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Frailty and the Burden of Concurrent and Incident Disability in Patients With Cirrhosis: A Prospective Cohort Study

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Frailty results from the chronic effects of malnutrition and muscle wasting in patients with cirrhosis. It is well-established that frailty is strongly associated with mortality in this population. However, little is known of its relationship with physical disability, a critical patient-centered outcome. Adults with cirrhosis underwent outpatient testing of frailty using the Liver Frailty Index (LFI) and disability using activities of daily living (ADL; range 0-6) and Instrumental ADL (IADL; range 0-8) scales at one center between 2012 and 2016. We used adjusted multilevel logistic mixed-effects regression to test the association between frailty and current disability (impairment with ≥1 ADL or IADL) and incident disability at 6 months among those without baseline disability. Of the 983 participants, 20% were robust, 32% were less robust, 33% were prefrail, and 15% were frail; 587 (60%) had at least 1 assessment. The percentage of participants with at least 1 baseline ADL or IADL impairment was 28% and 37%, respectively. In adjusted regression models, each point LFI increase was associated with a 3.3 and 4.6 higher odds of current difficulty with at least 1 ADL and IADL (P < 0.001 for each), respectively. Among participants without baseline disability, each point LFI increase was associated with a 2.6 and 1.7 higher odds of having difficulty with at least 1 ADL and IADL at 6 months, respectively. *Conclusion:* Frailty is strongly associated with concurrent and incident disability in patients with cirrhosis. In the clinic, the LFI can be used to identify those in greatest need for additional support/resources to maintain functional independence. In research settings, the LFI may help to identify an enriched population for clinical trials of interventions aimed at those most vulnerable to disability. (*Hepatology Communications* 2020;4:126-133).

In most patients with cirrhosis, chronic undernutrition and muscle loss manifest as physical frailty to at least some degree.[1,2] In 2017, we developed the Liver Frailty Index (LFI) to objectively capture these insidious (and sometimes lethal) conditions. Consisting purely of performance-based tests, the LFI enhances risk prediction above and beyond traditional, well-known predictors of mortality in patients with cirrhosis, including the Model for End-Stage Liver Disease ascites–sodium (MELD-Na), hepatic encephalopathy, and age.[3-5]

Although the three components of the LFI (grip strength, chair stands, and balance) intuitively contribute to functional independence (i.e., the ability to live without the assistance of other people), its relationship with functional independence, or lack thereof, has not yet been directly characterized. In the field of geriatrics, difficulty or dependency in carrying out activities essential to independent living (e.g., self-care, home care, food preparation, transportation management) is defined as "disability." Although the concepts of disability and physical frailty are interrelated, they can

Abbreviations: ADL, activities of daily living; CI, confidence interval; IADL, instrumental activities of daily living; LFI, Liver Frailty Index; MELD-Na, Model for End-Stage Liver Disease ascites–sodium.

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be observed independently of one another.[6] Both frailty and disability are widely recognized as potent predictors of mortality. Beyond predicting mortality, however, disability is also a fundamentally important outcome in and of itself.[7-9] In fact, the World Health Organization has identified disability as a major health issue that is responsible for more than half the burden of premature mortality.[10] Furthermore, the Patient-Centered Outcomes Research Institute recognizes the preservation of functional independence as a fundamental goal of medical care that is important to patients themselves.[11]

Using this prior work in the field of geriatrics as the scientific premise for our study, we aimed to evaluate the relationship between physical frailty and disability in patients with cirrhosis.

Patients and Methods

STUDY POPULATION

We used longitudinally collected data from participants enrolled in the Functional Assessment in Liver Transplantation (FrAILT) study from March 2012 through December 2016; the full FrAILT Study protocol has been published previously.[3] Briefly, adult outpatients with cirrhosis who were actively listed for liver transplantation at the University of California, San Francisco, were eligible for enrollment. Participants underwent study procedures (see subsequently) at enrollment and at every clinic visit. The timing of the clinic visits was determined at the discretion of the primary hepatologist, although general practice is to see patients awaiting liver transplantation every 3 to 6 months. For the purposes of this study, participants were followed through August 2018 or until they experienced a terminal wait-list event (such as transplant, death, or removal from the transplant list for other reasons).

