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Evaluating the Associations Between the Liver Frailty Index and Karnofsky Performance Status With Waitlist Mortality

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Background. Frailty has emerged as a critical determinant of mortality in patients with cirrhosis. Currently, the United Network for Organ Sharing registry only includes the Karnofsky Performance Status (KPS) scale, which captures a single component of frailty. We determined the associations between frailty, as measured by the Liver Frailty Index (LFI), and KPS with waitlist mortality. **Methods.** Included were 247 adult patients with cirrhosis listed for liver transplantation without hepatocellular carcinoma from February 2014 to June 2019, who underwent outpatient assessments using the LFI and KPS within 30 days of listing. “Frail” was defined using the established LFI cutoff of ≥ 4.4 . Competing risk models assessed associations between the LFI and KPS with waitlist mortality (death/delisting for sickness). **Results.** At a median 8 months follow-up, 25 (10%) patients died/were delisted. In this cohort, median Model for End-Stage Liver Disease-Sodium was 17, LFI was 3.9 (interquartile range 3.4–4.5), and KPS was 80 (interquartile range 70–90). In multivariable analysis, LFI (sub-hazard ratio 1.07, per 0.1 unit; 95% confidence interval, 1.01–1.12) was associated with waitlist mortality while KPS was not (sub-hazard ratio 1.00, per 10 units; 95% confidence interval, 0.78–1.29). **Conclusions.** Our data suggest that frailty, as measured by the LFI, may be more appropriate at capturing mortality risk than KPS and provide evidence in support of using the LFI more broadly in clinical transplant practice in the outpatient setting.

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Frailty is a well-established determinant of mortality in patients with cirrhosis.¹ Currently, the only metric available in the United Network for Organ Sharing (UNOS)/Organ

Procurement and Transplantation Network that approximates the concept of frailty is the Karnofsky Performance Status (KPS) score. The KPS score is a subjective assessment of a patient’s overall performance status that is assigned on a scale of 0–100 in increments of 10 (where a score of 0 is considered moribund and 100 is considered excellent health).² In patients awaiting liver transplantation, functional status has been associated with mortality both before and after liver transplantation.^{3,4} Severe functional impairment at the time of liver transplantation, as assessed by KPS, has been shown to be associated with a markedly increased risk of mortality and/or having graft failure at 1-year posttransplantation.^{5–7} However, while the KPS metric has the advantage of being simple and quick to use, it represents only one component of the multi-dimensional construct of frailty—functional status and is subjective, making it susceptible to bias.⁸

Recently, we developed the Liver Frailty Index (LFI) to assess frailty in patients with cirrhosis.⁹ The LFI consists of 3 tests to represent 3 major components of the multi-dimensional construct of frailty: grip strength (malnutrition), chair stands (muscle weakness), and balance (altered neuromotor coordination). The frailty tests chosen to be included in the LFI were originally established in the geriatric population^{10–13} and have demonstrated broad prognostic utility in non-geriatric,^{14,15} surgical,^{16,17} and non-liver transplant^{18–20} populations. We have shown in several studies that the LFI is strongly associated with outcomes in patients with cirrhosis.^{21–25} However, it is a performance-based metric that must

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be administered in person, raising concerns about its ability to be incorporated into the national UNOS/Organ Procurement and Transplantation Network registry.

Given the standardized acceptance of the KPS metric to approximate frailty in the UNOS registry—and the recent availability of a more comprehensive, liver-specific assessment of frailty with the LFI—we aimed to determine the associations between the LFI and KPS with waitlist mortality in patients with cirrhosis in the ambulatory setting.

MATERIALS AND METHODS

Study Population

We analyzed data available from adult patients with cirrhosis listed for liver transplantation at a single center from February 1, 2014 to June 1, 2019 who underwent outpatient assessments of frailty (using the LFI) and performance status (using the KPS scale) within 30 days of listing for liver transplantation [see Study Procedures below]. Excluded were patients with hepatocellular carcinoma listed with Model for End-Stage Liver Disease (MELD) exception points given their differential wait time. Patients were followed until they experienced an outcome including death, deactivation for being too sick, liver transplantation, or removal from the waitlist for other reasons.

