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Functional Impairment in Older Liver Transplant Candidates: From the Functional Assessment in Liver Transplantation (FrAILT) Study

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Abstract

The emerging epidemic of older cirrhotics has led to a sharp increase in the number of ≥65 year olds considering liver transplantation (LT). However, clinicians lack objective measures to risk stratify older patients. We aimed to determine whether the Short Physical Performance Battery (SPPB), a well-validated geriatric measure of physical function, has greater prognostic value in older versus younger LT candidates. Adult outpatients listed for LT with laboratory MELD ≥12 underwent physical function testing using the SPPB, consisting of gait speed, chair stands, and balance. Patients were categorized by age ("younger"= <65 years; "older"= ≥65 years) and SPPB ("impaired"= ≤9; "robust"= >9). Competing risks models associated age and SPPB with wait-list death/delisting. Of 463 LT candidates, 21% were ≥65 years; 18% died/delisted. Older patients had slower gait (1.1 vs.1.3m/sec; p<0.001), a trend of slower chair stands (12.8 vs.11.8sec; p=0.06), and a smaller proportion able to complete all balance tests (65 vs.78%; p=0.01); SPPB was lower in older vs. younger patients (10 vs.11; p=0.01). When compared to younger robust patients as a reference group, younger impaired patients (HR 1.77; p=0.03) *and* older impaired patients (HR 2.70; p=0.003) had significantly higher risk of wait-list mortality, but there was no difference in risk for older robust patients (HR 1.38; p=0.35) [test of equality p=0.01]. After adjustment for MELD-Na, only older impaired patients had an increased risk of wait-list mortality compared to younger robust patients (HR 2.36; p=0.01) [test of equality p=0.05]. In conclusion, functional impairment, as assessed by the SPPB, predicts death/delisting for LT candidates ≥ 65 years independent of MELD-Na. Further research into activity-based interventions to reduce adverse transplant outcomes in this population is warranted.

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Keywords

surgery; functional status; wait-list mortality; age; disability

The national liver transplant wait-list is aging. From 2005–2014, the proportion of patients ≥65 years who underwent liver transplantation increased from 11% to 19% (1). In light of the epidemic of older adults with cirrhosis from chronic hepatitis C (2) and non-alcoholic fatty liver disease (3), this proportion is anticipated to rise further. While older age is associated with poorer survival before and after liver transplant (4–6), small single center studies have demonstrated that acceptable outcomes can be achieved in *select* older patients (5, 7, 8). Since factors predictive of favorable outcomes are unknown, there is no consensus on objective and appropriate selection criteria for older patients.

We hypothesized that physical function is a key factor that contributes to differential outcomes in older versus younger cirrhotics. While we have previously shown that physical frailty and functional impairment predict wait-list mortality in liver transplant candidates of all ages (9), older cirrhotics may be particularly vulnerable to adverse health outcomes due to the combined, and likely synergistic, effects of chronic liver failure *and* impairments in physical function that are common in aging adults (4–6, 10). In this study, we aimed to compare physical function in older versus younger liver transplant candidates and evaluate the prognostic value of physical function by age.

PATIENTS AND METHODS

Study population

The Functional Assessment in Liver Transplantation (FrAILT) Study is an ongoing 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. In order to ensure an adequate number of events during the follow up period, only candidates with a Model for End-Stage Liver Disease (MELD) score ≥12 were included. Excluded were those with severe hepatic encephalopathy (n=14), defined as a Numbers Connection Test time of ≥120 seconds, given concerns about their ability to cooperate with physical function testing. Of the 470 patients who were asked to participate, 463 (99%) consented and enrolled in the study.

Study procedures and data collection

At enrollment into the FrAILT Study, all patients underwent testing of physical function using the Short Physical Performance Battery (SPPB) [Appendix]. This measure was selected for this specific study for two reasons: a) we have previously demonstrated its construct validity in liver transplant candidates (9) and b) it is a purely performance-based measure and therefore not susceptible to recall bias. Moreover, the SPPB has excellent reliability with an intraclass correlation coefficient of 0.88–0.92 for measures performed one week apart (11). At the time of physical function testing, information regarding demographics, medical co-morbidities (e.g., hypertension, diabetes, coronary artery disease), and laboratory tests were collected from the patient's electronic health record. The degree of

ascites – classified as absent, controlled, or severe/refractory – was assessed and determined by the candidate's primary hepatologist at the time of physical function testing. Hepatic encephalopathy was classified as none/mild versus moderate based on a Numbers Connection Test Score of ≤ or >60 seconds, respectively. The MELD-sodium (MELD-Na) score was calculated using the formula detailed in the paper by Kim *et al* (12).

