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Cognitive Impairment and Physical Frailty in Patients With Cirrhosis

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Physical frailty and impaired cognition are common in patients with cirrhosis. Physical frailty can be assessed using performance-based tests, but the extent to which impaired cognition may impact performance is not well characterized. We assessed the relationship between impaired cognition and physical frailty in patients with cirrhosis. We enrolled 1,623 ambulatory adult patients with cirrhosis waiting for liver transplantation at 10 sites. Frailty was assessed with the liver frailty index (LFI; "frail," LFI ≥ 4.4). Cognition was assessed at the same visit with the number connection test (NCT); continuous "impaired cognition" was examined in primary analysis, with longer NCT (more seconds) indicating worse impaired cognition. For descriptive statistics, "impaired cognition" was NCT ≥ 45 seconds. Linear regression associated frailty and impaired cognition; competing risk regression estimated subhazard ratios (sHRs) of wait-list mortality (i.e., death/delisting for sickness). Median NCT was 41 seconds, and 42% had impaired cognition. Median LFI (4.2 vs. 3.8) and rates of frailty (38% vs. 20%) differed between those with and without impaired cognition. In adjusted analysis, every 10-second NCT increase associated with a 0.08-LFI increase (95% confidence interval [CI], 0.07-0.10). In univariable analysis, both frailty (sHR, 1.63; 95% CI, 1.43-1.87) and impaired cognition (sHR, 1.07; 95% CI, 1.04-1.10) associated with wait-list mortality. After adjustment, frailty but not impaired cognition remained significantly associated with wait-list mortality (sHR, 1.55; 95% CI, 1.33-1.79). Impaired cognition mediated 7.4% (95% CI, 2.0%-16.4%) of the total effect of frailty on 1-year wait-list mortality. *Conclusion:* Patients with cirrhosis with higher impaired cognition displayed higher rates of physical frailty, yet frailty independently associated with wait-list mortality while impaired cognition did not. Our data provide evidence for using the LFI to understand mortality risk in patients with cirrhosis, even when concurrent impaired cognition varies. (*Hepatology Communications* 2022;6:237-246).

Frailty, a term that has been used to capture the end manifestations of malnutrition, muscle wasting, and functional impairment, in patients with cirrhosis is prevalent.[1] Given the predominance of muscle-related drivers of the frail phenotype in this population, frailty has been commonly assessed using tests of physical frailty,[1] including performance-based tests of physical

Abbreviations: BMI, body mass index; CI, confidence interval; FrAILT, Functional Assessment in Liver Transplant Study; HE, hepatic encephalopathy; IQR, interquartile range; LFI, liver frailty index; MELD-Na, Model for End Stage Liver Disease-sodium; NCT, number connection test-A; sHR, subhazard ratio.

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function (e.g., chair stands, balance testing). While these tests are objective and allow for standardization of frailty assessment in this population, it is possible that performance on tests of physical frailty may be influenced by impaired cognition, whether it be transient, as with hepatic encephalopathy (HE), or permanent, as with alcohol-induced dementias or other nonhepatic causes. Furthermore, frailty is associated with mortality, and HE is known to be, too.[2] However, the relationship between impaired cognition and performance on tests of physical frailty and their total effect on mortality has not been well characterized in patients with cirrhosis, leaving a knowledge gap as to how to best interpret the known association between frailty and mortality in patients with cirrhosis who also experience comorbid impaired cognition.

In this study, we aimed to quantify the relationship between physical frailty and impaired cognition. We used the liver frailty index (LFI) for physical frailty (grip strength, chair stands, and balance testing [http://liverfrailtyindex.ucsf.edu]) and the number connection test-A (NCT) as a proxy for increasing decrement in aspects of cognitive function. We hypothesized that performance on the components of the LFI would be worse in those with actively impaired cognition as physical reaction time and neuromuscular coordination would be expected to be compromised under these conditions.

