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BRIEF COMMUNICATION

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Hepatic encephalopathy impacts the predictive value of the Fried Frailty Index

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Frailty is increasingly recognized as a predictor of poor outcomes in solid organ transplantation. The most widely utilized frailty tool, the Fried Frailty Index (FFI), includes patient-reported exhaustion, weight loss, and physical activity as well as measured walk speed and handgrip. Although hepatic encephalopathy (HE) is common among liver transplant candidates, data are lacking regarding its impact on the interpretation of frailty. We prospectively enrolled 685 patients with cirrhosis during their transplant evaluation, following them until death or transplantation. Our cohort was aged 54.5 ± 10.3 years, 60% male, with an average MELD score of 14.7 ± 6.3. A history of HE was present in 39%. Frailty was present in 41%, associated with higher MELD, low albumin, ascites, and HE. HE was associated with frail performance on three components of the FFI-grip (odds ratio 1.41 95% CI, 1.03-1.92), walk speed (1.56 95% CI, 1.14-2.15), and decreased energy (1.44 95% CI, 1.05-1.99). These three components were associated with transplant free survival in the whole cohort: energy (hazard ratio 1.67 95% CI, 1.25-2.28), grip (1.63 95% CI, 1.24-2.16), and walk speed (1.56 95% CI, 1.19-2.04). However, among patients with HE, the FFI was not associated with survival. HE plays a critical role in the frailty phenotype and the implications of frailty among patients with cirrhosis evaluated for liver transplantation.

KEYWORDS
cirrhosis, clinical research/practice, health services and outcomes research, liver transplantation/hepatology, patient survival

1 | INTRODUCTION

Frailty is an emerging indicator of poor outcomes in solid organ transplantation. This is particularly true in the context of liver transplantation where mounting evidence has linked several measures of frailty with delisting and mortality.[1–7] Reflecting factors unaccounted for by the Model for End-Stage Liver Disease (MELD), tools that measure frailty quantify the patient's physiologic reserve. Frailty tools measure many features, including disability (ie, activities of daily living),[5,8] physical function (ie, handgrip, walk speed),[9] and muscle bulk/sarcopenia (ie, psoas size or morphomics).[10,11] The most widely utilized frailty tool in solid organ transplantation, the Fried Frailty Index (FFI), aggregates multiple domains of frailty. These include subjective report of exhaustion, weight loss, and physical activity as well as objectively measured walk speed and handgrip.[12] Beyond risk assessment, a diagnosis of frailty should trigger interventions aimed at restoring function. Indices such as the FFI are helpful; however, to guide therapy, it is important to define each patient's unique drivers of frailty.

A patient with cirrhosis can be frail for many reasons. These include aging, comorbidities, malnutrition, deconditioning, severe liver failure, and cognitive impairment. When present, hepatic encephalopathy (HE), likely plays a critical role in frailty. HE is caused in part by hyperammonemia, a potent driver of muscle catabolism which leads to weakness and sarcopenia.[13,14] Further, the symptoms of HE exacerbate frailty: anorexia compounds malnutrition and sarcopenia,[15] poor coordination leads to falls, and hospitalization for HE

Abbreviations: FFI, Fried Frailty Index; HE, Hepatic Encephalopathy; MELD, Model for End-Stage Liver Disease.

worsens physical decline. Despite a plausible relationship between HE and frailty, data are limited regarding how HE impacts both the frailty phenotype and the outcomes reported to be associated with frailty. Herein, we assessed the association between HE, frailty, and clinical outcomes in a prospective cohort study of frailty among liver transplant candidates.