On the same day as the clinic visit, the patient's hepatologist was asked to subjectively rate his or her patient's health using the following question:

> "We are interested in your general impression about your patient's overall health, as compared to other patients with underlying liver disease. How would you rate this patient's overall health today? Excellent (0), very good (1), good (2), fair (3), poor (4), or very poor (5)".

Statistical analysis

Subjects were categorized by an age cut-off of 65 years ("younger" = <65 years; "older" = ≥65 years), a clinically relevant and commonly-used cut-off to define "older". Differences in baseline characteristics by age categories were compared using chi-square or Wilcoxon rank sum tests for categorical and continuous variables, respectively. The primary predictor was physical function, as assessed by the SPPB. To facilitate interpretation and usability in clinical practice, this variable was dichotomized into >9 ("robust") and ≤9 ("functionally impaired"), as this would represent at least 1-point of impairment in each of the three components of the SPPB, or at least 2-points of impairment in one of the components (see Appendix for scoring system).

The primary outcome in this study was wait-list mortality, defined as death prior to liver transplantation or delisting for being too sick for transplant. Patients who were delisted for reasons other than being too sick (e.g., substance abuse, non-adherence) were censored from the FrAILT Study at the time of wait-list removal. We performed a sensitivity analysis censoring HCC patients delisted for tumor progression (n=7 [8% of total number who died/were delisted]), instead of counting them as having reached the primary outcome. Competing risks analysis evaluated the association between categories of age (< or ≥65 years) and SPPB score (> or ≤9) and wait-list mortality, with liver transplantation as the competing risk. Patients who received an organ by living donor liver transplantation were censored on the day prior to undergoing transplantation. All co-variates associated with a p-value <0.10 in univariable analysis were evaluated for inclusion in the multivariable model. We employed backwards step-wise regression to eliminate co-variates from the final multivariable model using a threshold p-value 0.05. Post-estimation tests of equality among age and SPPB categories were performed using the Wald test.

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

RESULTS

Baseline characteristics of the cohort

A total of 463 liver transplant wait-list candidates with MELD score ≥12 were included in the analyses: 95/463 (21%) patients were ≥65 years. Baseline characteristics of the cohort categorized by age category are shown in Table 1. Median (interquartile range [IQR]) follow-up time was 14 months for older patients and 17 months for younger patients (p=0.09). Older patients were similar to younger patients with respect to gender (39 versus 35% female), median body mass index (BMI) [29 kg/m^2 versus 28 kg/m^2], median MELD (15 versus 16), median MELD-Na (18 versus 18), prevalence of ascites (25 versus 34%) and prevalence of moderate hepatic encephalopathy (18 versus 17%) [p>0.05 for each]. However, older patients differed significantly from younger patients by etiology of liver disease (HCV: 35 versus 52%; NAFLD: 22 versus 10%; cholestatic: 5 versus 14%) [p<0.01]. Compared to younger patients, older patients were more likely to have hepatocellular carcinoma (37 versus 19%), hypertension (63 versus 37%), and coronary artery disease (11 versus 4%) [p<0.01 for each]. Notably, older and younger patients had similar overall health assessments by their primary hepatologists with median (IQR) ratings of 3 (2–3) versus 3 (1–3) [p=0.23, respectively].

Measurements of Physical Function

The median (IQR) score on the SPPB was significantly lower in older compared to younger patients [10 (9–11) versus 11 (9–12); p=0.01], although a similar proportion of older and younger patients had an SPPB score 9 (36 versus 29%; p=0.20) [Table 2]. With respect to the three individual components of the SPPB, older patients had slower gait speed (1.1 versus 1.3 m/sec; p<0.01), a trend toward slower chair stands (12.8 versus 11.8 seconds; p=0.06), and fewer were able to complete all three balance tests for 10 seconds each (65 versus 78%; p=0.01) [Table 2].

Associations between physical function and outcomes

By the end of follow-up, 83 (18%) patients died/were delisted for being too sick, 134 (29%) underwent liver transplant, and 25 (5%) were removed from the wait-list for other reasons. Older and younger patients experienced similar rates of death/delisting (22 versus 17%; p=0.23) and similar rates of transplant (25 versus 30%; p=0.38).