Participants and Methods

STUDY POPULATION

We used data from the Multi-Center Functional Assessment in Liver Transplantation (FrAILT) Study, which included the following 10 liver transplantation centers in the United States: University of California San Francisco (n = 975), Johns Hopkins Medical Institute (n = 172), Baylor University Medical Center (n = 120), Columbia University Medical Center (n = 99), Duke University (n = 85), Northwestern University (n = 60), University of Pittsburgh (n = 59), Loma Linda University (n = 31), University of Arkansas for Medical Sciences (n = 21), and University of Michigan (n = 1). Participants were eligible to enroll in the FrAILT Study if they 1) had cirrhosis, 2) were listed or eligible for listing for liver transplantation, and 3) were seen as an outpatient for clinical care. Patients were not eligible to enroll in the FrAILT Study if they had severe HE as defined by an NCT score >120 seconds at the time of initial screening because of concern regarding the ability to provide informed consent. Likewise, those who could not speak English or Spanish were ineligible because study consent forms were only available in English and Spanish languages. Trial enrollment began October 2011, and all subjects enrolled through May 2020 were included except for subjects listed with Model for End-Stage

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Liver Disease (MELD) exception points because the time these participants spend on the wait list is not dependent on native liver disease function (n = 941).

Written informed consent was obtained from each study participant. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institutional review boards at all participating sites. All coauthors had access to the study data and reviewed and approved the final manuscript.

STUDY PROCEDURES

On the day of enrollment at each site, participants underwent several tests administered by trained study personnel.

Physical Frailty

Physical frailty was assessed using the LFI, which consists of the following three performance-based tests: grip strength, chair stands, and balance testing. The LFI is calculated using the equation available at http://liverfrailtyindex.ucsf.edu. Frailty was assessed using LFI as both a dichotomous and continuous variable. For dichotomous assessments, frail was defined as LFI ≥ 4.4[3]

Impaired Cognition

Participants underwent cognitive function testing using the NCT. For primary analyses, because we hoped to detect any degree of decrement in cognitive ability, we analyzed NCT as a continuous variable, with longer test times indicating increasing degrees of impaired cognition. For the purposes of tabular illustration, we set a cut point for impaired cognition as NCT ≥ 45 seconds (past work, including from our research team, has used an NCT cutoff of 45 seconds to identify patients with HE, based on normative data comparing healthy controls to those with and without HE.[4,5]

ADDITIONAL DATA COLLECTION

Demographic data were extracted from clinic visit notes from the day of physical frailty testing. A diagnosis of hypertension, diabetes, or coronary artery disease was recorded if reported in their electronic medical record. Data on HE were collected from the medical record based on history of HE as mentioned in the progress note or by documented use of lactulose and/or rifaximin medications. Presence of ascites was determined from hepatologists' recorded physical exams or their documented management plan from the same clinic visit as enrollment/frailty assessment. Ascites was considered "present" if documented as present on physical exam and/or if participant was documented to be undergoing large volume paracenteses and "absent" when not present on exam. All laboratory data from within 3 months of enrollment were also extracted from the electronic health record.

STATISTICAL METHODS

Baseline demographics were presented as medians (interquartile ranges [IQRs]) for continuous variables and as percentages for categorical variables. We defined impaired cognition as NCT ≥ 45 seconds; past work has validated 45 seconds or higher as a cut-off value used in HE diagnosis.[4,6-8] We defined physical frailty (LFI) categories as follows: robust physical status scored <3.2; prefrail scored 3.2-4.3; and frail scored ≥4.4.[1,5,9] Comparisons between those with and without impaired cognition were made using Wilcoxon rank-sum or chi-squared tests.

We used linear regression to quantify the magnitude of the relationship between NCT and LFI, with and without confounder adjustments. For the multivariable analysis, variables with a univariate $P < 0.2$ or variables we believed might be a potential confounder based on clinical grounds or biologic plausibility (age, race, height, MELD-Na, albumin) were included in multivariable analysis. The final model was selected by backward elimination (P for removal >0.05). We also used logistic regression to quantify the relationship between NCT and LFI as a secondary analysis.

