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The Range and Reproducibility of the Liver Frailty Index

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Abstract

The Liver Frailty Index (LFI), composed of 3 performance-based tests (grip strength, chair stands, and balance), is a tool specifically developed in patients with cirrhosis to objectively measure physical function, a critical determinant of health outcomes. We aimed to (1) determine the range of LFI scores in adults with chronic liver disease but without cirrhosis, (2) determine the range of LFI scores in adults without known liver disease, and (3) evaluate reproducibility of the LFI in adults with cirrhosis listed for liver transplantation. Intraclass correlation coefficient (ICC) assessed interrater reliability of the LFI. Included were 91 adults with chronic liver disease, 109 adults without known liver disease, and 166 adults with cirrhosis with median Model for End-Stage Liver Disease–sodium of 16. Median (interquartile range) LFI was 3.6 (3.1–4.1) in adults with cirrhosis, 3.1 (2.5–3.7) in adults with chronic liver disease but not cirrhosis, and 2.7 (2.2–3.2) in adults without liver disease ($P < 0.001$). Using established LFI cutoffs for robust, prefrail, and frail categories, adults with cirrhosis or chronic liver disease were less likely to be robust (29% versus 53% versus 77%) and more likely to be prefrail (57% versus 42% versus 22%) or frail (14% versus 5% versus 1%) when compared with adults without liver disease ($P < 0.001$). The LFI had excellent reliability with ICC of 0.93 (95% confidence interval, 0.91–0.95). In conclusion, the LFI has external validity in noncirrhotic populations and is highly reproducible among different raters. This objective assessment tool can be implemented in outpatient clinical practice or research to operationalize the concept of physical frailty.

Physical frailty is increasingly being recognized as an important contributor to health-related outcomes in patients with end-stage liver disease (ESLD) who commonly suffer from malnutrition, muscle wasting, and deconditioning. A number of instruments to operationalize physical frailty have been established in the field of geriatrics, such as the Fried Frailty Index⁽¹⁾ and Short Physical Performance Battery⁽²⁾; however, these measures were originally developed using studies of community-dwelling older adults without known liver disease. To address the unmet need within the hepatology community for a frailty assessment tool specifically for patients with cirrhosis, our group developed the Liver Frailty Index (LFI) that comprises 3 tests—grip strength, chair stands, and balance testing.⁽³⁾ We have demonstrated that these direct measures of physical function objectively capture the

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construct of physical frailty in patients with cirrhosis and have distinct advantages over other frailty measures in that they are easily implemented at the bedside and can be followed longitudinally.⁽³⁻⁵⁾ In addition, the LFI improves prognostic accuracy of the subjective clinician assessment in predicting wait-list mortality.⁽⁶⁾

Given how recently the LFI was developed, there are no data to date describing the expected range of values of the LFI. To facilitate use of the LFI in both the clinical and research settings, we designed this study to (1) determine the range of LFI scores in adults with chronic liver disease but without cirrhosis, (2) determine the range of LFI scores in adults without known liver disease, and (3) evaluate the interrater reliability of the LFI in adults with cirrhosis.

Patients and Methods

STUDY POPULATION

Given the 3 distinct goals in this study, we analyzed data from 3 separate cohorts for each study aim. The following study cohorts assessed were as follows:

Range of LFI Scores in Adults With Chronic Liver Disease but Without Cirrhosis—Adult (> 18 years) patients with a diagnosis of chronic liver disease or those referred for abnormal liver tests were recruited for the study when seen in the outpatient hepatology clinic at the University of California, San Francisco. Enrollment occurred from November 2017 to April 2018. Degree of fibrosis was determined by liver biopsy (n = 24) or liver stiffness with transient elastography (n = 59). Patients were excluded if they had cirrhosis, were undergoing liver transplantation evaluation, or did not speak English.

Range of LFI Scores in Adults Without Known Liver Disease—Adults (> 18 years) who accompanied patients to the outpatient hepatology clinic at the University of California, San Francisco (eg, family members, friends) were recruited for the study from September 2017 to April 2018. Adults (> 18 years) who worked at the University of California, San Francisco were also recruited during the same time period. Exclusion criteria included participants who reported any history of chronic liver disease.