Table 3 shows the uni- and multi-variable analyses for associations with wait-list mortality. In univariable competing risks analysis, compared to the reference group of younger robust (SPPB >9) candidates, patients who were impaired (SPPB≤9) had significantly higher risk of wait-list mortality regardless of whether they were younger (HR 1.77; p=0.03) or older (HR 2.70; p=0.003), but older robust patients did not (HR 1.38; p=0.35) [Wald test of equality p=0.01; Table 3]. MELD-Na (per point; HR 1.09; p<0.001), serum albumin (per g/dL; HR 0.56; p=0.01), moderate hepatic encephalopathy (HR 1.70; p=0.04), and hepatocellular carcinoma (HR 1.65; p=0.04) were also associated with wait-list mortality in univariable analysis (Table 3). Other variables that were evaluated in univariable analysis include liver disease etiology (reference: alcoholic; HCV: HR 1.22, p=0.53; NAFLD: HR 0.99, p=0.97; cholestatic: HR 1.17, p=0.71), coronary artery disease (HR 1.58, p=0.23),

BMI (per kg/m^2; HR 0.98, p=0.46), and ascites (reference: absent; controlled: HR 1.33, p=0.23; severe/refractory: HR1.46, p=0.50), however these were not significantly associated with wait-list mortality. In multivariable analysis adjusting for MELD-Na and albumin, only older impaired patients demonstrated significantly higher risk of wait-list mortality compared to younger robust candidates (HR 2.36; p=0.01; Wald test of equality for all categories of age and SPPB: p=0.05; Table 3). Among younger candidates, the p-value for the comparison between robust versus impaired patients was 0.03. The p-value for the comparison among older adults was 0.01. In a sensitivity analysis censoring HCC patients delisted for tumor progression, the hazards of wait-list mortality associated with each age-SPPB category remained similar (Wald test of equality p=0.06).

DISCUSSION

Despite the growing demand for liver transplantation posed by older patients, liver transplant clinicians lack objective tools to measure non-liver related factors that reflect increased vulnerability of older cirrhotics to adverse outcomes. As a result, beyond strict criteria, selection of older cirrhotics for transplantation may be based on subjective assessments grounded in clinical intuition. While clinical assessments of overall health by transplant hepatologists can be accurate (13), its application to transplant decision-making varies by patient, provider, and clinical circumstance. Our data demonstrating the prognostic value of a measure of physical function in liver transplant candidates over 65 years of age fills a critical gap in clinical transplant practice.

Many measures of physical function exist (14), but the SPPB holds distinct advantages as a prognostic marker in older cirrhotics. Originally developed in 5,000 adults over 70 years of age (without chronic liver disease) to assess lower extremity strength (15), this three-component battery of tests predicts subsequent disability (16–18) and mortality (19–21). For cirrhotics, performance-based measures of physical function are particularly relevant given the association between muscle area of the psoas major – one of the muscles responsible for hip flexion necessary to complete a chair stand or lift one's legs to walk – with post-transplant mortality (22). While we have previously shown that each one-point decrease in the SPPB predicts increasing risk of wait-list mortality in liver transplant candidates of all ages (9), it is biologically plausible that this instrument might have greater prognostic value in older cirrhotics who are vulnerable to the overlapping effects of functional impairment from both aging- and cirrhosis-induced processes.

It is worth noting that our older and younger liver transplant candidates received similar overall assessments of health status by their primary hepatologists. This is surprising given the intuitive selection bias against listing older cirrhotics for liver transplantation due to data demonstrating worse post-transplant outcomes compared to younger patients (4, 5). Despite the similar subjective assessments by transplant clinicians, the SPPB identified functional differences between older and younger liver transplant candidates: older patients were consistently more impaired (by both the SPPB summary score as well as its individual components). These findings strongly support the clinical utility of this objective measure of physical function in transplant decision-making to detect clinically relevant factors in older

adults – that are missed by even the most trained transplant clinicians – that may increase vulnerability to adverse outcomes.