2 | METHODS

Adult (age ≥18 years) patients with cirrhosis were prospectively enrolled in an observational cohort study from the liver transplant clinic of the University of Michigan Hospital from July 24, 2009 to February 15, 2015. Informed consent in writing was obtained from each patient following approval by the Institutional Review Board of the University of Michigan Medical School. As reported previously, 31% of patients referred for transplant evaluation over the study period were included in this study (mainly due to variable availability of research coordinators).[16] Of the 830 patients enrolled, our sample for this study included 685 participants with only one patient lost to follow-up and 143 with missing data (mainly related to completing all elements of the frailty assessment). Results of the study were blinded to the transplant care teams during the study period. A baseline evaluation included demographic and clinical details with a laboratory assessment to determine the MELD score and serum albumin. The presence of HE was defined by a history of overt HE and/or the current use of medical therapy for HE (lactulose or rifaximin). We also further stratified by the intensity of therapy at the time of evaluation (lactulose, rifaximin, or both). The presence of ascites was defined by either medical therapy for or radiographic evidence of intraperitoneal fluid. Frailty was also assessed using the FFI performed in clinic by trained research assistants. Previously validated cutoffs for frailty by each of the above numerated components were applied to assign binary values for frailty for each component. Overall frailty was considered as a score of frail for three or more components.[12] Enrolled patients were then followed until the conclusion of data collection (May 1, 2016) for outcomes that included liver transplantation and death.

2.1 | Analysis

The primary outcome of interest was transplant-free survival, using Cox proportional hazards regression and adjusting for MELD score, ascites, and serum albumin. The principle exposure of interest was the FFI and its components in subsamples stratified by the presence (or absence) of HE. Sensitivity tests were performed for the varying intensities of HE therapies at the time of enrollment. Variables significantly associated with frailty were further explored using logistic regression to determine their impact on the FFI components in a logistic regression. Student *t* tests and Wilcoxon rank sum tests were used to compare differences in continuous variables between groups according to the normality of data categorical variables were compared using Fisher's exact tests. Significance was determined if a two-tailed *P*-value was <.05.

3 | RESULTS

Table 1 details the sample characteristics overall and according to the presence of frailty. In general, our sample was aged an average of 55 years, 60% male, and relatively free of cardiopulmonary comorbidities. By contrast, most patients were decompensated with a history of ascites (374/55%) or HE (268/39%), 203 (30%) of whom presented with both. At the time of evaluation, 153 (57%) were actively taking therapy (lactulose or rifaximin) for HE. Of these patients, 65 were taking lactulose monotherapy and 57 were taking combination lactulose and rifaximin. Twelve patients had transjugular intrahepatic portosystemic shunts at the time of evaluation. Clinical characteristics were balanced with respect to the presence of frailty save for MELD scores (higher with frailty), albumin concentrations (lower with frailty), and decompensations (more common with frailty).

The clinical associations with frailty as determined by performance measures are examined further in Table 2. MELD, albumin, HE, and ascites were all associated with frail walk speeds while only albumin and HE were associated with frail handgrip. Each variable with the exception of ascites was linked to frail energy expenditure while HE was the only variable not associated with frail activity. Ascites was the only variable associated with weight loss. We also repeated these analyses for the subgroups of patients with prior HE based on the intensity of HE therapy at the time of enrollment (Table S1).

In follow-up, 320 (47%) patients were waitlisted at our center, 228 (33%) patients died, and 136 patients (20%) received a liver transplant after a median of 76 IQR (19-198) days. Overall transplant-free survival was 659 IQR (208-1472) days. The variables associated with decreased survival were higher MELD, lower albumin, ascites, HE, and frailty (FFI ≥ 3). Placement on the waiting list for liver transplantation was associated with MELD (higher MELD, higher likelihood), albumin (lower albumin, lower likelihood), and frailty (lower likelihood).