To assess the relationship between NCT, LFI, and wait-list mortality, we performed Fine and Gray competing risk regression analyses[10]; wait-list mortality was defined as death or delisting for being too sick for liver transplantation, and deceased donor liver transplantation was used as the competing risk. For those participants who remained on the wait list without an end outcome, data were censored on April 13, 2018. We estimated the cumulative incidence of wait-list mortality at 12 months from listing and also modeled cumulative incidence to estimate the risk of

wait-list mortality associated with NCT, LFI, and other covariates. Participants were censored on the day of their transplant if they received living donor liver transplantation or on the day of their removal from the wait list for reasons other than being too sick (i.e., for social reasons; censored on the day of their removal from the wait list). We performed competing risk regressions of LFI alone, NCT alone, both LFI and NCT, and finally with LFI, NCT, and additional covariates in a backwards selection multivariable analysis of wait-list mortality (with the same *P*-value cutoffs as described in multivariable analyses of NCT and LFI) to derive the final model and determine subhazard ratios (sHRs). To ensure that these relationships held true when we used alternative definitions of impaired cognition, we performed sensitivity analyses, substituting history of HE and then active prescription of lactulose and/or rifaximin for NCT.

Finally, to quantify the contribution of impaired cognition to the frailty gap in wait-list mortality, we performed a survival analysis-based method for mediation analysis.[11-14] The Stata PREDICT, MEANSURV postestimation command uses estimation based on a fitted flexible parametric model.[13] We set impaired cognition (NCT per 10 seconds) as the mediator of the impact of frailty (LFI ≥ 4.4) on survival at 1 and 3 years and adjusted for the same covariates identified in our final multivariable competing risk model to determine proportion mediated at 1-year and 3-year survival, and we calculated 95% confidence intervals (CIs) using bootstrap methods with 2,000 replications.[15] Statistical analyses were performed using SAS version 9.4 (Cary, NC) and Stata 16 (College Station, TX).

Results

BASELINE CHARACTERISTICS OF THE PARTICIPANT POPULATION

Of the 1,623 participants, median age was 58 years, 42% were women, 67% were of non-Hispanic white race, and median body mass index (BMI) was 28.3. Hypertension was found in 38% of study participants, 30% had diabetes, 40% had ascites, and 63% had a history of HE. Participants' median MELD-Na was 18, and median creatinine was 0.9 (Table 1).

Among all study participants, the median time to complete the NCT assessment was 41 seconds. Impaired cognition, as identified by an NCT score of 45 seconds or more, was found in 42% of participants. Participants with and without impaired cognition were similar by sex and BMI and had similar rates of coronary artery disease and dialysis. Compared to those without impaired cognition, those with impaired cognition had higher MELD-Na and creatinine and lower albumin; they were also older, shorter, weighed less, and had higher rates of hypertension, diabetes, ascites, and HE.

RELATIONSHIP BETWEEN PHYSICAL FRAILTY AND IMPAIRED COGNITION

Median LFI was 4.0 (IQR, 3.5-4.5). Of all participants, 28% met criterion for physically frail (LFI ≥ 4.4), 58% for prefrail (3.2-4.3), and 14% for robust (≤3.2). With regards to participants' performance on the individual tests comprising the LFI, median balance time was 30 seconds (IQR, 30-30), with 20% unable to balance for the full 30 seconds; median chair stands per second was 0.36 (IQR, 0.25-0.48); and median sex-adjusted grip strength was −0.22 (−0.82 to 0.50) (Tables 2 and 3).

Compared to those without impaired cognition, participants with impaired cognition had a higher median LFI score (4.2 vs. 3.8) and a higher prevalence of physical frailty (38% vs. 20%). Those with impaired cognition also had worse performance on each individual component of the LFI. Twenty-eight percent of those with impaired cognition had balance performance <30 seconds (vs. 15% of those without impaired cognition, $P < 0.001$); they exhibited decreased median chair stands per second (0.3 vs. 0.4, $P < 0.001$); and they had decreased median grip strength (25 kg vs. 28 kg, $P < 0.001$). These relationships did not change in a sensitivity analysis where we defined impaired cognition as NCT of ≥60 seconds.

