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The relationship between frailty and cirrhosis etiology: From the Functional Assessment in Liver Transplantation (FrAILT) Study

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CX (acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript); YM (acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript); MK (acquisition of data, review of manuscript); BB (acquisition of data, review of manuscript); DG (acquisition of data, review of manuscript); MV (acquisition of data, review of manuscript); RR (acquisition of data, review of manuscript); AD (acquisition of data, review of manuscript); MM (acquisition of data, review of manuscript); DS (acquisition of data, review of manuscript); DL (acquisition of data, review of manuscript); EV (acquisition of data, review of manuscript); JG (acquisition of data, database preparation, statistical analysis); MT (acquisition of data, review of manuscript); MD (acquisition of data, review of manuscript); JL (study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content).

DISCLOSURES

The authors of this manuscript have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting Information may be found online in the Supporting Information section.

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Abstract

Background & Aims: Cirrhosis leads to malnutrition and muscle wasting that manifests as frailty, which may be influenced by cirrhosis aetiology. We aimed to characterize the relationship between frailty and cirrhosis aetiology.

Methods: Included were adults with cirrhosis listed for liver transplantation (LT) at 10 US centrer who underwent ambulatory testing with the Liver Frailty Index (LFI; 'frail' = LFI ≥ 4.4). We used logistic regression to associate aetiologies and frailty, and competing risk regression (LT as the competing risk) to determine associations with waitlist mortality (death/delisting for sickness).

Results: Of 1,623 patients, rates of frailty differed by aetiology: 22% in chronic hepatitis C, 31% in alcohol-associated liver disease (ALD), 32% in non-alcoholic fatty liver disease (NAFLD), 21% in autoimmune/cholestatic and 31% in 'other' ($P < .001$). In univariable logistic regression, ALD (OR 1.53, 95% CI 1.12-2.09), NAFLD (OR 1.64, 95% CI 1.18-2.29) and 'other' (OR 1.58, 95% CI 1. 06-2.36) were associated with frailty. In multivariable logistic regression, only ALD (OR 1.40; 95% 1.01-1.94) and 'other' (OR 1.59; 95% 1.05-2.40) remained associated with frailty. A total of 281 (17%) patients died/were delisted for sickness. In multivariable competing risk regression, LFI was associated with waitlist mortality (sHR 1.05, 95% CI 1.03-1.06), but aetiology was not ($P > .05$ for each). No interaction between frailty and aetiology on the association with waitlist mortality was found ($P > .05$ for each interaction term).

Conclusions: Frailty is more common in patients with ALD, NAFLD and 'other' aetiologies. However, frailty was associated with waitlist mortality *independent of* cirrhosis aetiology, supporting the applicability of frailty across all cirrhosis aetiologies.

Keywords

frailty; malnutrition; NAFLD; non-alcoholic fatty liver disease; physical function; sarcopenia

1 | INTRODUCTION

Frailty is common in patients with cirrhosis and is a powerful predictor of mortality.[1-8] In this population, frailty has been conceptualized to represent the end manifestation of chronic undernutrition, muscle wasting and functional impairment from chronic liver failure. Prior studies have identified some differences in these individual contributors to frailty between cirrhosis aetiologies. For instance, patients with alcohol-associated liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) have a higher prevalence of sarcopenia.[9] Patients with ALD are at increased risk for malnutrition and have poorer functional status at time of listing.[10,11] In addition, co-morbidities like metabolic or cardiovascular disease that are

more common in some cirrhosis aetiologies may also contribute to differences in frailty. However, the relationship between frailty and liver disease aetiology has not been well characterized. In this multi-centre study in the USA, we aimed to characterize frailty, as assessed by the Liver Frailty Index, by cirrhosis aetiology and assess whether liver disease aetiology impacts the relationship between frailty and waitlist mortality.