Interrater Reliability of the LFI in Adults With Cirrhosis—From March 2017 to December 2017, patients who were enrolled in the Functional Assessment in Liver Transplantation (FrAILT) Study underwent testing of physical frailty on 2 separate occasions occurring at least 1 hour apart in the same day: first, by trained FrAILT study personnel, and second, by trained clinical staff.

STUDY PROCEDURES

At enrollment into the study, all participants underwent objective measurement of physical frailty using the following tests:

1. Grip strength⁽¹⁾: measured in kilograms using a handheld dynamometer in the subject's dominant hand. The average of 3 trials was calculated for analysis.

2. Timed chair stands ⁽²⁾: measured as the number of seconds that the subject takes to complete 5 chair stands with the subject's arms folded across the chest.
3. Balance testing ⁽²⁾: measured as the number of seconds that the subject can balance in 3 positions (feet placed side-to-side, semitandem, and tandem) for a maximum of 10 seconds each.

With these 3 performance-based tests of physical function, the LFI was calculated using the following equation⁽³⁾ (calculator available at <http://liverfrailtyindex.ucsf.edu>):

$$\text{LFI} = (-0.330 \times \text{sex-adjusted grip strength}) + (-2.529 \times \text{number of chair stands per second}) + (-0.040 \times \text{balance time}) + 6$$

The classifications of frailty were determined by using previously established cutoffs of the LFI with robust defined as LFI <3.2, prefrail defined as LFI between 3.2 and 4.4, and frail defined as LFI ≥ 4.5.⁽³⁾

For patients with chronic liver disease and patients with cirrhosis in the FrAILT cohort, demographic data and laboratory results were collected from the electronic health record from the same day as objective frailty measurements. The degree of ascites—graded as none, mild/moderate, or refractory—was assessed and ascertained from the hepatologists' recorded physical examination or the management plan. Hepatic encephalopathy was determined from the time to complete the number connection test performed at the time of the frailty measurement and categorized as present if ≥ 60 seconds were needed to complete the test.⁽⁷⁾ Participants were considered to have a medical comorbidity (eg, hypertension or diabetes) if one was reported in their electronic health record. Demographic data and medical comorbidities were collected from participants without known liver disease using surveys administered by study personnel at the time of frailty testing.

STATISTICAL ANALYSIS

Participants were categorized by the presence or absence of liver disease and further categorized by sex or age <65 versus ≥ 65 years. Differences in baseline characteristics and physical frailty measurements among the 3 cohorts of participants were compared using chi-square or Kruskal-Wallis tests for categorical and continuous variables, respectively. Differences in physical frailty measurements by categories of liver disease (present/absent), sex, or age (<65 or ≥ 65 years) were compared using Wilcoxon rank sum tests. Intraclass correlation coefficient (ICC) estimates evaluated the interrater reliability of the LFI and the individual components of the LFI. The ICC and their 95% confidence intervals (CIs) were calculated based on an individual rating, absolute-agreement, 2-way random-effects model. ICC values vary from 0 (no agreement) to 1 (perfect agreement). Values for ICC between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability, and values greater than 0.90 indicate excellent reliability.⁽⁸⁾ The κ statistics assessed the interrater reliability within the categorizations of participants as frail, prefrail, or robust. Values for κ range from 0 (no agreement) to 1 (perfect agreement): Values from 0.60 to 0.80 indicate substantial agreement and values from 0.80 to 1.0 indicate almost perfect or perfect agreement.⁽⁹⁾

Statistical analyses were performed using STATA, version 13 (Stata Corp., College Station, TX). The institutional review board at the University of California, San Francisco, approved this study.