The associations between covariables and physical frailty are displayed in Table 3. The associations between covariables and odds of physical frailty are included in Supporting Table S1. In univariable linear regression, a 10-second increase in NCT was associated with a 0.11 increase in LFI (95% confidence interval [CI], 0.09-0.12; $P < 0.001$). The following variables were also significantly associated with LFI:

TABLE 1. CHARACTERISTICS OF THE 1,623 PATIENTS WITH CIRRHOSIS INCLUDED IN THIS STUDY CATEGORIZED BY IMPAIRED COGNITION STATUS

			By Cognition Status		
Characteristics*		All n = 1,623	With Impaired Cognition (NCT ≥45 seconds) n = 683 (42%)	Without Impaired Cognition (NCT <45 seconds) n = 940 (58%)	*P* Value
Age, years		58 (50-63)	60 (55-65)	55 (47-62)	<0.001
Female sex		674 (42%)	273 (40%)	401 (43%)	0.28
Hispanic race/ethnicity		324 (20%)	184 (27%)	140 (15%)	<0.001
Height, cm		170 (163-178)	170 (163-178)	173 (165-180)	<0.001
Weight, kg		83.4 (70.8-97.5)	81.7 (69.4-94.7)	85.2 (71.3-99.8)	<0.01
BMI kg/m^2		28.3 (24.9-32.6)	28.2 (24.9-32.3)	28.4 (24.9-33.1)	0.31
Etiology of liver disease	Alcohol	469 (29%)	198 (29%)	272 (29%)	<0.001
	Chronic hepatitis C	369 (23%)	171 (25%)	199 (21%)	
	Nonalcoholic fatty liver disease	347 (21%)	157 (23%)	189 (20%)	
	Autoimmune/cholestatic	257 (16%)	75 (11%)	181 (19%)	
	Other	181 (11%)	82 (12%)	99 (11%)	
Hypertension		616 (38%)	287 (42%)	332 (35%)	0.01
Diabetes		485 (30%)	239 (35%)	245 (26%)	<0.001
Coronary artery disease		99 (6%)	55 (8%)	47 (5%)	0.03
Stroke		26 (2%)	14 (2%)	12 (1%)	0.22
MELD-Na		18 (15-23)	19 (15-23)	18 (15-22)	<0.01
Total bilirubin, mg/dL		2.5 (1.6-4.1)	2.5 (1.5-4.0)	2.5 (1.6-4.3)	0.19
Creatinine, mg/dL†		0.9 (0.7-1.2)	1.0 (0.8-1.3)	0.9 (0.7-1.1)	<0.001
Albumin, g/dL		3.1 (2.7-3.5)	3.0 (2.6-3.5)	3.2 (2.8-3.6)	<0.001
Dialysis		68 (4%)	33 (5%)	35 (4%)	0.28
Ascites		643 (40%)	297 (44%)	346 (37%)	<0.01
HE history		983 (63%)	465 (70%)	518 (57%)	<0.001
HE medications	None	643 (41%)	215 (32%)	428 (47%)	<0.001
	Lactulose only	300 (19%)	142 (21%)	158 (17%)	
	Rifaximin only	92 (6%)	34 (5%)	58 (6%)	
	Lactulose + rifaximin	536 (34%)	272 (41%)	264 (29%)	
Outcome	Died/delisted	281 (17%)	149 (22%)	132 (14%)	<0.01
	DDLT	522 (32%)	218 (32%)	304 (32%)	
	Other removal (including LDLT)	430 (26%)	157 (23%)	273 (29%)	
	Waiting	390 (24%)	159 (23%)	231 (25%)	

*Median (IQR) or %.
†Among those who were not on dialysis.
Abbreviations: DDLT, deceased donor liver transplant; LDLT, living donor liver transplant.

age (coefficient, 0.02; $P < 0.0001$), height (coefficient, –0.01; $P < 0.01$), liver disease etiology (hepatitis C virus coefficient, –0.13; $P = 0.03$; nonalcoholic fatty liver disease coefficient, 0.12; $P = 0.04$; autoimmune/cholestatic coefficient, –0.27; $P < 0.0001$), diabetes (coefficient, 0.27; $P < 0.0001$), MELD-Na (coefficient, 0.03; $P < 0.0001$), creatinine (coefficient, 0.04; $P < 0.001$), international normalized ratio (coefficient, 0.09; $P < 0.01$), sodium (coefficient, –0.03; $P < 0.0001$), ascites (coefficient, 0.37; 95% CI, 0.29-0.45; $P < 0.0001$), albumin (coefficient, –0.09; $P < 0.01$), history of HE (coefficient, 0.18; $P < 0.0001$), and HE medication use (coefficient, 0.20; $P < 0.0001$). In logistic regression, every 10-second increase in NCT was associated with 23% increased odds of frailty (95% CI, 18%-29%; $P < 0.001$).