2 | METHODS

2.1 | Study population

We analysed data available from the multi-centre Functional Assessment in Liver Transplantation (FrAILT) Study, a prospective study dedicated to understanding frailty in patients with cirrhosis awaiting liver transplantation. Included were ambulatory adult patients with cirrhosis listed for liver transplantation at 10 centres in the USA: 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 Pittsburg (n = 59), Loma Linda University (n = 31), University of Arkansas for Medical Sciences (n = 21), University of Michigan (n = 1). Patients with hepatocellular carcinoma listed with MELDNa exception points were excluded because of their differential wait time.

2.2 | Study procedures and data collection

All participating centres used a standardized protocol. Study personnel underwent rigorous training at each site, led by UCSF to execute the protocol. Quality checks of data were performed weekly. At enrollment, all patients underwent ambulatory physical frailty testing using the Liver Frailty Index, which consists of three performance-based tests administered by trained study personnel: (a) grip strength; (b) timed chair stands and (c) balance. The Liver Frailty Index was calculated using the calculator available at http://liverfrailtyindex.ucsf.edu. At the time of frailty assessment, information regarding demographics, medical co-morbidities (ie BMI, hypertension, diabetes, coronary artery disease), dialysis dependence, degree of ascites, presence of hepatic encephalopathy and laboratory tests were collected from the patient's electronic medical record. At the baseline study visit, ascites was categorized as mild/moderate based on physical examination or severe if the patient was undergoing large volume paracenteses. The presence of hepatic encephalopathy was also determined at the baseline study visit if the patient had a history of or currently had hepatic encephalopathy.

The aetiology of liver disease was categorized as chronic hepatitis C (HCV), alcohol-associated liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), autoimmune/cholestatic diseases (AI/CD) or 'other' (ie cryptogenic, alpha-1-antitrypsin, Wilson's disease, haemochromatosis). Once enrolled, waitlist outcomes were ascertained prospectively and were categorized as: death prior to liver transplant, delisting for being too sick for transplant, deceased donor liver transplantation or removal from the waitlist for other causes, including deactivation for social reasons. Patients who underwent living donor liver transplantation were censored at the time of their living donor liver transplantation.

2.3 | Statistical analysis

Baseline demographics were presented as medians [interquartile ranges (IQR)] for continuous variables or percentages for categorical variables. Participants were classified as 'frail' if they had a Liver Frailty Index of ≥ 4.4, 'pre-frail' if they scored between 3.2 and 4.4 and 'robust' if they scored < 3.2 on the Liver Frailty Index, based on previously determined cut points.[1,12] Differences in baseline characteristics by cirrhosis aetiology were compared using χ^2 test or Kruskal-Wallis tests for categorical and continuous variables respectively. We also assessed for interactions between cirrhosis aetiologies and other clinical and demographic variables with frailty. Variables with $P < .05$ on univariable analysis were included in the final multivariable logistic regression model.

The primary endpoint in our study was waitlist mortality, defined as a combined endpoint of death prior to liver transplant or delisting for being too sick for transplant. Follow-up time for those who did not achieve a terminal waitlist event was censored on February 4, 2020. Competing risk regression evaluated the associations between frailty, cirrhosis aetiology and waitlist mortality with deceased donor liver transplantation as the competing risk. All variables with $P < .2$ in univariable analysis were considered for inclusion in the final multivariable model. Backward stepwise regression was performed to arrive at the final multivariable model, using a threshold $P < .05$ for all retained variables.

The Institutional Review Boards at every site approved this study. All statistical analyses were performed using STATA v. 15 (College Station, TX).

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of the 451 frail (Liver Frailty Index ≥ 4.4) participants categorized by cirrhosis aetiology are listed in Table 1. In this cohort, 44% were female and 70% were non-Hispanic White. The most common aetiology of cirrhosis was ALD (32%), followed by NAFLD (25%), HCV (18%), 'other' (13%) and AI/CD (12%). Patients comprising the 'other' category predominantly had cryptogenic cirrhosis (65%), followed by alpha-1-antirypsin (10%), haemochromatosis (6%) and drug-induced liver injury (6%). Median MELDNa and Child Pugh scores were clinically similar between the groups. Compared to other aetiologies, frail patients with NAFLD were older and had significantly higher BMI ($P < .001$) and rates of hypertension and diabetes ($P < .001$). Frail patients with ALD, NAFLD and 'other' had higher rates of ascites compared to all other groups ($P = .02$).