Study Procedures

Frailty was measured using the LFI, which consists of 3 performance-based tests administered by trained study personnel: (1) grip strength, (2) timed chair stands, and (3) balance. The LFI was calculated using the following equation (calculator available at <http://liverfrailtyindex.ucsf.edu>):

“Frail” was defined using the previously established LFI cutoff of ≥ 4.4 from the study by Kardashian et al²⁶ In this study, the optimal cutoff was determined using the area under the curve in an analysis of waitlist mortality by 3, 6, and 12 months. The optimal (highest area under the curve) LFI cutoff for waitlist mortality was 4.4 at 3 months and 4.2 at 6 and 12 months. On the same day as the frailty assessment, KPS was assessed by trained transplant coordinators independent of the LFI assessment. Patients were assigned a score from 0 to 100, where a score of 0 is considered moribund and 100 is considered perfect health.

Additional data were collected from the electronic health record. These included age, sex, ethnicity, body mass index, MELD-Sodium (MELDNa), albumin, the presence of ascites, dialysis dependence, hepatic encephalopathy at time of listing, and co-morbidities (diabetes, hypertension, and coronary artery disease). Cause of liver disease was categorized as chronic hepatitis C, hepatitis B, alcohol, nonalcoholic steatohepatitis, autoimmune or cholestatic, and other.

Statistical Analysis

Baseline demographics were presented as a median (interquartile range [IQR]) for continuous variables or frequency for categorical variables. Differences in KPS by group were compared by frailty status using χ^2 test. Correlation between the LFI and KPS was evaluated using Spearman’s rank-order correlation test.

The primary outcome was waitlist mortality, defined as the combined outcome of death before transplantation or deactivation for being too sick for liver transplantation. Uni- and multivariable analyses assessed associations between the LFI

and KPS with waitlist mortality using competing risk models, with liver transplantation as the competing risk. Variables with $P < 0.2$ in univariable analysis were considered for inclusion in multivariable models. Variables with $P < 0.05$ were retained in the final multivariable models.

This study was approved by the institutional review board at the University of California, San Francisco (IRB approval number: 11-07513). Statistical analyses were performed using STATA 15 (StataCorp, College Station, TX).

RESULTS

Characteristics of the Patient Population

Baseline characteristics of the 247 patients with cirrhosis listed for transplantation are displayed in Table 1. Fifty-nine percent of the patients were male and median (IQR) age was 57 (50–63). The 2 most common primary etiologies of liver disease were alcoholic cirrhosis (36%) and nonalcoholic steatohepatitis (28%). Median (IQR) laboratory MELDNa score was 17 (14–20), LFI was 3.9 (3.4–4.5), and KPS was 80 (70–90).

Assessments of and Correlations Between Frailty and Performance Status

Among the 247 outpatients, 66 (27%) met criteria for frailty. One hundred sixty-three (66%) patients had a KPS of 80–100, 81 (33%) had a KPS of 50–70, and 3 (1%) had a KPS of 10–40 (Table 1). Among the 66 patients who were categorized as frail, median (IQR) KPS was 75 (60–90) and 33 (50%) were considered impaired by the KPS with scores in the ranges of 10–40 and 50–70. On the other hand, among patients who were not frail, 51 (28%) were categorized as having some level of impairment by the KPS. The correlation between the LFI and KPS by Spearman’s rank-order test was -0.32 ($P < 0.001$) (Figure 1).

Associations Between the LFI and the KPS With Waitlist Mortality

At a median of 8 months follow-up, 25 (10%) patients died or were deactivated for being too sick for liver transplantation. In univariable competing risk analysis, the LFI was associated with a 9% increased risk of waitlist mortality per 0.1 unit (95% confidence interval [CI], 1.03–1.14) whereas KPS was not (sub-hazard ratio [sHR] 0.92, per 10 units; 95% CI, 0.70–1.22). These associations did not change for either variable in bivariable analysis including both the LFI and KPS (Table 2). A sensitivity analysis evaluating KPS by group (10–40, 50–70, 80–100), did not qualitatively change the association between the LFI, KPS, and waitlist mortality (data not shown). We then performed forward stepwise regression to determine whether adjustment for other factors changed these associations. After adjustment for other factors that were associated with waitlist mortality in univariable analysis (MELDNa, age, ascites, and albumin), the LFI remained significantly associated with waitlist mortality (sHR 1.07, per 0.1 unit; 95% CI, 1.01–1.12) while KPS was not (sHR 1.00, per 10 units; 95% CI, 0.78–1.29) (Table 2).