TABLE 2. BASELINE PHYSICAL FRAILTY ASSESSMENTS BY IMPAIRED COGNITION STATUS

		By Cognition Status		
Frailty metric*	All n = 1,623	With Impaired Cognition (NCT ≥ 45 seconds) n = 683 (42%)	Without Impaired Cognition (NCT <45 seconds) n = 940 (58%)	*P* Value
LFI, units	4.0 (3.5-4.5)	4.2 (3.8-4.8)	3.8 (3.3-4.3)	<0.001
Physical frailty level				
Frail (LFI ≥ 4.4)	451 (28%)	262 (38%)	189 (20%)	<0.001
Prefrail (3.2 ≤ LFI < 4.4)	947 (58%)	382 (56%)	565 (60%)	
Robust (LFI <3.2)	225 (14%)	39 (6%)	186 (20%)	
Individual components				
Grip strength, kg	26.7 (20.0-34.7)	24.7 (18.0-32.0)	28.0 (21.3-37.0)	<0.001
Sex-adjusted grip	–0.22 (–0.82 to 0.50)	–0.49 (–1.02 to 0.13)	0.01 (–0.62 to 0.70)	<0.001
Balance, seconds	30.0 (30.0-30.0)	30.0 (26.6-30.0)	30.0 (30.0-30.0)	<0.001
% with balance <30 seconds	328 (20%)	189 (28%)	139 (15%)	<0.001
Chair stands per second	0.36 (0.25-0.48)	0.32 (0.20-0.42)	0.40 (0.28-0.52)	<0.001

*Median (IQR) or %.

TABLE 3. FACTORS ASSOCIATED WITH PHYSICAL FRAILTY

		Univariable Models*	Multivariable Model†
Factor		Coefficient (95% CI), *P* Value	Coefficient (95% CI), *P* Value
NCT, per 10 seconds		0.11 (0.09-0.12) $P < 0.0001$	0.08 (0.07-0.10) $P < 0.0001$
Age, per year		0.02 (0.01-0.02) $P < 0.0001$	0.01 (0.01-0.01) $P < 0.0001$
Hispanic race/ethnicity		0.04 (–0.07 to 0.14) $P = 0.49$	–0.10 (–0.20 to –0.01) $P = 0.04$
Female sex		0.10 (0.04-0.01) $P = 0.01$	–
Height, per cm		–0.01 (–0.01 to –0.001) $P = 0.01$	–0.004 (–0.01 to –0.0002) $P = 0.04$
Weight, per kg		–0.001 (–0.003 to 0.001) $P = 0.37$	–
BMI		0.002 (–0.005 to 0.009) $P = 0.58$	–
Etiology of liver disease	Alcohol	Reference	Reference
	Chronic hepatitis C	–0.13 (–0.24 to –0.02) $P = 0.03$	–0.14 (–0.24 to –0.03) $P = 0.01$
	Nonalcoholic fatty liver disease	0.12 (0.01-0.24) $P = 0.04$	–0.002 (–0.11 to 0.11) $P = 0.97$
	Autoimmune/cholestatic	–0.27 (–0.40 to –0.14) $P < 0.0001$	–0.10 (–0.22 to 0.01) $P = 0.08$
	Other	0.03 (–0.11 to 0.18) $P = 0.66$	0.03 (–0.10 to 0.16) $P = 0.64$
Hypertension		0.08 (–0.01 to 0.16) $P = 0.07$	–
Diabetes		0.27 (0.18-0.36) $P < 0.0001$	0.15 (0.06-0.23) $P = 0.001$
MELD-Na, per point		0.03 (0.02-0.04) $P < 0.0001$	0.02 (0.02-0.03) $P < 0.0001$
Bilirubin		0.01 (–0.004 to 0.02) $P = 0.20$	–
Creatinine		0.04 (0.02-0.06) $P < 0.001$	–
INR		0.09 (0.023-0.16) $P < 0.01$	–
Sodium		–0.03 (–0.04 to –0.02) $P < 0.0001$	–
Albumin, per g/dL		–0.09 (–0.15 to –0.02) $P < 0.01$	–
Ascites		0.37 (0.29-0.45) $P < <0.0001$	0.25 (0.17-0.33) $P < 0.0001$