After adjusting for MELD, albumin, and ascites, the specific components of the FFI that were linked with transplant-free survival were energy (HR 1.67 95% CI, 1.25-2.28), grip (HR 1.63 95% CI, 1.24-2.16), and walk speed (HR 1.56 95% CI, 1.19-2.04). In Figure 1, we show the impact of each component of frailty as well as the overall frailty score (out of 5) on transplant-free survival in patients with and without HE. Adjusting for MELD, albumin, and the presence of ascites, frailty scores were significantly associated with death for patients without HE but not in patients with HE. In patients without HE, walk speed, handgrip, and energy expenditure were the three components of frailty associated with mortality. These findings are present in patients who are on any therapy for HE; however, for patients not currently on therapy there is a notable difference. While frailty overall was not associated with mortality in patients with prior HE, frail walk speed did predict increased mortality in the cohort of patients with HE who were not on therapy at the time of enrollment (HR 1.51 95% CI, 1.07-2.12) (Figure S1).

TABLE 1 Demographics and clinical characteristics

	Overall (N = 685)	Non-frail (n = 406)	Frail (n = 279)	*P*-value
Age	54.5 ± 10.3	54.2 ± 10.5	54.8 ± 10.0	.42
Male	409 (60%)	247 (61%)	162 (59%)	.58
Non-white	96 (14%)	55 (14%)	41 (15%)	.65
Major etiologies				
Hepatitis C	156 (23%)	97 (24%)	59 (21%)	
Alcohol	166 (24%)	92 (23%)	74 (27%)	
NASH	157 (23%)	90 (22%)	67 (24%)	.27
Body mass index	29.6 ± 7.1	29.6 ± 6.5	29.6 ± 7.9	.88
Congestive heart failure	14 (2%)	9 (2%)	5 (2%)	.79
Chronic obstructive pulmonary disease	32 (5%)	14 (3%)	18 (7%)	.10
Diabetes mellitus	199 (29%)	111 (28%)	88 (32%)	.23
Coronary artery disease	32 (5%)	17 (4%)	15 (5%)	.47
Dialysis	17 (2%)	9 (2%)	8 (3%)	.62
MELD	14.7 ± 6.3	13.4 ± 5.2	16.5 ± 7.3	<.0001
Albumin (g/dL)	3.2 ± 0.7	3.3 ± 0.7	3.0 ± 0.7	<.0001
Hepatic encephalopathy	268 (39%)	144 (35%)	124 (44%)	.02
Ascites	374 (55%)	204 (50%)	170 (61%)	.006

dL, deciliter; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis. Frailty is defined by a Fried Frailty Index of 3 or greater.
Continuous variables are presented as mean ± standard deviation.

TABLE 2 The impact of clinical predictors on frailty determination

	Grip	Walk speed	Weight loss	Energy	Activity
Odds ratio of being classified as frail (95% CI)					
MELD (per unit)	1.01 (0.99-1.04)	1.08 (1.06-1.11)	1.02 (0.99-1.05)	1.07 (1.04-1.10)	1.07 (1.05-1.10)
Albumin (per g/dL)	1.29 (1.03-1.61)	2.0 (1.56-2.57)	0.98 (0.77-1.25)	1.95 (1.53-2.49)	1.59 (1.26-2.02)
Hepatic encephalopathy	1.41 (1.03-1.92)	1.56 (1.14-2.15)	0.94 (0.68-1.32)	1.44 (1.05-1.99)	1.13 (0.83-1.56)
Ascites	1.18 (0.87-1.60)	1.53 (1.12-2.11)	1.40 (1.01-1.95)	1.29 (0.95-1.75)	1.52 (1.11-2.07)

CI, confidence interval; dL, deciliter; MELD, Model for End-Stage Liver Disease.
The association of clinical variables and performance scored as frail for each component of the Fried Index is presented as the results of a logistic regression. A confidence interval that does not cross 1.0 is our criterion for statistical significance.

4 | DISCUSSION

Within the field of solid organ transplantation, the presence of HE raises unique questions regarding the interpretation and management of frailty specific to patients with cirrhosis evaluated for liver transplant. The relative contribution of HE to the frailty phenotype with respect to other factors is unclear. These data from a prospective cohort study of 685 patients evaluated for liver transplantation show that although HE increases the risk of frailty, frailty is not associated with mortality in patients with HE.