Results

BASELINE CHARACTERISTICS

A total of 91 participants with chronic liver disease without cirrhosis, 109 participants without liver disease, and 166 participants from the FrAILT cohort were included in the analyses. Baseline characteristics of each cohort are shown in Table 1. Participants with chronic liver disease had a median age of 56 years, 57% were women, and 43% were non-Hispanic white. Median height, weight, and body mass index (BMI) were 165 cm, 75 kg, and 27 kg/m², respectively. The etiology of liver disease was chronic hepatitis C virus (HCV) in 13%, alcoholic in 29%, and nonalcoholic steatohepatitis (NASH) in 16%. In the cohort without known liver disease, the median age was 50 years, 67% were women, 55% were non-Hispanic white, and median height, weight, and BMI were 168 cm, 82 kg, and 28 kg/m², respectively. The FrAILT cohort had a median age of 60 years, 40% were women, 46% were non-Hispanic white, and median height, weight, and BMI were 170 cm, 83 kg, and 28 kg/m², respectively. In this cohort, 37% had HCV, 6% had chronic hepatitis B virus (HBV) 30% had alcoholic liver disease, and 15% had NASH. For standard markers of liver disease severity, the median Model for End-Stage Liver Disease (MELD) score was 14, Model for End-Stage Liver Disease–sodium (MELD-Na) was 16, and albumin was 3.2 g/dL. Hepatic encephalopathy, defined as a number connection test time \geq 60 seconds, was present in 14% of the cohort, and ascites was present in 14%.

DETERMINING THE RANGE OF LFI SCORES IN PARTICIPANTS WITH CHRONIC LIVER DISEASE WITHOUT CIRRHOSIS AND IN PARTICIPANTS WITHOUT KNOWN LIVER DISEASE

Table 2 presents a summary of the LFI and its individual components for each cohort categorized by participants without liver disease, with chronic liver disease but not cirrhosis, or with cirrhosis. Higher LFI scores indicate a higher degree of frailty. Median (interquartile range [IQR]) LFI scores were 3.6 (3.1–4.1) in participants with cirrhosis and 3.1 (2.5–3.7) in participants with chronic liver disease but not cirrhosis, whereas the median (IQR) LFI score was 2.7 (2.2–3.2) in participants without liver disease ($P < 0.001$). Using previously established LFI cutoffs of <3.2 , 3.2–4.4, and ≥ 4.5 for robust, prefrail, and frail participants, respectively, participants with cirrhosis or chronic liver disease were less likely to be robust (29% versus 53% versus 77%) and more likely to be prefrail (57% versus 42% versus 22%) or frail (14% versus 5% versus 1%; $P < 0.001$) as compared with those without chronic liver disease. With respect to the individual components of the LFI, participants with cirrhosis or chronic liver disease had weaker grip strength (29 versus 25 versus 32 kg; $P < 0.001$) and completed fewer chair stands (0.5 versus 0.7 versus 0.7 per second; $P < 0.001$) compared with those without liver disease. However, all cohorts performed similarly with respect to balance (30 versus 30 versus 30 seconds; $P = 0.09$; Table 2).

We then examined how men compared with women and how participants <65 years of age (the younger group) compared with those ≥65 years of age (the older group) performed on the LFI when categorized by presence or absence of chronic liver disease. Men with chronic liver disease and men without liver disease were similar with respect to chair stands (0.7 versus 0.6 per second), balance (30 versus 30 seconds), and LFI score (3.0 versus 2.9; $P > 0.05$ for each); however, they differed significantly in grip strength (34 versus 40 kg; $P = 0.005$). Compared with women without known liver disease, women with chronic liver disease were worse in grip strength (22 versus 27 kg; $P < 0.001$), chair stands (0.6 versus 0.8 per second; $P = 0.01$), balance (30 versus 30 seconds; $P = 0.04$), and LFI score (3.2 versus 2.5; $P < 0.001$; Table 3). Among younger participants, those with chronic liver disease performed worse on grip strength (25 versus 32 kg; $P = 0.001$), balance (30 versus 30 seconds; $P = 0.01$), and LFI scores (2.9 versus 2.5; $P = 0.001$), although they performed similarly on chair stands (0.7 versus 0.8 per second; $P = 0.33$) compared with those without liver disease. Older participants with chronic liver disease and without liver disease were similar in chair stands (0.5 versus 0.6 per second), balance (30 versus 30 seconds), and LFI scores (3.5 versus 3.3; $P > 0.05$ for each) but were weaker in grip strength (25 versus 28 kg; $P = 0.05$; Table 4).