DISCUSSION

The process of evaluating patients for transplant candidacy is one that is very complex and depends on more than just

TABLE 1.
Characteristics of the 247 patients with cirrhosis in this study categorized by frailty status

Characteristics	All (N = 247)	By frailty status		P
		Not frail (LFI < 4.4) (N = 181; 73%)	Frail (LFI ≥ 4.4) (N = 66; 27%)	
Age (years)	57 (50–63)	56 (49–63)	60 (54–65)	0.03
Female	102 (41%)	76 (42%)	26 (39%)	0.71
Race				
Non-Hispanic white	213 (86%)	154 (85%)	59 (89%)	0.03
Black	6 (2%)	6 (3%)	—	
Asian or Pacific Islander	17 (7%)	15 (8%)	2 (3%)	
Native American	3 (1%)	3 (2%)	—	
Other	8 (3%)	3 (2%)	5 (8%)	
Body mass index (kg/m ²)	27.9 (24.6–32.3)	27.9 (25.2–32.3)	27.8 (23.2–34.1)	0.22
Cause of liver disease				
Chronic HCV	33 (13%)	23 (13%)	10 (15%)	0.44
Alcohol	90 (36%)	67 (37%)	23 (35%)	
Nonalcoholic steatohepatitis	69 (28%)	46 (25%)	23 (35%)	
Autoimmune or cholestatic	32 (13%)	25 (14%)	7 (11%)	
HBV	4 (2%)	4 (2%)	—	
Other	19 (8%)	16 (9%)	3 (5%)	
Hypertension	71 (29%)	49 (27%)	22 (33%)	0.34
Diabetes	113 (46%)	83 (46%)	30 (45%)	0.96
Coronary artery disease	7 (3%)	4 (2%)	3 (5%)	0.33
KPS				
80–100	163 (66%)	130 (72%)	33 (50%)	0.003
50–70	81 (33%)	50 (28%)	31 (47%)	
10–40	3 (1%)	1 (1%)	2 (3%)	
MELDNa score	17 (14–20)	16 (14–20)	18 (14–21)	0.27
Total bilirubin (mg/dL)	2.9 (1.9–4.8)	2.9 (2.0–4.8)	2.8 (1.6–4.8)	0.77
Creatinine (mg/dL)	0.86 (0.68–1.1)	0.84 (0.67–1.03)	0.96 (0.76–1.25)	0.01
INR	1.5 (1.3–1.7)	1.5 (1.3–1.7)	1.5 (1.3–1.7)	0.94
Sodium (mEq/L)	135 (132–137)	135 (133–138)	133 (129–136)	<0.001
Albumin (g/dL)	3.0 (2.6–3.4)	3.0 (2.6–3.4)	3.1 (2.6–3.4)	0.82
Dialysis	11 (4%)	7 (4%)	4 (6%)	0.46
Ascites				
Absent	165 (67%)	129 (71%)	36 (55%)	0.01
Mild/moderate	64 (26%)	44 (24%)	20 (30%)	
Severe	18 (7%)	8 (4%)	10 (15%)	
Hepatic encephalopathy	114 (46%)	76 (42%)	38 (58%)	0.01
Outcome				
Waiting	108 (44%)	84 (46%)	24 (36%)	0.18
Death or delisted for being too sick	25 (10%)	15 (8%)	10 (15%)	
Transplanted	72 (29%)	55 (30%)	17 (26%)	
Other	42 (17%)	27 (15%)	15 (23%)	

All continuous variables are expressed as median (interquartile range) or percentage.