STUDY PROCEDURES

All participants underwent objective measurement of frailty using the following tests: (1) grip strength: the average of three trials, measured in the subject's dominant hand using a hand dynamometer; (2) timed chair stands: measured as the number of seconds it takes to do five chair stands with the subject's arms folded across the chest; and (3) balance testing: measured as the number of seconds that the subject can balance in three positions (feet placed side-to-side, semi-tandem, and tandem) for a maximum of 10 seconds each.

These three tests were administered by trained study personnel. With these three individual tests of frailty, the LFI was calculated using the following equation[3] (calculator available at http://liverfrailtyindex.ucsf.edu):

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

On the same day as the frailty assessment, we assessed disability using two validated scales: (1) activities of daily living[12] (ADLs) and (2) instrumental ADLs (IADLs).[13] ADLs consist of six activities: bathing, dressing, toileting, transferring, continence, and feeding. IADLs consist of eight activities distinct from the six ADLs: using a telephone, shopping, food preparation, housekeeping, doing laundry, transportation, managing finances, and managing medications. For each activity, study personnel asked through verbal interviews, "Do you have difficulty with _____?" Participants were considered to have disability in a particular ADL/IADL if they

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answered yes to that question. The maximum number of affirmative responses for ADLs was six, and for IADLs was eight.

Demographic data were extracted from the clinic visit note from the same day as the LFI and disability assessments. Participants were considered to have a diagnosis of hypertension, diabetes, or coronary artery disease if reported in their electronic health record. Ascites was ascertained at each study visit from the hepatologist's recorded physical exam or the management plan associated with the clinic visit that occurred on the same day at the assessment of frailty. Ascites was categorized as "absent" if ascites was not present on physical exam or "present" if ascites was present on exam and/or the participant was noted to be undergoing large-volume paracenteses. Hepatic encephalopathy was determined at each study visit from the time to complete the Numbers Connection Test A[14] performed at the time of the frailty measurement. Hepatic encephalopathy was categorized as "present" if the participant took 45 or more seconds to complete the task. This cutoff of 45 seconds was selected based on normative data determined from healthy participants and compared with individuals with and without hepatic encephalopathy.[14]

STATISTICAL ANALYSIS

Baseline demographics were presented as medians (interquartile ranges) for continuous variables or percentages for categorical variables and compared by frailty status using Kruskal-Wallis or chi-square tests with exact methods as needed. Trends by frailty status were assessed using ordinary least-squares regression or the Cochran-Armitage trend test. The primary outcome was disability using ADL (range 0-6) and IADL (range 0-8) scales; disability was defined as difficulty with at least 1 ADL or at least 1 IADL, each corresponding to the presence of at least one disability. Frailty was categorized as robust, less robust, prefrail, and frail using established LFI cut-off points: fewer than 3.2, 3.2-3.7, 3.8-4.4, and 4.5 or more.[3]

Multilevel mixed-effects logistic regression modeled longitudinal data from each clinic visit to evaluate the association between the LFI and (1) current disability among all participants and (2) incident disability at 6 months (±2 months) among participants with no disability at baseline (ADL = 6 or IADL = 8). This 6-month time frame for the outcome was selected to facilitate clinical interpretation. In these models, a single participant could contribute multiple observations such that the LFI was modeled as a time-dependent predictor. We structured the models with two levels (participant and visit), nesting the longitudinal visit-level observations within the participant to address correlation. Baseline age and gender, as well as time-varying LFI, MELD, hepatic encephalopathy, ascites, body mass index and time, were modeled as fixed effects. These characteristics were selected beforehand and included in the multivariable models, regardless of statistical significance, given their biologically plausible associations with frailty. A participant was modeled as a random effect to allow for random intercepts. Random slopes were also assessed but did not improve the model fit. From the multivariable models, we calculated the predicted probabilities of incident disability at specific LFI values while holding covariates at the mean.

Data analysis was completed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata/IC version 14.2 (StataCorp, College Station, TX).

