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Performance-based measures associate with frailty in patients with end-stage liver disease

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Abstract

Background—Physical frailty, as measured by the Fried Frailty Index, is increasingly recognized as a critical determinant of outcomes in cirrhotics. However, its utility is limited by the inclusion of self-reported components. We aimed to identify performance-based measures associated with frailty in patients with cirrhosis.

Methods—Cirrhotics ≥50 years underwent: 6-minute walk test (6MWT, cardiopulmonary endurance), chair stands in 30 seconds (muscle endurance), isometric knee extension (lower extremity strength), unipedal stance time (static balance), and maximal step length (dynamic balance/coordination). Linear regression associated each physical performance test with frailty. Principal components exploratory factor analysis evaluated the inter-relatedness of frailty and the 5 physical performance tests.

Results—Of forty cirrhotics, with a median age of 64 years and Model for End-stage Liver Disease (MELD) MELD of 12,10 (25%) were frail by Fried Frailty Index ≥3. Frail cirrhotics had poorer performance in 6MWT distance (231 vs. 338 meters), 30 second chair stands (7 vs. 10), isometric knee extension (86 vs. 122 Newton meters), and maximal step length (22 vs. 27 inches) [p≤0.02 for each]. Each physical performance test was significantly associated with frailty (p<0.01), even after adjustment for MELD or hepatic encephalopathy. Principal component factor analysis demonstrated substantial, but unique, clustering of each physical performance test to a single factor – frailty.

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Conclusion—Frailty in cirrhosis is a multi-dimensional construct that is distinct from liver dysfunction and incorporates endurance, strength, and balance. Our data provide specific targets for prehabilitation interventions aimed at reducing frailty in cirrhotics in preparation for liver transplantation.

INTRODUCTION

Frailty is commonly defined as a "distinct biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple systems".[1] One of the most commonly used instruments is the Fried Frailty Index, which combines 5 domains of physical frailty – weakness, exhaustion, weight loss, low activity, and slowness – into a single 5 point score.[1] Originally developed in community-dwelling adults over the age of 65 years to predict overall mortality, the Fried Frailty Index also predicts mortality in chronologically younger patients (median age 60 years) with end-stage liver disease.[2] Furthermore, some components of the frail phenotype, such as sarcopenia, have been associated with worse outcomes after transplantation.[3]

One potential application for the Fried Frailty Index in liver transplantation is to identify those in greatest need of prehabilitation – with the goal of both reducing mortality on the waitlist and improving survival after transplantation. However, the individual components within the index itself do not necessarily lend themselves to clear targets for prehabilitation. For example, exhaustion is a common, nonspecific complaint, and weight loss can be confounded by volume status. Furthermore, it is unknown what domains of physical functioning – cardiopulmonary reserve, muscle endurance, strength, balance, or agility – are most strongly affected;[4] or, whether all of them contribute to the frail phenotype.

Therefore, in preparation for developing pre habilitation programs for cirrhotics awaiting liver transplantation, we aimed to more clearly define the measures of physical performance that are impaired in frail ESLD patients.

METHODS

We recruited outpatients age 50 years and older with cirrhosis from an academic liver clinic. Patients who could not speak English were excluded, as well as those confined to bed or a wheelchair. After providing informed consent, enrolled subjects underwent the Fried Frailty Index and the following tests of physical performance:

1. Six-minute walk test distance, a test of walking endurance[5] This is the maximal distance (meters) that an individual covered in 6 minutes.
2. Chair stands, a test of lower extremity muscle strength and endurance. This is the number of chair stands completed in 30 seconds without using arms to stand up. The mean of 2 trials was used for analysis.
3. Isometric knee extension, an objective test of maximal lower extremity strength (Newton-meters). This was assessed in a standard seated configuration with the knee in 60 degrees of flexion, using an isometric

dynamometer (Biodex System 3, Biodex Medical Systems, USA).[6] The maximum value of 3 trials was used for analysis.

4. Unipedal stance time, a test of static balance. This is the time (up to 30 seconds) that an individual is able to balance on the right leg, with arms across chest. The mean value of 2 trials is used for analysis.

5. Maximal step length, a test of dynamic balance. This is the maximal distance the participant is able to step with the right foot, in the forward direction, and return to the start position in 1 motion.[7] The mean of 2 trials was used for analysis.

All tests were administered in a mobility research laboratory by trained research staff, in the same order to each patient, in 1 single session.