INTERRATER RELIABILITY OF THE LFI

We analyzed data from 166 participants with cirrhosis enrolled in the FrAILT study using 2 trained individuals administering the LFI tests (Table 5). There was an excellent degree of agreement for the LFI with ICC of 0.93 (95% CI, 0.91–0.94). For the individual components of the LFI, there was excellent reliability for grip strength (ICC, 0.93; 95% CI, 0.91–0.95), good reliability for chair stands (ICC, 0.87; 95% CI, 0.83–0.90), and moderate reliability for balance (ICC, 0.73; 95% CI, 0.65–0.79). Finally, we evaluated the interrater reliability for frailty categories using κ statistics. With respect to categorizing participants as frail, prefrail, or robust, the κ coefficients were 0.78 (95% CI, 0.62–0.93), 0.67 (95% CI, 0.52–0.82), and 0.73 (95% CI, 0.58–0.89), respectively, for each category.

Discussion

The lack of consensus for a feasible, reliable, and objective test of physical frailty for clinical use in liver transplantation has limited the application of the diagnosis of the frailty phenotype in clinical hepatology practice.⁽¹⁰⁾ We developed the LFI specifically for patients with cirrhosis using a parsimonious battery of tests that have been incorporated into composite frailty indices in the field of geriatrics for decades.^(1,2) Thus far, we have demonstrated that the LFI improves risk prediction of wait-list mortality over the MELD-Na alone,⁽³⁾ can enhance subjective clinician assessments of a patient's global health status,⁽⁶⁾ and is strongly associated with robustness of physical function after liver transplantation.⁽¹¹⁾

In this study, we aimed to fill in gaps in our understanding of the practical aspects of the LFI — specifically, how to interpret values of this metric and how it might perform in the clinical setting. We observed that the median LFI score was 3.1 for participants with chronic liver disease without cirrhosis and 2.7 for participants without chronic liver disease. As a comparison, the median LFI for liver transplant candidates with decompensated cirrhosis (in

our original derivation study) was 3.8; for those with hepatocellular carcinoma and a low MELD-Na score (<12), whom we deemed to be the “healthiest” of patients with ESLD, the median LFI was 3.2.⁽³⁾ Therefore, the LFI appears consistent with the level of physical function in each cohort of patients one might expect based on degree of liver disease. Moreover, the cohort with chronic liver disease can aid our understanding of what LFI values should be expected after liver transplantation when patients no longer have cirrhosis but may still have underlying liver disease, whereas the cohort without known liver disease can set a target value of what can be achieved in patients who do not suffer from liver disease or cirrhosis. Importantly, our results also demonstrated that the LFI is reproducible among different raters with a high ICC for the LFI and its individual components.

What does the LFI measure? The LFI is not intended to be a measure of cirrhosis or chronic liver disease but rather to capture the constellation of “extrahepatic” manifestations of malnutrition, muscle wasting, and functional impairment commonly seen in patients with cirrhosis. These complications often overlap with chronologic aging, and, in fact, there is a natural prevalence of frailty—as measured by the geriatric instrument Fried Frailty—in the general population.⁽¹⁾ We observed a median LFI score of 3.3 among participants 65 years old without liver disease compared with a median LFI score of 3.8 among patients of all ages with cirrhosis. This finding suggests patients with cirrhosis may physiologically behave similarly to a cohort that is chronologically older in age and experience increased risk for adverse health outcomes as a result. In support of this, we previously demonstrated that the LFI enhances risk prediction for wait-list mortality in patients awaiting liver transplant over MELD-Na alone, particularly in patients who were older.⁽³⁾

How might the LFI facilitate medical decision making for clinicians and patients in liver transplantation? Such decisions and discussions might involve the following:

1. Encouraging alternatives to shorten wait-list time (eg, living donor liver transplantation, acceptance of livers from donors of increased risk).
2. Establishing objective goals for prehabilitation using the range of LFI scores observed in the cohort with chronic liver disease.
3. Setting expectations of functional recovery after liver transplantation using the range of LFI scores observed in the cohort without known liver disease.