*The following metrics of HE, in addition to NCT, were also associated with physical frailty: history of HE (coefficient, 0.18; 95% CI, 0.10-0.26; $P < 0.0001$) and lactulose and/or rifaximin HE medication (coefficient, 0.20; 95% CI, 0.09-0.31; $P < 0.0001$). Sensitivity analyses with these metrics did not change significant associations between covariates and physical frailty in the final multivariable model.
†Final multivariable model determined by stepwise backward selection. Female sex not included in multivariable model due to collinearity with height. Alternate multivariable models with *a priori* selection of covariates were built for sensitivity analyses. In these alternate models, including one that substituted female sex for height and another that included all covariates presented in univariable analysis, did not substantively change the results.
Abbreviation: INR, international normalized ratio.

In multivariable linear analysis, after adjustment for age, race, height, liver disease etiology, diabetes, MELD-Na, albumin, and ascites, NCT remained significantly associated with LFI, with every 10-second increase in NCT associated with an increase in LFI of 0.082 (95% CI, 0.07-0.10; $P < 0.0001$) (Table 3). The significant associations between covariates and physical frailty did not change in sensitivity analyses. In logistic multivariable regression, every 10-second increase in NCT was independently associated with 22% increased odds of frailty (95% CI, 15%-28%).

RELATIONSHIP OF PHYSICAL FRAILTY AND IMPAIRED COGNITION TO WAIT-LIST MORTALITY

Median follow-up time for the entire cohort was 13.1 months (IQR, 5.3-31.1). By the end of follow-up, 17% died or were delisted for sickness, 32% received a deceased donor liver transplant, 24% remained on the wait list, 10% received a living donor liver transplant, and 17% were removed from the wait list for other reasons. Compared to those without impaired cognition, a greater proportion of those with impaired cognition died or were delisted for being too sick for transplant (22% vs. 14%, $P < 0.001$) (Table 4).

In univariable competing risk analyses (Table 4), both physical frailty (LFI per 1 unit sHR, 1.6; 95% CI, 1.4-1.9; $P < 0.0001$) and impaired cognition (NCT per 10 seconds sHR, 1.07; 95% CI, 1.04-1.10; $P < 0.0001$) were associated with wait-list mortality. In bivariable analysis, both remained significantly associated with wait-list mortality (LFI per 1 unit sHR, 1.6; 95% CI, 1.4-1.8; $P < 0.0001$; and NCT per 10 seconds sHR, 1.04; CI, 1.01-1.07; $P = 0.01$). However, after multivariable adjustment, only frailty remained significantly associated with wait-list mortality (LFI per 1 unit sHR, 1.5; 95% CI, 1.3-1.8; $P < 0.0001$); impaired cognition was not (NCT per 10 seconds sHR, 1.00; 95% CI, 0.96-1.03; $P = 0.91$).

In mediation analysis, the proportion of physical frailty's total effect on wait-list mortality at 1 year that was mediated by impaired cognition was 7.4% (95% CI, 2.0%-16.4%). At 3 years, the proportion of frailty's total effect that was mediated by impaired cognition was 12.2% (95% CI, 3.3%-27.6%).

In sensitivity analyses in which we replaced NCT score with history of HE or with HE medication use in the multivariable model, the primary association between physical frailty and wait-list mortality remained unchanged.

Discussion

In this multicenter prospective study of 1,623 ambulatory participants with cirrhosis awaiting liver transplantation, we observed that participants with impaired cognition displayed poorer performance on tests of physical frailty. Specifically, they performed worse in all three components of the LFI (hand grip strength, chair stands, and balance). LFI scores were strongly associated with NCT time, with participants displaying a worsening of LFI by 0.08 units for every 10-second increase in NCT time, i.e., every 10-second

TABLE 4. UNIVARIABLE, BIVARIABLE, AND MULTIVARIABLE COMPETING RISK MODELS EVALUATING THE ASSOCIATION BETWEEN NCT, FRAILTY, AND WAIT-LIST MORTALITY WITH THE ADDITION OF CONFOUNDING VARIABLES

