.5 (16-31)	13 (9-17)	10 (7-14)
Laboratory MELD pretransplant	29.5 (22-37)	15 (11-24)	12 (9-13)
Creatinine, mg/dL	1.5 (1.0-3.0)	0.9 (0.7-1.5)	0.9 (0.8-1.1)
Total bilirubin, mg/dL	8.6 (3.8-18.8)	2.8 (1.4-6.4)	1.5 (0.9-3.4)
International normalized ratio	2.0 (1.7-2.6)	1.3 (1.1-1.7)	1.2 (1.1-1.4)
Albumin, g/dL	3.1 (2.5-3.4)	2.9 (2.4-3.3)	2.8 (2.6-3.5)
Child-Pugh			
B	4.8	38.2	47.4
C	95.2	52.7	26.3
Portal vein thrombosis	17.7	14.6	10.5
Medical condition			
Not hospitalized	9.7	85.5	94.7
Hospitalized, not ICU	46.8	10.9	5.3
ICU	43.6	3.6	0
Life support	22.6	3.6	0

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MELD, Model for End-Stage Liver Disease

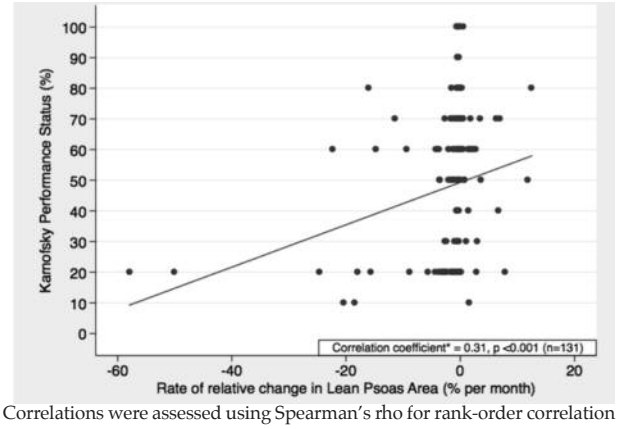
Results are shown as percent, mean (standard deviation), or median (interquartile range).

Sarcopenia and functional status

Functional impairment (moderate or severe physical limitations per KPS) was present in 117 patients (86.0%) at transplant. The mean KPS score was 47.3%, with 31.6% having KPS of 20%. The KPS distributions did not vary by sex ($P = .92$).

Figure 2 illustrates the relationship between continuous functional status and rate of LPA loss. A moderate correlation was identified (Spearman rho = 0.31; $P < .001$). Table 8 shows the correlations stratified by recipient characteristics of interest, with average LPA rates displayed for each category of functional status.

Figure 2. Correlationa Between Pretransplant Functional Status and Rate of Change in Lean Psoas Area From Baseline to Pretransplant in Study Group (N = 131)



Correlations were assessed using Spearman's rho for rank-order correlation between 10-point Karnofsky Performance Status scale and continuous sarcopenia and restricted to the range of lean psoas area values for which test assumptions were not violated: below (+) 20% increase in the rate of relative Lean Psoas Area change/month.

Table 9 shows the results of logistic regression models for severe functional impairment/disability by 3 different measures of muscle wasting. Severe impairment or disability was more common among patients with higher rates of muscle wasting and among those with pretransplant sarcopenia. Mean LPA among severely impaired patients was 1215.4 mm^2 versus 1473.9 mm^2 for patients who had moderate or normal functional status ($P = .001$).

Compared with patients with minimal or no evidence of sarcopenia on CT scan, those who displayed muscle wasting of ≥ 1% per month had 2.83 times the risk (95% CI, 1.18-6.80) of being severely impaired, disabled, and/or moribund pretransplant (adjusted for age, sex, and race). The adjusted odds ratio observed for those with pretransplant sarcopenia

Table 8. Rate of Muscle Wasting Versus Functional Status Pretransplant: Stratified Distributions and Correlations of Study Group (N = 136)