Results

A total of 983 participants with cirrhosis were included in the analyses: at baseline, 197 (20%) were robust (LFI < 3.2), 312 (32%) were less robust (LFI 3.2-3.7), 323 (33%) were prefrail (LFI 3.8-4.4), and 151 (15%) were frail (LFI ≥ 4.5). Baseline characteristics of the cohort are found in Table 1. The groups were clinically similar in age and proportion with hypertension or coronary artery disease. The groups differed by proportion who were female, race/ethnicity, etiology of liver disease, HCC, diabetes, and body mass index. Metrics of liver disease severity increased as frailty increased, including MELD-Na scores and prevalence of ascites and hepatic encephalopathy (test of trend $P < 0.001$ for each). Median follow-up time was longer in the robust and prerobust participants than the prefrail and frail participants.

CROSS-SECTIONAL ASSOCIATION BETWEEN THE LFI AND CURRENT DISABILITY

The proportion of participants who had difficulty with at least one ADL or with at least one IADL

TABLE 1. CHARACTERISTICS OF THE 983 STUDY PARTICIPANTS INCLUDED IN THIS STUDY

		By Frailty Phenotype				
Characteristics*	All n = 983	Robust n = 297 (30%)	Prerobust n =3 12 (32%)	Prefrail n = 323 (33%)	Frail n = 151 (15%)	Test of Trend *P* Value
Age, years	60 (53-64)	59 (51-63)	60 (55-64)	60 (54-64)	59 (51-64)	0.07
Women	34%	25%	33%	36%	43%	<0.001
Race/Ethnicity						
Non-Hispanic white	57%	64%	55%	53%	56%	0.04
Black	4%	4%	4%	5%	2%	0.46
Hispanic	24%	17%	23%	28%	30%	<0.001
Asian/Pacific Islander	7%	9%	10%	6%	3%	0.02
Other	8%	6%	8%	8%	10%	0.16
Body mass index, kg/m^2	28 (25-32)	27 (24-31)	28 (25-32)	29 (25-33)	29 (25-34)	<0.001
Etiology of liver disease						
Chronic hepatitis C	49%	53%	57%	47%	33%	<0.001
Alcohol	18%	15%	13%	22%	26%	<0.001
Nonalcoholic steatohepatitis	11%	7%	8%	13%	20%	<0.001
Autoimmune/cholestatic	10%	12%	12%	9%	8%	0.09
Other	11%	14%	10%	9%	13%	0.63
Hepatocellular carcinoma	37%	46%	43%	35%	16%	<0.001
Hypertension	42%	38%	41%	46%	40%	0.38
Diabetes	28%	20%	27%	29%	40%	<0.001
Coronary artery disease	6%	5%	6%	8%	3%	0.96
MELD-Na	17 (13-21)	15 (12-19)	16 (12-19)	17 (14-22)	21 (16-26)	<0.001
Creatinine, mg/dL†	0.9 (0.7-1.2)	0.8 (0.7-1.0)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.1 (0.8-1.6)	<0.001
Dialysis	4%	2%	2%	4%	9%	<0.001
Albumin, g/dL	3.1 (2.7-3.6)	3.4 (2.9-3.8)	3.1 (2.7-3.6)	3.0 (2.6-3.4)	3.0 (2.5-3.4)	<0.001
Ascites	27%	12%	23%	31%	47%	<0.001
Hepatic encephalopathy	39%	18%	37%	48%	54%	<0.001
Follow up time, months	9.8 (4.4-18.4)	11.9 (4.9-20.5)	10.5 (5.6-18.4)	7.9 (4.2-16.6)	9.0 (3.7-16.4)	0.04

*Median (interquartile range) or percentage.
†Among those who were not on dialysis.

at baseline was 28% and 37%, respectively. For both ADLs and IADLs, this proportion increased with worsening LFI category (test of trend $P < 0.001$ for both). For ADLs, the proportions were 11% for robust, 18% for prerobust, 35% for prefrail, and 56% for frail. For IADLs, the proportions were 15% for robust, 23% for prerobust, 46% for prefrail, and 75% for frail. These observations remained for each individual ADL (Fig. 1) and IADL (Fig. 2) (test of trend $P \leq 0.001$ in all cases). In adjusted multilevel mixed-effects logistic regression analyses, each one-unit increase in the LFI (i.e., worsening) was associated with a 3.3-fold higher odds of reporting difficulty with at least 1 ADL (95% confidence interval [CI], 2.7-4.1; $P < 0.001$) and a 4.6-fold higher odds of reporting difficulty with at least 1 IADL (95% CI, 3.6-6.0; $P < 0.001$).