Demographic and laboratory data were obtained from the electronic health record. Ascites was ascertained by the presence of free intraperitoneal fluid on imaging or the use of diuretic therapy. Hepatic encephalopathy was identified by the proportion of correct lures on the Inhibitory Control Test, an established test to diagnose minimal hepatic encephalopathy.[8] Questionnaires were administered to determine the number of falls the patients had within the last 6 months, difficulty with Activities of Daily Living[9] (ADL) and Instrumental ADLs.[10]

Statistical analysis

Patients with a Fried Frailty Index score ≥3 were classified as "frail" as originally defined in older adults[1] and validated in cirrhotics.[2] Chi-square or Wilcoxon rank sum tests compared characteristics between frail and nonfrail cirrhotics. We employed univariable linear regression to evaluate the association between each physical performance test and the Fried Frailty Index as a continuous variable. Given the conceptual correlation and potential for collinearity among the 5 measures, we performed principal component exploratory factor analysis to investigate relationships between each of the 5 tests of physical performance. We applied the Kaiser criterion to retain any latent factors with eigenvalues equal to or greater than 1.[11] Factor loadings of >0.5 were deemed to be highly relevant to the latent factor.

This study was approved by the University of Michigan Institutional Review Board. All analyses were performed with Stata v14.1 (College Station, Texas).

RESULTS

Baseline characteristics of the 40 cirrhotics who participated in this study are shown in Table 1. Median age was 64 years, 43% were female, and 90% were nonHispanic White. The most common principal etiologies of cirrhosis in the cohort were nonalcoholic steatohepatitis (NASH, 30%), viral hepatitis (30%), alcoholic liver disease (18%), with the remainder other varied chronic liver diseases. Median MELD score was 12 and median albumin was 3.4. About half had documented ascites (55%). The median proportion of correct lures on the Inhibitory Control test was 75%. The proportion with Child Pugh class A, B, and C was 40%, 40%, and 20%, respectively. One-third of patients reported a fall within the last 6 months. The median number of independent ADLs was 6 (out of 7) and independent IADLs was 8 (out of 8).

Median [interquartile (IQR)] Fried Frailty Index for the cohort was 2 (1–3). The proportion who scored 0 (least frail), 1, 2, 3, 4, and 5 (most frail) was 20%, 27%, 27%, 8%, 13%, and 5%, respectively. Forty-eight percent met Fried criteria for low grip strength, 53% for exhaustion, 15% for unintentional weight loss, 33% for low physical activity, and 31% for slow gait speed.[1] Ten (25%) of the 40 subjects were classified as frail using a Fried Frailty Index cut-off ≥3.[1] Frail, compared to non-frail, cirrhotics had a numerically different distribution of liver disease etiologies (alcohol: 0 vs. 23%; NASH: 60 vs. 27%; p=0.16), higher MELD score (15 vs. 11, p=0.16), lower serum albumin (3.0 versus 3.5 g/dL, p=0.09), and higher proportion of those with Child Pugh Class C (40% vs. 13%, p=0.14). The proportion of patients with a fall within the last 6 months was also numerically higher in the frail versus the nonfrail patients (50% vs. 23%; p=0.11). Frail patients experienced greater difficulty with IADLs than nonfrail patients (median 7 vs. 8, p=0.003). Baseline characteristics were otherwise similar between the 2 groups.

Table 2 shows results from the tests of physical performance, by frail phenotype, along with normative data for community-dwelling adults 60–69 years of age for comparison (normative data not available for adults <60 years). Cirrhotics classified as frail had significantly lower 6-minute walk speed distance (231 vs. 338 meters; p<0.001), fewer chair stands in 30 seconds (7 vs. 10; p=0.001), shorter maximal step length (22 vs. 27 inches; p=0.01), and weaker isometric knee extension (86 vs. 122 Nm; p=0.02). There was also a trend toward shorter unipedal stance time (4.5 vs. 13.2 seconds; p=0.10).

In univariable linear regression, all 5 tests of physical performance were significantly associated with the Fried Frailty Index: 6MWD (coeff −0.99 per 100m, 95%CI −1.35- −0.63; p<0.001), chair stands per 30 seconds (coeff −0.31 per number, 95%CI −0.43- −0.18; p<0.001), isometric knee extension (coeff −0.01 per Nm, 95%CI −0.02- −0.003; p=0.009), unipedal stance time (coeff −0.07 per second, 95%CI −0.11- −0.04; p<0.001), and maximal step length (coeff −0.18 per inch, 95%CI −0.28- −0.07; p=0.001). This remained true even after adjustment for MELD score: 6MWD (coeff −0.93 per 100m, 95%CI −1.30- −0.52; p<0.001), chair stands per 30 seconds (coeff −0.29 per number, 95%CI −0.43- −0.15; p<0.001), isometric knee extension (coeff −0.01 per Nm, 95%CI −0.02- −0.002; p=0.02), unipedal stance time (coeff −0.06 per second, 95%CI −0.10- −0.03; p=0.002), and maximal step length (coeff −0.16 per inch, 95%CI −0.26- −0.06; p=0.003).