Sarcopenia, Rate of Change	No.	Functional Impairment/Disability			Correlation (*P* Value)
		Severe (n = 62)	Moderate (n = 55)	None (n = 19)	
All	131	-0.66 (-2.62 to -0.12)	-0.29 (-1.43 to 0.56)	-0.20 (-0.53 to 0.02)	.31 (< .001)
Age, y					
< 55	55	-0.83 (-3.71 to -0.12)	-0.23 (-1.43 to 1.82)	-0.08 (-0.31 to 0.25)	.36 (< .01)
≥ 55	76	-0.63 (-2.62 to -0.00)	-0.39 (-1.39 to 0.26)	-0.33 (-0.65 to -0.09)	.25 (.03)
Sex					
Women	42	-0.52 (-2.62 to 2.91)	-0.06 (-0.95 to 0.56)	0.45 (-0.57 to 6.54)	NA
Men	89	-0.72 (-2.5 to -0.33)	-0.50 (-1.43 to 0.52)	-0.21 (-0.53 to -0.09)	.30 (< .01)
Primary liver disease					
Hepatitis C/viral	63	-0.72 (-2.44 to -0.13)	-0.25 (-1.51 to 0.26)	-0.20 (-0.36 to -0.09)	.34 (< .01)
Alcohol, Other	68	-0.65 (-5.55 to 1.50)	-0.37 (-1.30 to 0.66)	-0.18 (-0.63 to 0.13)	NA
Hepatocellular carcinoma					
None	82	-0.90 (-2.80 to -0.20)	-0.25 (-1.95 to 0.26)	-0.20 (-0.28 to 6.18)	.37 (< .01)
Present	42	-0.21 (-0.56 to -0.05)	-0.35 (-1.02 to 0.67)	-0.20 (-0.63 to 0.02)	NA
Child-Pugh					
A or B	43	-0.33 (-0.65 to -0.18)	-0.18 (-1.21 to -0.75)	-0.20 (-0.53 to 0.02)	NA
C	88	-0.72 (-2.69 to -0.03)	-0.39 (-1.51 to 0.04)	-0.20 (-0.36 to -0.18)	.28 (< .01)

Abbreviations: LPA, lean psoas area; NA, not available

Sarcopenia was determined as relative change in LPA per month = ([LPA within 90 days before transplant minus baseline LPA]/baseline LPA/months between CT scans) and shown as median (interquartile range). Correlations were not reported for groups that were not sufficiently powered (< 80%). Correlations were assessed using Spearman rho for rank-order correlation between 10-point Karnofsky Performance Status scale and continuous sarcopenia and restricted to the range of LPA values for which test assumptions were not violated: below (+) 20% increase in the rate of relative LPA change/month.

Table 9. Unadjusted and Adjusted Odds Ratios (95% Confidence Intervals) for Severe Functional Impairment/Disability by Rate of Muscle Wasting, Pretransplant Sarcopenia, and Decrease in Lean Psoas Area in Study Group (N = 136)

	Severe Impairment/Disability (patients with KPS 10%-40% versus 50%-100%)		
	%Impaired	Unadjusted	Adjusted[a]
Rate of muscle wasting[b]			
High (≥ 1% loss/mo)	56.5	2.60 (1.11-6.09)	2.83 (1.18-6.80)
Moderate (< 1%-0.1% loss/mo)	46.7	1.75 (0.75-4.11)	1.84 (0.75-4.51)
Minimal/none (< 0.1%/mo)	33.3	Referent	Referent
Sarcopenia pretransplant[b]			
> 1 SD below normal	56.7	2.46 (1.23-4.91)	2.67 (1.29-5.52)
Within normal limits	34.8	Referent	Referent
Lean psoas area pretransplant[c]			
Per SD unit decrease		1.83 (1.24-2.69)	2.32 (1.44-3.75)

Abbreviations: CT, computed tomography; KPS, Karnofsky Performance Status; SD, standard deviation

[a]Adjusted for age (≥ 55/< 55 years), sex, and race (white/non-white).

[b]Lean psoas area on pretransplant (≤ 90 days) abdominal CT that is > 1 SD below sex-specific averages (cutoff points of 1488.4 mm^2 for men and 974.8 mm^2 for women) reported in a study of 1279 patients admitted for elective general surgery procedures.[37]

[c]Decrease relative to sample distribution at single pretransplant time point.

compared with those without was similar (2.67; 95% CI, 1.29-5.52). The odds of severe functional impairment/disability more than doubled for each SD decrease in lean muscle size on pretransplant CT (2.32; 95% CI, 1.44-3.75).

Discussion

We present results from the first study to evaluate the relationship between KPS scale and objective measures of frailty (sarcopenia) in a liver transplant population. Prevalence of muscle wasting and prevalence of functional impairment (KPS ≤ 70%) pretransplant were almost identical (86.8% vs 86.0%, respectively). Pretransplant sarcopenia, defined relative to average in a general surgery population,[37] was present in about one-half of the sample.