ASSOCIATION BETWEEN THE LFI AND FUTURE DISABILITY

A total of 587 participants had at least two assessments of both frailty and disability. Comparison of the characteristics of those with only one assessment versus more than one assessment are presented in Supporting Table S1. Participants in our cohort with only one assessment were similar to those with more than one assessment in demographic characteristics but, as expected, were sicker by liver disease

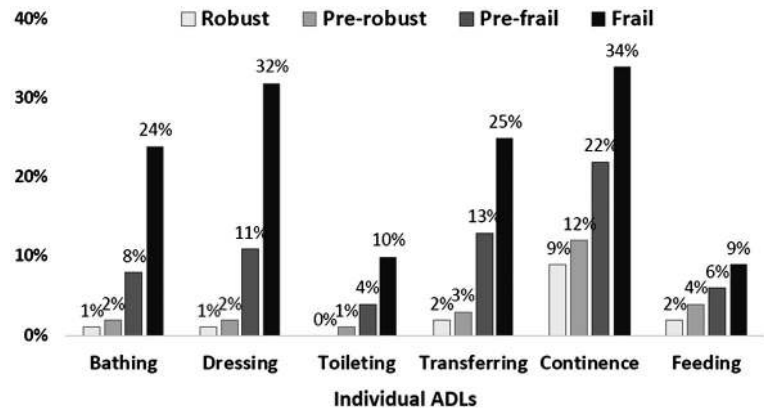

FIG. 1. Proportion of patients with difficulty with each ADL at baseline, by frailty category (test of trend $P \leq 0.001$ for each).

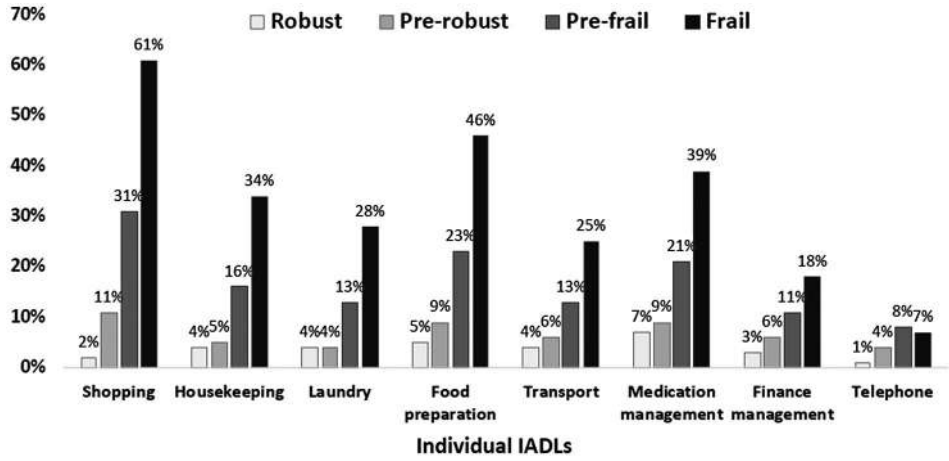

FIG. 2. Proportion of patients with difficulty with each IADL at baseline, by frailty category (test of trend $P < 0.001$ for each).

severity (MELD-Na). Wait-list outcomes were similar between the two groups ($P = 0.77$).