A correlation matrix for the 5 tests of physical performance revealed that each of the 5 tests correlated with the other 4 tests with a correlation coefficient of at least 0.4 (data not shown). Principal component exploratory factor analysis revealed only 1 single factor associated with an eigenvalue >1. This single factor, presumed to be physical frailty, explained 60% of the total variance in the analysis. Factor loadings, shown in Table 3, revealed high correlations (with uniqueness factors ≤0.5) between each of the 5 tests of physical performance and the latent factor. This suggested that these 5 variables each contributed substantially to the latent factor's dimensionality. On the other hand, MELD score revealed only a modest primary factor loading of −0.49 with the latent factor and high uniqueness value, suggesting less relevance to the latent factor as well as the 5 tests of physical performance.

DISCUSSION

The liver transplant community has increasingly recognized physical frailty as a critical determinant of outcomes in liver transplant candidates. At the current time, the primary application for frailty in cirrhotics is prognostication: a clinician can use such information to counsel a frail cirrhotic that his or her risk of death is much higher than a nonfrail cirrhotic with a similar MELD score. For the patient awaiting liver transplantation, this can provide strong motivation to seek alternatives to standard deceased donor liver transplantation, such as living donor transplant, acceptance of higher risk donors, or evaluation at transplant centers at other regions with lower transplant MELD scores.

But the concept of physical frailty has the potential to impact our patients in much broader ways. Perhaps its most important application is to identify cirrhotics in greatest need of intervention, with the goal of preventing or even reversing the factors that contribute to excess mortality in this population. Defining frailty criteria in terms of physical performance allows us to target the physical capacities that underlie functional deficits – through exercise or more comprehensive prehabilitation programs. In this study, we have identified 5 tests of physical performance that are independently associated with physical frailty (as defined by the Fried Frailty Index), representing walking endurance, strength, and balance. Adjustment for liver disease severity (defined by the MELD score) did not substantially alter the relationship between these tests and frailty at all, suggesting that frailty in cirrhotics is better explained by physical performance than liver dysfunction.

Despite significant inter-correlation between the f5 tests of physical performance, each test contributed substantially in principal component exploratory factor analysis to 1 single latent factor – physical frailty. The high factor loadings (>0.5) associated with the 5 tests, as well as low uniqueness values, suggests unique contributions from each individual test to the dimensionality of frailty. Confirming our bivariate regression analyses, this latent factor (ie, frailty) appeared to be separate from the MELD score. Furthermore, frailty was associated with real-world tests of functional ability such as activities of daily living and falls.

How do these data improve our understanding of frailty? Although this study included a cohort of only 40 subjects, it represents an evaluation of multiple components of physical performance that can contribute to frailty specifically in patients with end-stage liver disease. These data represent a critical step toward developing multi-faceted interventions to prehabilitate frail liver transplant candidates. Examples of specific facets include lower extremity resistance training to improve functional lower extremity strength,[12] training (eg, Tai Chi or yoga) to improve balance and movement coordination,[13] or physical activity coaching to improve endurance.[14] Such interventions improve not only physical capacity, but ultimately enhance physical function and reduce frailty. These tests can also serve as practical outcomes in research studies given that they are each reported on a continuous scale without a ceiling. Given the known importance of early mobility after surgery at reducing postoperative complications in the general population, we speculate that prehabilitation of patients on the transplant waitlist would facilitate early posttransplant mobility, thereby, improving early posttransplant outcomes.

It bears discussion that rates of ascites were similar between the frail and nonfrail groups. Conceptually, we would expect rates of frailty to increase as ascites worsens. But objective measures of frailty and physical performance allow us to capture the extent to which ascites – in addition to hepatic encephalopathy and medical comorbidities, such as long-standing diabetes – contributes to mortality in patients with cirrhosis. They also allow us to capture the impact of the combination of these factors in our patients. For example, a patient with ascites, hepatic encephalopathy, *and* diabetes may be more vulnerable adverse outcomes than a patient with only 1 of these factors. We believe that this is a distinct strength of the measures of frailty and physical performance.