We acknowledge several limitations to our study. There were relatively few deaths and delistings among the older liver transplant candidates during the study period. As a result, this limits our ability to adjust for multiple confounders in our analyses. However, we evaluated all clinically relevant factors in univariable competing risks analysis and only MELD-Na and albumin remained statistically significant in the multivariate model. While this study included a large, diverse cohort of liver transplant candidates, its results need to be confirmed in other cohorts or a multi-center study. Because all of the patients enrolled in the cohort were outpatients, the median MELD score of our cohort is relatively low. Additional studies that include inpatients are needed to evaluate the role of physical function in higher MELD cohorts. Lastly, although we selected specific cut-offs for both age and physical function, we feel that both cut-offs are clinically justifiable. Age 65 years is not only a well-accepted cut-off to define an “older” adult but, in our clinical experience, is also the age at which transplant clinicians begin to incorporate age into their transplant decision-making. To receive an SPPB score of 9 or less, a patient would have to be somewhat impaired in each of the three tests, or significantly impaired in one or two. Using these cut-offs enhances the clinical applicability of our analyses as clinicians can easily translate our findings into clinical practice.

Despite these limitations, our findings have important implications for clinical transplant practice. First, functional impairment, as assessed by the SPPB, can identify the older candidates most vulnerable to poor outcomes and facilitate conversations between older patients, their caregivers, and clinicians regarding the likelihood of surviving to transplant. Those unlikely to reach the transplant goal may elect for care focused on quality of life, possibly decreasing suffering for both patients and caregivers. Conversely, and of equal importance, this objective and transparent measure may justify and compel access to liver transplantation for older robust candidates who, in our study, experienced rates of wait-list mortality similar to younger candidates. Although there is no data on post-transplant functional outcomes of older candidates, we are currently conducting a prospective study to evaluate the importance of pre-transplant physical function on outcomes and recovery after liver transplantation. Lastly, our data regarding functional impairment, a modifiable risk factor, provide a solid foundation for the development of activity-based interventions to improve functional status and potentially, improve liver transplant wait-list outcomes.

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List of abbreviations

BMI	body mass index

HCV	hepatitis C virus
HR	hazard ratio
IQR	interquartile range
MELD	model for end-stage liver disease
MELD-Na	model for end-stage liver disease-sodium
NAFLD	non-alcoholic fatty liver disease
SPPB	short physical performance battery

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Table 1

Baseline characteristics of 463 liver transplant candidates with MELD ≥12 by age (< or ≥65 years).

Characteristic*		Age ≥ 65 years n= 95 (21%)	Age <65 years n= 368 (79%)	p-value
Follow up time, months		14 (9–23)	17 (9–26)	0.09
Age, years		67 (66–69)	56 (49–60)	<0.001
Female		39%	35%	0.48
Race/ ethnicity	**White**	66%	56%	0.30
	Black	3%	3%	
	Hispanic	19%	29%	
	Asian	4%	6%	
	Other	8%	6%	
Etiology of liver disease	**HCV**	35%	52%	<0.001
	Alcohol	23%	16%	
	NAFLD	22%	10%	
	Cholestatic	5%	14%	
	Other	15%	8%	
Hepatocellular carcinoma		37%	19%	<0.001
Weight, kg		84 (71–97)	85 (72–99)	0.99
BMI (kg/m^2)		29 (26–33)	28 (25–34)	0.51
Medical co-morbidities				
Hypertension		63%	37%	<0.001
Diabetes		33%	28%	0.35
Coronary artery disease		11%	4%	0.01
Laboratory tests				
Laboratory MELD		15 (13–18)	16 (13–19)	0.18
MELD–Na		18 (16–21)	18 (16–22)	0.43
Total bilirubin, mg/dL		2.1 (1.6–3.0)	2.8 (1.9–4.0)	<0.001
INR		1.4 (1.3–1.7)	1.4 (1.3–1.6)	0.35
Creatinine, mg/dL		1.0 (0.8–1.4)	1.0 (0.7–1.3)	0.43
Sodium, mEq/L		136 (134–138)	137 (134–139)	0.85
Albumin, g/dL		2.9 (2.6–3.3)	2.9 (2.6–3.3)	0.74
Ascites	**Absent**	75%	66%	0.21
	Controlled	21%	30%	
	Severe/refractory	4%	4%	
Moderate hepatic encephalopathy†		18%	17%	0.78
Child Pugh Score	**A**	15%	14%	0.51
	B	70%	66%	
	C	15%	20%	
Clinician Assessment‡		3 (2–3)	3 (1–3)	0.23

[*] Median (interquartile range) or %

[†] Moderate hepatic encephalopathy was defined as a Numbers Connection Test score between 60–120 seconds. Patients with Numbers Connection Test ≥120 seconds were excluded from the study.