Identification of frailty in liver transplant candidates using the LFI could also result in improvements in secondary care and specialist services, such as nutrition or physical therapy, or, for patients who are not eligible for transplant, timely initiation of hospice care services. Beyond the clinical setting, an objective continuously scored metric of physical function enables the development of interventions targeting individual components of physical frailty in patients with cirrhosis.

This study has several limitations. The grading of ascites was based on the primary hepatologists’ physical examination and management plan but did not incorporate abdominal imaging. We did this in order to ascertain the degree of ascites on the same day of frailty testing, as not all patients have imaging obtained on the day of assessment. We determined the presence of hepatic encephalopathy using the number connection test that

was not adjusted for age or education. This test is better used to identify subclinical or minimal hepatic encephalopathy but is limited by its ability to grade severity. Given that the study population included only patients seen in the outpatient clinic, these results are not generalizable to the inpatient setting. Yet, identifying patients with increased frailty in the outpatient setting may be more optimal to allow additional time for discussion with the patient or an intervention. Lastly, there is the possibility for classification bias among cohorts based on presence or absence of liver disease, as the lack of liver disease was determined by self-report. However, there was a 99.7% negative agreement for participants reporting the absence of cirrhosis in a population-based US military cohort study evaluating self-reported medical conditions compared with electronic medical record data.⁽¹²⁾

In conclusion, the LFI is an objective assessment tool that operationalizes the concept of physical frailty for use in outpatient clinical practice with excellent reliability. Additional studies are needed to examine how key patient features, such as age, BMI, and medical comorbidities, may explain variability in the LFI and impact the prediction of clinical outcomes. Implementation of the LFI into routine clinical practice of liver transplantation would represent a major advancement in the care of liver transplant candidates to anchor clinical decision making and facilitate clinician-patient discussions with objective measures of physical function.

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Abbreviations:

BMI	body mass index
CI	confidence interval
ESLD	end-stage liver disease
FrAILT	Functional Assessment in Liver Transplantation
HBV	hepatitis B virus
HCV	hepatitis C virus
ICC	intraclass correlation coefficient
IQR	interquartile range
LFI	Liver Frailty Index
MELD	Model for End-Stage Liver Disease
MELD-Na	Model for End-Stage Liver Disease–sodium
NASH	nonalcoholic steatohepatitis

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TABLE 1.

Baseline Characteristics of Participants Without Liver Disease, Participants With Chronic Liver Disease, and Participants in the FrAILT Cohort

Characteristic	No Liver Disease Cohort* (n = 109)	Chronic Liver Disease Cohort (n = 91)	FrAILT Cohort (n = 166)	P Value
Age, years	50 (34–63)	56 (43–65)	60 (53–65)	<0.001
Sex, female	67	57	40	<0.001
Race				0.002
White	56	43	46	
Black	5	3	5	
Hispanic	24	18	31	
Asian	12	34	13	
Other	3	2	5	
Height, cm	168 (161–175)	165 (158–173)	170 (163–178)	0.01
Weight, kg	82 (69–92)	75 (61–87)	83 (69–94)	0.01
BMI, kg/m ²	28 (25–32)	27 (24–30)	28 (25–34)	0.01
Hypertension	14	27	44	<0.001
Diabetes	7	11	30	<0.001
Etiology of liver disease				<0.001
HCV		13	37	
HBV		1	6	
Alcoholic		29	30	
NASH		17	15	
Cholestatic		14	8	
Other		26	4	
Markers of liver disease severity				
Laboratory MELD			14 (10–18)	
MELD-Na			16 (12–21)	
Total bilirubin, mg/dL			1.9 (1.2–3.2)	
INR			1.4 (1.2–1.6)	
Creatinine, mg/dL			0.8 (0.7–1.0)	
Sodium, mEq/L			136 (134–139)	
Albumin, g/dL			3.2 (2.8–3.6)	

Characteristic	No Liver Disease Cohort* (n = 109)	Chronic Liver Disease Cohort (n = 91)	FrAILT Cohort (n = 166)	P Value
Ascites				
Mild/moderate			10	
Refractory			4	
Hepatic encephalopathy			14	
Dialysis			3	

NOTE: Data are presented as median (IQR) or %.