There are two principle implications of these findings. First, HE is associated with frailty. Frailty—like HE—is a biomarker of diminished physiologic reserve, both of which are linked to adverse outcomes. HE and frailty share similar associations: poor patient-reported outcomes,[15] sarcopenia,[13,14] poor coordination (and falls),[8,17] and hospitalization.[18] However, given that the pathophysiology of hyperammonemia and HE cause many of these factors which would be captured clinically as frailty, HE is a crucial step in the causal pathway of frailty among patients with advanced liver disease.

Interventions for frailty should be multimodal with attention paid to enhanced nutrition, physical training, and cognitive function.[19] In many cases, these modalities are simultaneously effective for the treatment of HE. Although further research is needed to determine if HE-related frailty

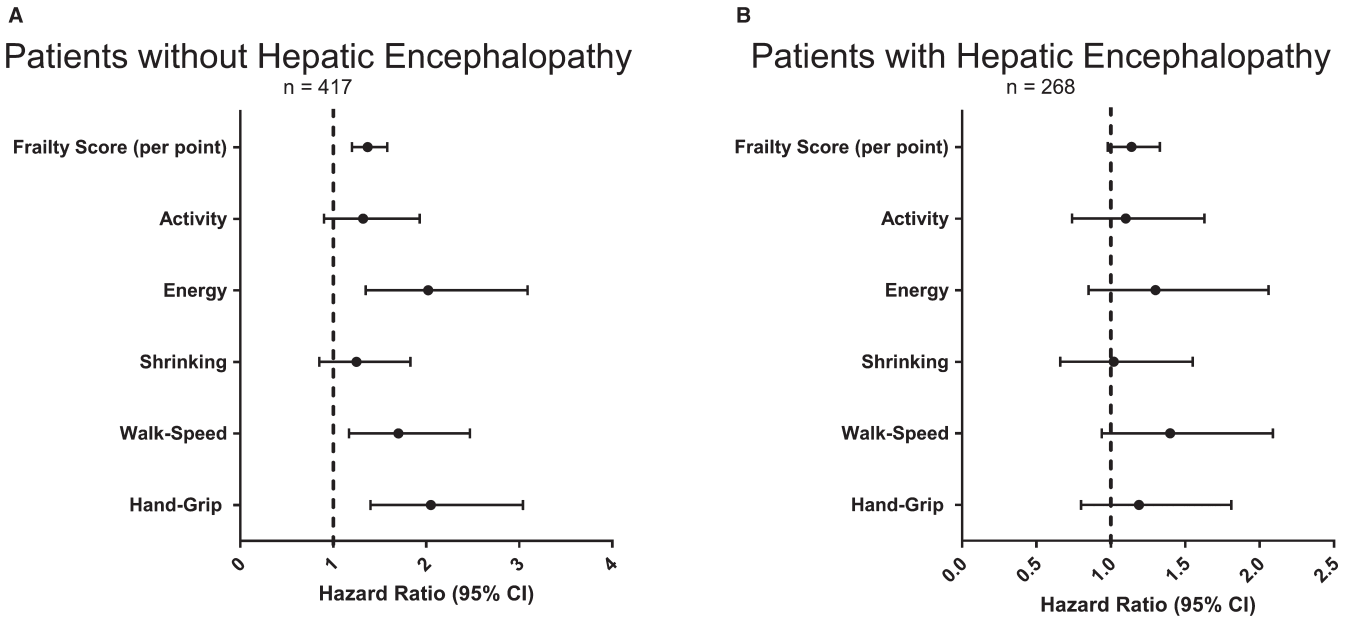

FIGURE 1 Frailty is not predictive of transplant-free survival in patients with hepatic encephalopathy. This figure delineates the association of frailty with transplant-free survival in patients without (panel A) and with (panel B) hepatic encephalopathy. While three components of the Fried Frailty Index are significantly predictive of survival in patients without encephalopathy, none are for patients with encephalopathy. Hazard ratios are presented with 95% confidence intervals (CI) with a dashed line to indicate 1.0; intervals that cross 1.0 are not significant. All estimates are adjusted for Model for End-Stage Liver Disease Score, albumin concentration, and the presence of ascites