It is important to note here that all patients enrolled in this study were ambulatory outpatients, and while 75% of the cohort of cirrhotics was deemed "not frail" by Fried Frailty criteria, average physical capacity scores *for the entire group* were well below age-referenced means for healthy older adults (Table 2). As we think about how to integrate physical rehabilitation programs into our care as a routine prescription for cirrhotics – particularly those awaiting liver transplantation for whom this would be "pre-hab" in preparation for transplant surgery – we need to identify the optimal timing for referral. Should we wait until a patient has reached the "frail" threshold? Given that it is easier to remediate small deficits rather than larger ones, perhaps the more optimal timing for intervention is when a patient has become prefrail rather than frail. Incorporation of objective tests of physical performance, such as the ones we present here, into our regular clinic visits would allow us to systematically identify – and then refer – cirrhotics for pre/rehabilitation interventions when they can most benefit. Once enrolled in a prehabilitation program, these objective tests of physical performance could be used to identify when a patient has achieved optimal benefit from the program – particularly for situations such as living donor transplantation where the timing is elective.

In summary, frailty is not synonymous with liver dysfunction or even with sarcopenia; it is a multi-dimensional construct that incorporates walking endurance, muscle strength, and balance. With an improved understanding of the specific components that contribute substantially to frailty, the next step is to develop interventions to reverse it.

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Abbreviations

MELD	Model for End-stage Liver Disease
ESLD	end-stage liver disease
6MWT	6-minute walk test

ADL	activities of daily living
NASH	nonalcoholic steatohepatitis

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Table 1

Baseline characteristics of the 40 cirrhotics in this study.

Characteristic*		Entire cohort n=40	Non-frail n=30	Frail n=10	p-value
Age, years		64 (57–69)	64 (57–69)	65 (63–69)	0.41
Female		43%	43%	40%	0.85
Race	**White**	90%	90%	90%	0.14
	Black	8%	10%	0%	
	Other	2%	0%	10%	
Etiology	**Alcohol**	18%	23%	0%	0.16
	Viral hepatitis	30%	33%	20%	
	NASH	35%	27%	60%	
	Other	18%	17%	20%	
MELD		12 (9–15)	11 (9–15)	15 (11–16)	0.16
Albumin, g/dL		3.4 (2.9–3.9)	3.5 (3.1–3.9)	3.0 (2.8–3.4)	0.09
Ascites		55%	53%	60%	0.71
Proportion of correct lures on Inhibitory Control Test		0.65 (0.00–0.98)	0.76 (0.55–0.83)	0.70 (0.65–0.80)	0.91
Child class	**A**	40%	40%	40%	0.14
	B	40%	47%	20%	
	C	20%	13%	40%	
Fall within the last 6 months		30%	23%	50%	0.11
# of independent ADLs†		6 (6–6)	6 (6–6)	6 (6–6)	0.98
# of independent Instrumental ADLs‡		8 (7–8)	8 (8–8)	7 (5–8)	0.003

*Median (interquartile range) or %

†ADL=Activities of daily living. Range 0–6, with 6 being independent.

‡IADL=Instrumental activities of daily living. Range 0=8, with 8 being independent.

Table 2

Scores on the performance-based tests in the entire cohort and categorized by frail phenotype.

Measure	Normative Data for each test	n=40	Non-frail n=30	Frail n=10	p-value
Six-minute walk test distance, meters	Men: 572 (92) Women: 538 (92)[15]	317 (240–354)	338 (281–363)	231 (171–244)	<0.001
Number of chair stands per 30 seconds	14 (2.4)[16]	9 (7–11)	10 (8–12)	7 (6–8)	0.001
Isometric knee extension, Nm	Men: 254 (51) Women: 159 (34)[17] Not available	117.7 (88.5–166.2)	122.4 (93.5–193.6)	86.0 (72.3–110.4)	0.02
Unipedal stance time, seconds	22.5 (8.6)[18]	10.9 (2.5–20.7)	13.2 (2.9–21.4)	4.5 (2.1–7.8)	0.10
Maximal step length, inches	>36[7]	26.4 (22.9–28.5)	27.0 (24.5–29.3)	21.6 (18.8–27.3)	0.01

* Mean (SD) for 60–69 year olds without chronic liver disease

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Table 3

Factor loadings and uniqueness based on a principal components exploratory factor analysis for the 5 tests of physical performance.

Measure	Factor loadings	Uniqueness
Six-minute walk test distance, per 100 meters	0.93	0.14
Number of chair stands per 30 seconds	0.90	0.19
Isometric knee extension, Nm	0.77	0.41
Unipedal stance time, seconds	0.77	0.41
Maximal step length, inches	0.70	0.50
MELD score	−0.49	0.76