KPS, Karnofsky Performance Status; LFI, Liver Frailty Index; MELDNa, Model for End-Stage Liver Disease-Sodium.

the severity of liver disease. Frailty is becoming increasingly recognized as a key determinant of outcomes in patients with cirrhosis, which calls for standardized tools that are able to capture its multi-dimensionality. In this study, we examined 2 available indices that have been studied independently in the transplant setting. We sought to ascertain the relationship between the LFI and KPS, which are measurements of frailty and performance status (a component of frailty), respectively, and found that there was a modest correlation. While the LFI was predictive of waitlist mortality in our outpatient cohort of liver transplant candidates with a median MELDNa of 17, KPS was not. Our study suggests that frailty, as measured by the LFI, may be more appropriate to assess mortality risk than performance status alone.

While the KPS has the benefit of being a very rapid test that does not require specialized equipment, the LFI has several advantages over the KPS. Because it consists of 3 components, it is better able to capture the dominant contributors to physical frailty in patients with cirrhosis: malnutrition (grip strength), muscle weakness (chair stands), and altered neuro-motor coordination (balance). By measuring grip strength, the LFI also accounts for sarcopenia, which has been recognized as an independent risk factor of mortality on the transplant waitlist and after liver transplantation.^{27–29}

In our study, among the patients who were categorized as frail by the objective LFI, only half were considered impaired by the KPS scale. Conversely, among those who were not frail by the objective LFI, more than one-quarter were classified

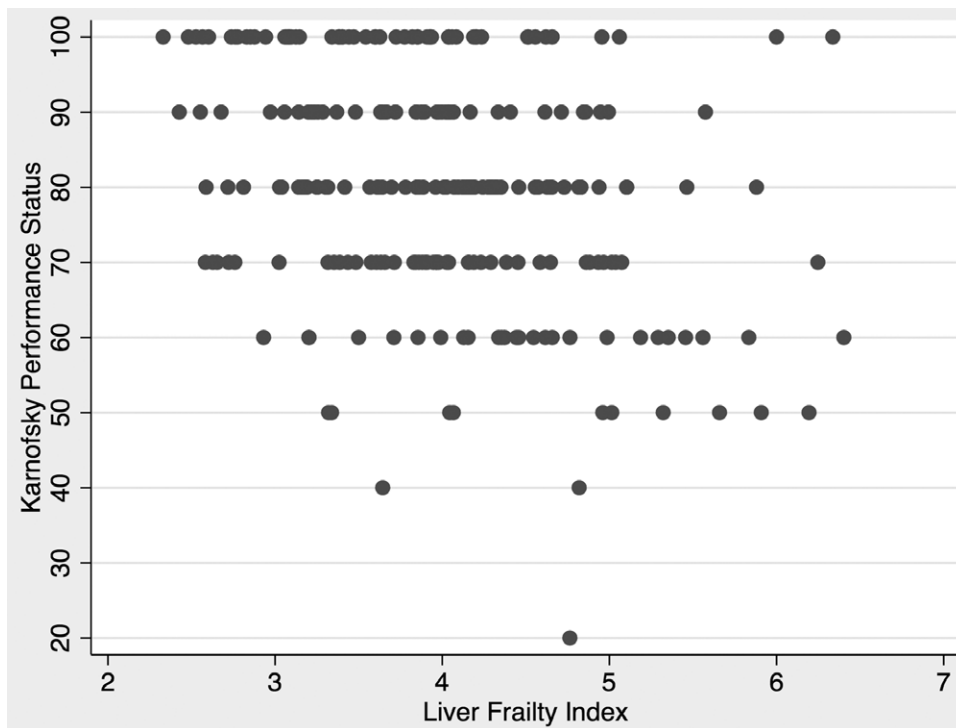


FIGURE 1. Correlation between the Liver Frailty Index and Karnofsky Performance Status scores (Spearman's $P = -0.32$, $P < 0.001$)

TABLE 2.