* Missing data on race, height, weight, and BMI for 35 participants.

TABLE 2. LFI Score and Individual Physical Frailty Components Categorized by Absence of Liver Disease, Presence of Chronic Liver Disease, and Patients With Cirrhosis (FrAILT Cohort)

Measure	No Liver Disease (n = 109)	Chronic Liver Disease (n = 91)	FrAILT Cohort (n = 166)	P Value
LFI	2.7 (2.2–3.2)	3.1 (2.5–3.7)	3.6 (3.1–4.1)	<0.001
Individual components				
Grip strength, kg	32 (26–36)	25 (20–34)	29 (20–35)	<0.001
Chair stands, number per second	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.5 (0.4–0.6)	<0.001
Balance, seconds	30 (30–30)	30 (30–30)	30 (30–30)	0.09
Able to complete all balance tests, %	95	90	91	0.30
Frailty categories				
Robust	84 (77)	48 (53)	48 (29)	<0.001
Prefrail	24 (22)	38 (42)	95 (57)	
Frail	1 (1)	5 (5)	23 (14)	

NOTE: Data are given as n (%) or median (IQR) unless otherwise noted.

TABLE 3.

LFI Score and Individual Physical Frailty Components of Patients With Chronic Liver Disease and Patients Without Liver Disease Categorized by Sex

Measure	Men			Women		
	Chronic Liver Disease (n = 39)	No Liver Disease (n = 36)	P Value	Chronic Liver Disease (n = 52)	No Liver Disease (n = 73)	P Value
LFI	3.0 (2.3–3.7)	2.9 (2.3–3.3)	0.44	3.2 (2.6–3.7)	2.5 (2.0–3.0)	<0.001
Individual components						
Grip strength, kg	34 (26–41)	40 (35–48)	0.005	22 (17–26)	27 (24–33)	<0.001
Chair stands, number per second	0.7 (0.5–0.9)	0.6 (0.5–0.8)	0.41	0.6 (0.5–0.8)	0.8 (0.6–0.9)	0.01
Balance, seconds	30 (30–30)	30 (30–30)	0.96	30 (30–30)	30 (30–30)	0.04
Able to complete all balance tests, %	92	92	0.92	88	97	0.05

TABLE 4.

LFI Score and Individual Physical Frailty Components of Patients With Chronic Liver Disease and Patients Without Liver Disease Categorized by Age <65 or Age 65 Years

Measure	Age <65 Years		P Value	Age 65 Years		P Value
	Chronic Liver Disease (n = 68)	No Liver Disease (n = 86)		Chronic Liver Disease (n = 23)	No Liver Disease (n = 23)	
LFI	2.9 (2.3–3.6)	2.5 (2.0–3.0)	0.001	3.5 (3.0–4.2)	3.3 (2.9–3.7)	0.10
Individual components						
Grip strength, kg	25 (21–35)	32 (26–37)	0.001	25 (19–31)	28 (24–35)	0.05
Chair stands, number per second	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.33	0.5 (0.4–0.7)	0.6 (0.4–0.7)	0.24
Balance, seconds	30 (30–30)	30 (30–30)	0.01	30 (30–30)	30 (30–30)	0.43
Able to complete all balance tests, %	90	99	0.01	91	83	0.38

TABLE 5.

Interrater Reliability for LFI and Individual Components

Measure	ICC (95% CI)
LFI	0.93 (0.90–0.94)
Individual components	
Grip strength	0.93 (0.91–0.95)
Chair stands	0.87 (0.83–0.90)
Balance	0.73 (0.65–0.79)

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