Among those with at least two assessments, higher categories of baseline LFI values were associated with increasing proportions of participants who experienced worsening of at least one ADL at a subsequent study visit. Specifically, the proportion of robust, prerobust, prefrail, and frail participants who experienced subsequent worsening in their ADLs was 21%, 35%, 40%, and 50% (test of trend $P < 0.001$). Similarly, the proportion of participants who experienced any worsening in their IADLs at a subsequent assessment increased with worsening frailty category: 23% for robust, 36% for prerobust, 40% for prefrail, and 52% for frail (test of trend $P < 0.001$).

ASSOCIATION BETWEEN THE LFI AND FUTURE DISABILITY AMONG THOSE WITHOUT ANY DISABILITY AT BASELINE

Finally, given the clinical relevance of transitioning from complete independence in ADLs or IADLs to having any disability in ADLs or IADLs, we performed secondary analyses in only those participants who had no disability at baseline and had a second assessment at 6 months (±2 months). For ADLs, we analyzed 595 assessments among 294 participants, and for IADLs, we analyzed 524 assessments among 265 participants.

In multilevel mixed-effects logistic regression, each one-unit increase in the LFI was associated with a

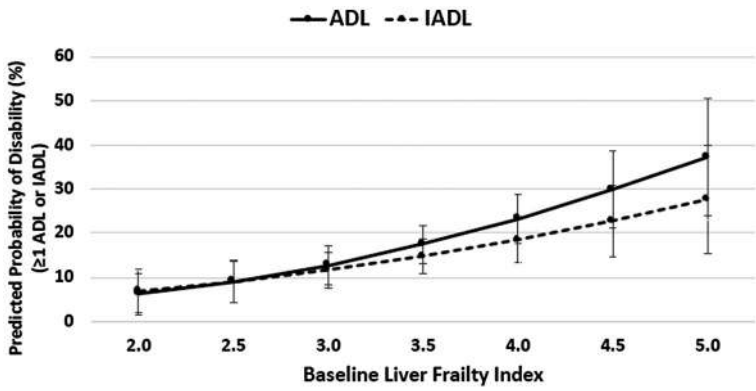

FIG. 3. Predicted probability of incident disability, defined as difficulty with at leat one ADL or IADL at 6 months, by baseline LFI, among patients with no reported disability at a prior assessment.

2.6-fold higher adjusted odds of developing subsequent difficulty with at least one ADL at 6 months (95% CI, 1.4-4.6; P = 0.001) and a 1.7-fold higher adjusted odds of developing subsequent difficulty with at least one IADL (95% CI, 1.0-2.9; P = 0.05). Figure 3 shows the predicted probabilities of incident ADL and IADL disability at 6 months. For example, at LFI values of 3.0, 4.0, and 5.0, the predicted probabilities (95% CI) for 6-month incident disability in at least one ADL are 13% (9%-18%), 23% (17%-29%), and 36% (23%-49%), and the predicted probabilities for 6-month incident disability in at least one IADL are 12% (8%-16%), 17% (12%-22%), and 24% (12%-39%) (Fig. 3a).

Discussion

When the cure or reversal of a disease process is not feasible, the goal of medical care is to reduce patient suffering through treatments that optimize functioning, reduce disability, and improve health-related quality of life. Cirrhosis is a quintessential example of a condition for which there is no cure, except for liver transplantation, which is accessible to only a minority of those with end-stage liver disease.[15] Yet, to date, the biomedical literature on treatment for cirrhosis and its complications is largely focused on the outcomes of liver disease progression and/or mortality. Although these outcomes are critically important, quantifying the burden of cirrhosis on patients' daily life beyond disease progression and death is crucial to developing strategies to improve the quality and patient-centeredness of care.

With this in mind, we offer several observations from this study. First, the observed that rates of disability were unexpectedly high for an outpatient population with a median age of only 60 years. Indeed, 28% of participants reported disability in at least one ADL and 37% reported disability in at least one IADL. Our findings are similar to a sample of about 300 individuals with cirrhosis in the national Health and Retirement Study.[16] To contextualize our findings, approximately 3%-10% of more than 8,000 community-dwelling older adults (age range: 65-90+ years) participating in the National Health and Aging Trends Study reported impairment with any one ADL (rate varied by individual ADL).[17] Second, frailty, as measured by the LFI, was strongly associated with current disability with both ADLs and IADLs. In fact, the proportion of participants reporting disability in ADLs and IADLs increased in a stepwise fashion as frailty worsened. Lastly, among those who were not disabled at baseline, frailty was strongly associated with the development of *future* disability in both ADLs and IADLs.