Our reported prevalence of sarcopenia is consistent with other studies of liver transplant patients of 45% and 41%.[15,19] We observed differences between men and women in terms of type of muscle wasting experienced, with men showing change in total area and women showing change in quality (density); these findings are also supported in earlier reports.[12,14,15,19,37] We also report a new finding: after we accounted for changes in density, relative change from baseline as a percent, and months over which the changes occurred, we found that degree of muscle wasting was no longer statistically different for men and women ($P = .07$).

Compared with a study that examined change in psoas muscle perioperatively (90 days before or after transplant) in a cohort of general and major vascular surgery patients, we showed a similar but smaller proportion of patients who showed declined TPA (73% vs 83%).[45] This minor difference could be explained by the period of observation: the body goes through a rollercoaster of physiologic changes in recovering from major surgery, and trunk muscle size may substantially decline for bed-bound patients with postoperative complications from not only misuse but physiologic stress (eg, infection). Perioperative change in psoas muscle has been shown to independently predict mortality among patients with cirrhosis who are undergoing transjugular intrahepatic portosystemic shunt procedures.[46] For these reasons, we did not include CT scans performed within 90 days posttransplant, as the aforementioned postoperative setting is generally very intensive but also variable for liver transplant patients.

We found that functional status was associated with sarcopenia on pretransplant CT and with change in muscle mass and/or quality (loss of LPA). Our findings are supported by studies of sarcopenia in general surgery patients at the University of Michigan.[34,37] In a study of patients ≥ 70 years of age who were admitted for general surgery procedures, 42% exhibited functional impairment on in-clinic assessment of physical function (eg, walk test) and only 22% reported difficulty with activities of daily living.[34] The prevalence of functional impairment in this population was substantially lower than in our sample of 136 liver transplant recipients (86.0%). Despite these differences, the estimates of effect that the authors found for TPA in relation to difficulties performing instrumental activities of daily living were almost identical to our findings (OR of 0.53 per SD of TPA versus OR of 0.55 per SD increase in LPA [or TPA] pretransplant) (note that these results are currently presented in Table 9 as the inverse: OR of 1.83 per SD decrease). We also showed that muscle wasting of as little as 1% per month is associated with an almost 3-fold higher risk of severe functional impairment compared with patients with no sign of muscle wasting and after adjusting for age, sex, and race (OR of 2.83; 95% CI, 1.18-6.80).

Implications of results

Around 2005, UNOS/SRTR replaced the previously collected activities of daily living as the primary measure of functional status with KPS. However, the Liver and Intestinal Transplant Committee of OPTN recently asked that research on using KPS nationally be pursued as there is concern in the transplant community about whether it is appropriate to risk-adjust center outcomes for case mix using a variable that has not been specifically validated in a liver transplant population.[33] This study found moderate correlations between provider-assessed KPS and objective markers of frailty, but more research is warranted.

Although age was originally conceptualized as the primary driver of frailty among geriatric populations and although cachexia, an irreversible progressive inflammation-based disease, is the driver of frailty in oncology populations, it is actually "secondary sarcopenia," due to chronic disease, malnutrition, and endocrine abnormalities[47] that drives frailty in end-stage liver disease. This has important implications for both designing potential

interventions and for prognostic indications of sarcopenia in liver transplant patients compared with other populations.

Because underlying causes of frailty are hypothesized to vary across different groups in which sarcopenia has been recognized as a strong predictive variable for outcomes, interventions may also need to target different deficits or approach the deficits from different angles. In results of nutrition supplementation in liver disease, meal-induced albumin synthesis was impaired even in compensated cirrhotic patients,[48] which may be insufficient to overcome underlying endocrine abnormalities.

Disease courses and prognoses in elderly versus cirrhosis populations also dramatically differ. In general populations, frailty is conceptualized as progressive and mostly irreversible; in contrast, liver disease populations may have some or potentially all of these processes reversed after the nonfunctioning organ is replaced with a new, nondiseased organ. We call for further research on understanding whether and which preventive measures (or "prehabilitation" interventions), some thus far shown to be effective in other types of major surgeries such as cardiac surgery, may be needed in a liver transplant population. Although the literature has shown that sarcopenia predicts mortality, in a liver transplant population, functional status predicts mortality, and now we add that functional status maps onto objective measures of sarcopenia adequately.