Univariable and stepwise additive multivariable models using competing risks models (with liver transplantation as competing risk)

	Sub-hazard ratio (95% CI), <i>P</i>					
	Univariable analysis		Stepwise multivariable analyses			
LFI, per 0.1 unit	1.09 (1.03-1.14), <i>P</i> = 0.001	1.09 (1.04-1.14), <i>P</i> = 0.001	1.08 (1.03-1.13), <i>P</i> = 0.001	1.07 (1.02-1.12), <i>P</i> = 0.003	1.07 (1.02-1.11), <i>P</i> = 0.01	1.07 (1.01-1.12), <i>P</i> = 0.01
KPS, per 10 units	0.92 (0.70-1.22), <i>P</i> = 0.57	1.02 (0.79-1.31), <i>P</i> = 0.90	1.02 (0.79-1.31), <i>P</i> = 0.90	1.00 (0.78-1.27), <i>P</i> = 0.98	1.00 (0.78-1.29), <i>P</i> = 0.99	1.00 (0.78-1.29), <i>P</i> = 0.99
MELDNa, per 1 unit	1.04 (0.98-1.10), <i>P</i> = 0.25		1.03 (0.97-1.09), <i>P</i> = 0.40	1.04 (0.97-1.10), <i>P</i> = 0.28	1.03 (0.97-1.10), <i>P</i> = 0.36	1.03 (0.96-1.10), <i>P</i> = 0.44
Age, per year	1.07 (0.99-1.15), <i>P</i> = 0.08			1.06 (0.98-1.14), <i>P</i> = 0.15	1.06 (0.98-1.14), <i>P</i> = 0.14	1.06 (0.98-1.14), <i>P</i> = 0.15
Ascites	2.21 (1.02-4.80), <i>P</i> = 0.05				1.75 (0.81-3.79), <i>P</i> = 0.16	1.73 (0.79-3.79), <i>P</i> = 0.17
Albumin (g/dL)	0.60 (0.30-1.20), <i>P</i> = 0.146					0.68 (0.35-1.33), <i>P</i> = 0.26

CI, confidence interval; KPS, Karnofsky Performance Status; LFI, Liver Frailty Index; MELDNa, Model for End-Stage Liver Disease-Sodium.

as having at least some impairment in performance status. This highlights the subjective nature of the KPS and raises the possibility that subjective assessments of performance status may be influenced by factors that are not accurately tied to physical performance. The fact that the LFI was associated with waitlist mortality and not KPS in our cohort suggests that these subjective factors may not be important in risk prediction. Thus, the LFI is especially useful in the ambulatory setting to identify frail patients who may have subjectively higher KPS scores.

Although we did not observe an association between KPS with waitlist mortality in our study, there are several studies that demonstrate its prognostic value in this context. Both Orman et al³ and McCabe et al³⁰ showed that worse

functional status as measured by the KPS was significantly associated with waitlist mortality in cirrhotic patients. Thuluvath et al⁷ found a significant association between lower KPS scores and with mortality pre- and post-liver transplantation. However, in a study examining the relationship between KPS and another more objective assessment, the 6-minute walk test, only the 6-minute walk test was associated with waitlist mortality.³¹ Despite its subjectivity, KPS has been shown to have good inter-observer reliability at least among oncology patients, but it is less well-validated amongst patients with cirrhosis.^{32,33} In comparison, the LFI is specific to patients with liver disease and has external validity in non-cirrhotic patients with excellent inter-observer reliability.³⁴

We acknowledge the following limitations to our study. Our cohort was restricted to patients seen in clinic as outpatients, as the LFI has only been validated in the ambulatory setting. As a result, there were few patients with low KPS scores in this population. Therefore, these findings are not generalizable to the entire liver transplant waitlist as a whole; KPS may indeed be equally prognostic among inpatients. We also restricted our analyses to patients who had assessments of frailty and performance status within 30 days of listing to create a more homogeneous cohort of patients who were just beginning their time on the waitlist. However, we did not evaluate changes in either frailty or performance status over time, which may be prognostically valuable.^{7,25,35} A recent multi-center study by Lai et al²⁵ showed that patients who experienced improvements in frailty over time had a lower risk of death/delisting than patients who experienced worsening frailty, regardless of their baseline frailty and disease severity.

Despite these limitations, our study adds to the growing body of evidence that frailty should be incorporated into transplant decision-making. Frailty, as measured by the LFI, is a significant predictor of waitlist mortality. While we acknowledge the advantages of using the KPS as a rapid screening tool, we strongly advocate for the LFI to be used more broadly in clinical transplant practice in the outpatient setting as it offers a more comprehensive assessment of frailty and accurate estimation of mortality risk.

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