[‡] Clinician assessment was on a scale of 0 = excellent to 5 = very poor.

Table 2

Short Physical Performance Battery (SPPB) scores and its components, by age (< or ≥65 years).

Measure*	Age ≥ 65 years n= 95 (21%)	Age <65 years n= 368 (79%)	p-value
Short Physical Performance	10 (9–11)	11 (9–12)	0.01
Battery Summary Score†			
% SPPB ≤9	36%	29%	0.21
Individual SPPB Components‡			
Walk speed, meters/second	1.1 (0.9–1.4)	1.3 (1.1–1.6)	<0.001
Balance, seconds	30 (27–30)	30 (30–30)	0.03
Chair stands, seconds	12.8 (10.3–15.7)	11.8 (9.5–14.8)	0.06

*Median (interquartile range) or %

†Performance-based instrument that consists of three tests: gait speed, balance testing, and repeated chair stands. Range 0 = impaired to 12 = robust (see appendix for scoring method).

‡Faster walk speed (greater distance per second), longer balance (maximum 30 seconds), and faster chair stands (fewer seconds) all indicate a more robust patient.

Table 3

Unadjusted and adjusted risk of wait-list mortality associated with each category of age and Short Physical Performance Battery* (SPPB) score ("robust" = SPPB >9; "impaired" = SPPB≤9).

		Hazard Ratio (95% CI) p-value	
		Univariable Analysis†	**Multivariable analyses§**
Younger (age<65y)	**Robust**	--	--
	Impaired	***1.77 (1.06–2.95) 0.03***	1.40 (0.83–2.39) 0.21
Older (age ≥65y)	**Robust**	1.38 (0.71–2.68) 0.35	1.57 (0.81–3.05) 0.18
	Impaired	***2.70 (1.40–5.24) 0.003***	***2.36 (1.19–4.66) 0.01***
MELD-Na (per point)		1.09 (1.05–1.13) <0.001	1.08 (1.03–1.13) 0.001
Albumin (per g/dL)		0.56 (0.37–0.85) 0.01	0.66 (0.44–0.99) 0.046
Moderate hepatic encephalopathy‡		1.70 (1.02–2.75) 0.04	--
Hepatocellular carcinoma		1.65 (1.03–2.63) 0.04	--

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

†Listed are variables associated with a p-value <0.10 in univariable analysis.

‡Moderate hepatic encephalopathy was defined as a Numbers Connection Test score between 60–120 seconds. Patients with Numbers Connection Test ≥120 seconds were excluded from the study.

§The p-value for the comparison between those who were robust versus impaired among *younger* adults was 0.03. The p-value for the comparison between those who were robust versus impaired among *older* adults was 0.01. The Wald test of equality for all categories of age and SPPB: p=0.05.

Appendix

The Short Physical Performance Battery scoring system (15)

Component	Instructions	Grading
Timed repeated chair stands	Ask the subject to fold his arms over his chest while sitting in a chair, then stand up and sit down five times. Time begins when the subject begins to stand up and ends when he has sat down completely for the 5th time.	4 = < 11.1 sec 3 = 13.6–11.2 sec 2 = 16.6–13.7 sec 1 = > 16.7 sec 0 = unable
Balance testing	Ask subject to stand in 3 positions for up to 10 seconds each: **1** Semitandem (side of the heel of one foot touching the big toe of the other foot) **2** Side-by-side (feet together, side- by-side) **3** Tandem (heel of one foot in front and touching the toes of the other foot)	4 = tandem 10 sec 3 = semitandem 10 sec, tandem 3–9.9 sec 2 = semitandem 10 sec, tandem 0–2.9 sec 1 = side by side 10 sec, semitandem <10 sec 0 = side by side 0–9.9 sec or unable
8 foot walk (2.44 meters)	Subject walks at his usual pace from the start to the end of a walking course (flat 8 foot walking surface)	4 = <3.1 sec (>0.78 m/sec) 3 = 3.2–4.0 (0.61–0.77 m/sec) 2 = 4.1–6.5 sec (0.44–0.60 m/sec) 1 > 5.7 sec (<0.43 m/sec) 0 = could not do