However, it is unclear whether there is a causal relationship between either variable (functional status, sarcopenia) and posttransplant outcomes, and therefore, whether interventions to improve muscle mass measures would improve outcomes. As has been shown in the cardiac surgery literature, intervening to improve muscle mass through physical training and protein supplementation may not bear meaningful effects on improving outcomes in transplant patients. Pathophysiologically, transplant patients have limited protein metabolism due to cirrhosis, although, after a new functioning liver is transplanted, the mechanism improves. In contrast, in cardiac patients, sarcopenia is likely more related to peripheral muscle breakdown from underuse, poor circulation, and so forth, while their ability to metabolize protein is unaffected. Therefore, interventions to improve recovery time and outcomes after surgery by increasing muscle mass with increased protein intake and physical rehabilitation may be more limited in liver transplant patients preoperatively due to their inability to metabolize protein. In contrast to a cardiac surgery population where sarcopenia is a marker of overall frailty, in a liver transplant population, sarcopenia is a reflection of the combination of liver dysfunction and overall weakness and frailty, which limits our ability to infer from interventional studies on cardiac surgery patients directly to a liver transplant population.

Strengths and limitations

This work must be considered in the context of its limitations. Our primary limitation is the relatively small sample size. This limited the number and types of analyses that we were sufficiently powered to conduct. A potential limitation of using single-center data is generalizability of findings. To address generalizability of measures, we evaluated sarcopenia variable definitions using a referent from previously published averages in a general surgery population and used percent loss for within-patient changes. A limitation to the averages that we used as "normal," however, is that, although elective general surgery patients may be healthier than the average liver transplant patient overall, they are likely sicker than a general healthy population, as the general surgery population may include those with trauma and those who have sarcopenia from other causes (including cancer and advanced age). This limitation is inherent to the literature available thus far, and we call for further research describing general population prevalence and definition of "normal" for analytic morphomic methods, which measure psoas at the L4 level specifically and for which no referent values are published. However, the use of single-center data is also a strength of this retrospective study, as KPS assessment protocols and patient population norms are likely to be more consistent and more homogenous within a single transplant center than between centers.

Another major but unavoidable limitation is the retrospective design of the study, which introduced potential selection bias. There was potential for survivor bias by including only transplant recipients rather than all wait list candidates. In contrast, the sample may have been biased toward patients who are sicker, as these patients are more likely to undergo more frequent abdominal CT scans. We compared characteristics among patients excluded versus those

included and found some indication that excluded patients were less sick. However, the primary outcome variable, functional status, was not significantly different between groups. Because sarcopenia and muscle wasting were associated with cirrhosis severity, it is possible that our results are exaggerated by focusing on a subset of sicker patients. The retrospective design also meant we were also likely not able to capture true "baseline" psoas muscle measures.

This study was innovative in its approach by focusing on clinical translation of our process and results: we worked with a radiologist with fellowship training in abdominal imaging to collect data in real time. In contrast, most research studies on sarcopenia rely on expensive and technically sophisticated Matlab engineering/image processing software to collect and interpret data. Although having a single rater for psoas muscle measures could be a limitation, the high level of technical expertise and high agreement between measures (97%) on assessment of intrarater reliability virtually eliminated this potential threat to validity. We defined the primary variables, specifically "sarcopenia" and functional status, using universally available cutoff points or relative to the patient's own baseline rather than only reporting tertiles within our unique population, which may not necessarily translate to another center or allow assessment of an individual patient.

Conclusions

Our results show a moderate correlation between clinically evident functional impairment/disability, assessed by providers using the KPS scale, and sarcopenia, an objective marker of frailty syndrome that can be measured on abdominal CT scan. Both the extent and rate of muscle wasting were significantly associated with pretransplant functional status on regression modeling, increasing risks of severe functional impairment/disability by 2- to 3-fold after adjustment for age, sex, and race/ethnicity. However, if sarcopenia were a direct objective representation of clinical functional status, the correlation coefficients and odds ratios would be many times greater than we observed. We hypothesize that sarcopenia and functional status likely measure different aspects of liver failure and that global health status in liver transplant patients may be affected by an array of heterogeneous disease manifestations that we were unable to dissect due to limited sample size. More research on the utility of using either or both measures in prognostication and care of high-risk liver transplant patients is warranted. Better understanding and characterization of frailty syndrome in liver transplant patients holds great potential for improving clinical care and informing decision-making for patients on transplant wait lists.

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