Factor	Univariable* sHR *P* Value	Bivariable Model sHR *P* Value	Multivariable Model sHR *P* Value
NCT, per 10 seconds	1.07 (1.04-1.10) $P < 0.0001$	1.04 (1.01-1.07) $P = 0.01$	1.00 (0.96-1.03) $P = 0.91$
Physical frailty, per 1 unit	1.6 (1.4-1.9) $P < 0.0001$	1.6 (1.4-1.8) $P < 0.0001$	1.5 (1.3-1.8) $P < 0.0001$
Age, per year	1.03 (1.02-1.05) $P < 0.0001$	–	1.03 (1.01-1.04) $P < 0.001$
Hispanic race/ethnicity	1.78 (1.39-2.29) $P < 0.0001$	–	1.79 (1.38-2.31) $P < 0.001$
Height, per cm	0.98 (0.97-0.99) $P < 0.01$	–	–
MELD-Na, per point	1.05 (1.03-1.07) $P < 0.0001$	–	–
Albumin, per g/dL	0.60 (0.50-0.73) $P < 0.0001$	–	0.64 (0.53-0.79) $P < 0.0001$

*The following variables were not significant in univariable analysis: etiology of liver disease, hypertension, diabetes, ascites, weight, BMI.
†In a sensitivity analysis, delisted subjects were censored at the time of delisting rather than included in the primary event. This did not qualitatively change the association between frailty and wait-list death/delisting (NCT per 10 seconds sHR, 1.03; 95% CI, 0.99-1.08; $P = 0.18$; LFI per 1 unit sHR, 1.7; 95% CI, 1.4-2.0; $P < 0.0001$).

increase in NCT was independently associated with 22% increased odds of physical frailty (95% CI, 15%-28%; $P < 0.0001$). Despite this relationship, physical frailty remained significantly associated with wait-list mortality even after adjustment for NCT and other covariables.

Our results build on past work that has reported an association between neurocognition and adults who were frail and community dwelling,[16] in those with end-stage renal disease,[17,18] and in patients with cirrhosis.[5,19-22] Prior studies differed in their use of frailty metrics that were subjective[21,23] and/or not validated in the ambulatory cirrhosis population.[19-22] Our paper also adds to the body of literature, including previous research by our team,[5] by more precisely quantifying this association. In addition to using a continuous performance-based metric of physical frailty that has been well validated in patients with cirrhosis, we employed a continuous assessment of cognitive function that was contemporaneous with frailty testing. Given that individuals with decompensated cirrhosis can experience a range of severity and tempo of neuropsychiatric disturbance, our choice of a continuous measure of cognition, in particular, better approximates the way these patients present to clinic. Our analysis helps to show how any decrement in ability to think is associated with frailty metrics and risk of death.

Our analyses further demonstrated that accounting for impaired cognition did not substantially reduce the association between physical frailty and wait-list mortality. While impaired cognition (in the form of HE) has long been recognized as a risk factor for death in participants with cirrhosis, quantifying this in routine clinical practice has been challenging due to cumbersome tools for neurocognitive assessment in this population. Our data raise the possibility that tests of physical frailty may objectively capture the extent to which neurocognitive impairment leads to adverse outcomes in this population.

We highlight that the NCT is one of many psychometric tests that have been developed to detect the neuropsychological and neurophysiologic disturbances characteristic of minimal and overt HE.[4,24] This timed paper and pencil test assesses aspects of executive function, including visuospatial orientation and processing speed, as well as selective attention. This test has been validated as a sensitive, although not specific, measure of detecting impaired cognition in HE.[4,6,25] Nonetheless, we acknowledge that the NCT is an imperfect metric for HE and it is not a comprehensive cognitive assessment, especially compared to other available tools.[2] Indeed, the NCT is likely not a purely cognitive test, just as HE is not just a cognitive condition, but may be affected by motor dysfunction, especially any fine-motor dysfunction affecting holding a pen to paper. To this end, the NCT in our cohort was not more associated with the grip strength component of the LFI but rather equally predictive of all subcomponents of the LFI (Table 2). This suggests that the motor effects of impaired cognition on the LFI are less likely due to an outsized effect of dysfunction in specific motor groups but perhaps better indicate a holistic deficit in brain–body integration.