is reversible, there is evidence that therapy can improve aspects of the HE phenotype that are consistent with frailty. These include improvements after HE therapy of poor patient-reported outcomes,[20] coordination (in a driving simulator),[21] and, although it has been studied only in preclinical models, ammonia-lowering therapy may reverse ammonia-induced sarcopenia.[14] Additionally, at a minimum, owing to the adverse impact of sarcopenia on frailty and waitlist mortality and the salutary effect of improved nutrition on HE, protein intake should be increased in patients with HE to 1.25 g/kg ideal bodyweight.[22] Further study of the role of screening tests for subclinical HE on longitudinal assessments of frailty, potentially by using point-of-care tests such as the EncephalApp Stroop,[23,24] are warranted.

Second, we found that the components of the FFI that are associated with mortality (energy, grip, walk speed) are identical to those associated with HE. Whereas others have shown that patients with HE report more subjective disability[5] and worse patient-reported outcomes (including poor balance),[15] these data highlight a global impact of HE on frailty measures. At the same time, among patients actively receiving therapy for HE, the impact of HE on survival appears equivalent to frailty's impact on survival for patients without HE. Three large studies (two from one center[3,25]) have examined and confirmed the predictive value of the FFI on mortality in the pre-transplant setting.[3,19,25] However, these studies did not evaluate the impact of HE on FFI. To avoid the pitfalls of subjective assessments of frailty, the field of liver transplantation may be moving toward the strictly objective measures such as the Liver Frailty Index (handgrip, chair stands, and balance).[8] However, our data show that the relative impact of HE and cognitive dysfunction will not diminish for objective measures and will need to be addressed even as our frailty indices improve and become more standardized.

These data must be interpreted in the context of study design. First, we neither directly analyzed cognitive function nor did we directly measure sarcopenia for correlation with frailty. The specific underlying mechanism of HE's impact on frailty in this work is therefore speculative and ought to be evaluated in future studies by testing for sarcopenia and cognitive dysfunction. Further, because we did not evaluate cognitive function at the time of enrollment, we cannot know whether patients with prior HE who were not on therapy were more cognitively intact than those, for example, on combination therapy. Second, we do not evaluate the duration or trajectory of our patients' frailty which would speak to physiologic reserve and potential for reversibility. Worsening frailty may be associated with increased mortality and additional data are needed to determine whether HE is as associated with a specific trajectory. Third, independent of HE, cirrhotic complications can contribute to diminished cognitive reserve, or the ability to preserve cognitive function in the context of a neurological insult. Decreased cognitive reserve is associated with poor health-related quality of life which could be a driver of the subjective components of the FFI.[26] Fourth, though this cohort of 268 patients with HE is the largest evaluated for the presence of frailty to date, we cannot exclude the possibility that an effect of frailty on mortality would be observed in a larger sample. Finally, we did not evaluate indices of frailty other than the FFI and future studies, particularly those that measure cognitive function directly, should include the liver frailty index.[8]

In conclusion, as data on frailty accrue, efforts to understand the underlying mechanisms of frailty are essential for the interpretation of its impact and to inform therapeutic strategies. Our data suggest that HE appears to be an important determinant of both

the frailty phenotype and adverse health outcomes associated with frailty. Given that HE is responsive to pharmacological and nutritional therapy, prospective study of HE-directed treatment for frail patients with cirrhosis is indicated.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

Elliot Tapper is the guarantor of this article. Concept: Tapper, Sonnenday; Analysis: Tapper, Konerman, Murphy, Sonnenday; Data acquisition: Sonnenday; Writing: Tapper; Critical revision: Konerman, Murphy, Sonnenday.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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