Although notable, our findings likely underestimate the burden of cirrhosis on the lived experience of our patients, as the ADL and IADL disability scales quantify *advanced* physical disabilities. Indeed, a person in need of help with an ADL is unable to live alone without assistance on a daily basis. A person in need of help with an IADL will have difficulty living alone or, at the very least, have impaired

health-related quality of life without regular assistance. The ADL and IADL scales are crude measures of disability in younger ambulatory populations, as there are often floor effects in which most patients score "well" and do not appear to change over time. By the time impairment in an ADL or IADL develops, patients have long been disabled in other, more discretionary activities that require less effort. As a disease increasingly affects physical performance and energy, people will often first sacrifice "discretionary" activities that provide pleasure and give life meaning in order to preserve their capacity to perform those activities required for survival within their home (ADL) and their community (IADL). While we did not directly measure health-related quality of life in our study, the ability to perform such activities are essential to one's quality of life; therefore, the development of ADL or IADL difficulty may serve as a surrogate for impaired quality of life. Our data demonstrating high rates of ADL and IADL disability in relatively young adults with cirrhosis should raise awareness of the enormous burden of disability in this population. Our data also suggest that routinely assessing disability and addressing disability could result in marked improvements in patient outcomes, as has been shown in the field of geriatrics.

However, the main barriers to using patient-reported scales in measuring patient-oriented outcomes such as disability or health-related quality of life are the instruments' subjectivity and limited ability to predict future outcomes. This is a particularly relevant barrier in the field of hepatology, in which many patients with end-stage liver disease may ultimately become candidates for liver transplantation, when objectivity of risk assessment is paramount. The LFI, a reliable, reproducible, performance-based metric that can be administered by medical assistants in approximately 90 seconds,[18] can help to identify patients with concurrent *and* future risk for subsequent ADL and IADL disability beyond what is routinely collected as part of today's standard clinical practice.

We acknowledge that our study is limited by the fact that we only assessed patients at their regular outpatient clinic visit; not all patients had more than one assessment. Although this would not affect analyses evaluating the association between the LFI and current disability, it is possible that this could introduce bias in the analyses of longitudinal assessments. Our use of multilevel mixed-effects modeling allowed us to account for intrapatient characteristics that were similar from one observation to another, and our secondary analyses evaluating only those with an assessment at 6 months (±2 months), may minimize the influence of differential, nonrandom follow-up. Second, our cohort included only patients at a single center, which could potentially limit the generalizability of these data to other populations. Finally, the development and reporting of disability may be influenced by one's culture and native language; our study may not be broadly applicable to patients who identify as races that are relatively underrepresented in this study.

Despite these limitations, our study is the largest study to evaluate disability in patients with cirrhosis, a fundamentally important patient-centered outcome. Our observation that the LFI is strongly associated with current and subsequent disability has important implications for the hepatology community. Routine assessment of patients with cirrhosis using the LFI in the outpatient clinical setting can help to quickly identify those who are most vulnerable to disability, and therefore in greatest need of more supportive services. These services might be more frequent follow-up, targeted exercise programs, multidisciplinary outpatient chronic disease management, or in-home services, as has been shown to be effective in individuals with other disabling conditions.[19-22] Furthermore, the Food and Drug Administration emphasizes patient-focused drug development for selecting outcomes in interventional trials. They recommend including measures of how a patient "feels or functions."[23] Given its association with both mortality and disability, the LFI should be considered for validation as a surrogate endpoint in clinical trials with respect to patient-oriented outcomes. The LFI may further facilitate efficient trial design by allowing investigators to identify study participants who could most benefit from certain interventions. If the focus of care of patients with cirrhosis is to reduce suffering, then we, as a community, must begin to introduce the tools to assess current disability and risk for progressive disability into our clinical and research settings.

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