Although the NCT has limitations as a metric of HE, including the fact that the diagnosis of HE typically requires abnormal results in at least two validated tests,[26,27] our intent was to understand the relationship between aspects of cognitive function (inclusive of but not solely due to HE) and performance on tests of physical frailty. While the test can identify subtle changes in cognition, like deficits in attention or processing speed, it does not distinguish between different possible etiologies of cognitive dysfunction, nor is it meant as a comprehensive diagnostic battery of all cognitive domains. Patients with cirrhosis, for example, commonly experience pain, depression, lack of sleep, and metabolic derangements, such as hyponatremia, all of which can affect cognitive function and especially in the attentional domain.[28-31] Worse NCT performance would not identify whether a patient has diminished attentional ability due to HE or due to another factor common to patients with cirrhosis. We used this characteristic of the NCT test to our advantage as we sought to identify participants experiencing a milieu of cognitive and psychomotor derangements common in this population, whether due to HE or another etiology. Still, it remains a limitation of our study that we were unable to directly account for other causes of neurologic impairment. Our study, therefore, should serve as the foundation for future work to investigate precise relationships between domain-specific measures of cognition and frailty.

In sum, not all manifestations of altered cognition in participants with cirrhosis are due to HE, nor are all aspects of cognition captured by the NCT. On the other hand, the NCT as a metric for impaired

cognition in cirrhosis has the advantages of 1) being highly sensitive for acute attentional and psychomotor derangements, 2) being a direct indicator of cognitive status in this participant population (as opposed to indirect metrics, like HE history documented in a medical chart), 3) being a current indicator of cognitive status and, when measured on the same day as physical frailty assessments, increases the validity of cross-sectional findings associating the two variables, and 4) being a continuous variable, enabling us to quantify the linear relationship between cognition and LFI, which has not been done before.

Our findings of a strong association between impaired cognition and physical frailty are consistent with conceptual models that have been proposed for the biological mechanism linking the two in cirrhosis. Acutely, impaired cognition can lead to worse performance on tests of physical frailty. Past work has demonstrated that cognition itself likely influences motor function. Prior results demonstrated that participants with cirrhosis with minimal HE displayed altered postural control compared to those with cirrhosis but without minimal HE, consistent with other work showing that attentional processing is required for balance, reaction times, and other neuromuscular control.[19,32] However, a participant with impaired cognition in clinic today likely has additional, if not prolonged, episodes of impaired cognition outside of clinic. Chronically impaired cognition can lead to poor oral intake and decreased physical activity that can exacerbate physical frailty. If due to HE, hyperammonemia can exert myotoxic effects causing sarcopenia, which can also worsen frailty.[33,34] But there are plausible explanations for causality in the other direction or even a cyclical feedback loop, some of which perhaps contribute to the mechanism by which impaired cognition mediates frailty's effect on mortality. Physical frailty can lead to decreased mobility (leading to decreased access to food and/or ability to prepare food), gut dysmotility with altered absorption, or muscle wasting with impaired ability to detoxify ammonia.[35] Hyperammonemia, in turn, could further exacerbate sarcopenia (a major component of physical frailty), contributing to a cycle of impaired cognition and frailty influencing each other. Our observational study was not designed to conclude directionality of the cognition–frailty relationship

However, it was due to the likelihood of this bidirectional mechanism that we found it critical to evaluate the effect of the NCT and LFI relationship on mortality risk prediction. We evaluated NCT both as a covariate in frailty's effect on mortality and also as a mediator. Our results suggest that the LFI remains an extremely important clinically feasible metric for patients whether or not they are experiencing transient alterations in cognitive function at the time of assessment. In sum, the strength of the LFI is its ability to capture the myriad factors that contribute to the frail phenotype, including acute or chronic assaults on brain function, in order to understand someone's total physiologic reserve in the setting of cirrhosis.

In conclusion, any decrement in performance on impaired cognition testing was found to correlate with increasing physical frailty in patients with cirrhosis. Despite this correlation, physical frailty remained strongly associated with wait-list mortality independent of one's degree of impaired cognition as if the effect of impaired cognition on mortality in patients with cirrhosis was subsumed by physical frailty. Our results provide additional evidence in support of incorporating physical frailty assessments into the management of cirrhosis, regardless of a patient's cognitive status. Our study lays the foundation for investigating the role of improving cognitive function to improve frailty, using the LFI as a pragmatic tool to assess response.

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