3.2 | Rates of frailty

Table 2 presents a summary of the Liver Frailty Index and its individual components by cirrhosis aetiology of all 1,623 participants in the cohort. Liver Frailty Index scores differed significantly by cirrhosis aetiologies, with NAFLD patients having a higher median Liver Frailty Index of 4.1 (3.7-4.6) ($P < .001$). With respect to individual Liver Frailty Index components, patients with NAFLD, AI/CD and 'other' had weaker grip strength (24 kg), compared to patients with HCV and ALD (29 kg vs 28 kg) ($P < .001$). NAFLD patients also

displayed slower chair stands time (0.3 stands per second) compared to all other groups ($P <$ .001).

Using established Liver Frailty Index cutoffs of < 3.2, 3.2-4.3 and ≥ 4.4 for robust, pre-frail and frail participants, respectively, the proportion of frailty differed significantly by cirrhosis aetiology and was highest among patients with NAFLD (32%), followed by ALD (31%), 'other' (31%), HCV (22%) and AI/CD (21%). The majority of patients across all liver disease categories were categorized as pre-frail by the Liver Frailty Index with scores in the range of 3.2-4.3 [Table 2].

3.3 | Correlations between cirrhosis aetiology and frailty

In univariable logistic regression, the odds of being frail were significantly higher in patients with ALD (OR 1.53; 95% CI 1.12-2.09), NAFLD (OR 1.64; 95% CI 1.18-2.29) and 'other' aetiologies (OR 1.58; 95% CI 1.06-2.36). After adjustment for age, MELDNa and ascites, only ALD (OR 1.40; 95% CI 1.01-1.94) and 'other' aetiologies (OR 1.59; 95% CI 1.05-2.40) remained associated with frailty (Table 3).

3.4 | Associations between frailty and cirrhosis aetiology and waitlist mortality

At a median follow-up of 13 months, 281 (17%) patients died or were delisted for sickness. In univariable competing risk analysis, the Liver Frailty Index was associated with a 5% increased risk of waitlist mortality per 0.1 unit (95% CI 1.04-1.07) while cirrhosis aetiologies were not ($P >$ .05 for each aetiology category). These associations did not change in multivariable analysis after adjustment for MELDNa, albumin, hepatic encephalopathy, age and Hispanic race (Table 4). There was no significant interaction between frailty and cirrhosis aetiology (p-values for each interaction term were $P =$ .69 for ALD, $P =$ .58 for NAFLD, $P =$ .48 for AI/CD and $P =$ .96 for 'other'). Among frail patients, there was no statistically significant difference in waitlist mortality across all aetiologies ($P =$ .17) [Table S1].

4 | DISCUSSION

In this large multi-centre cohort of ambulatory patients with cirrhosis, we observed that rates of frailty differed by cirrhosis aetiology, with highest frailty rates seen in those with NAFLD, ALD and 'other'aetiologies. In addition, patients with NAFLD, ALD, and 'other' also had higher rates of ascites, which has previously been demonstrated to be strongly associated with physical frailty.[6] Despite these varying rates of frailty by cirrhosis aetiology, we did not observe a differential effect of frailty by cirrhosis aetiology. In other words, the association between frailty and waitlist mortality was the same regardless of the aetiology of cirrhosis.

We embarked upon this study with the hypothesis that frailty would differ by disease aetiology. Frailty is commonly conceptualized as the end manifestation of an individual's co-morbidities, such as cardiovascular disease, diabetes and chronic renal dysfunction,[13] that can lead to chronic under-nutrition, systemic inflammation and hormonal dysregulation. Under this framework, patients with multiple co-morbidities (eg patients with NAFLD) or chronic under-nutrition (eg patients with ALD) would be expected to display higher rates

of frailty. Interestingly, patients with cholestatic liver diseases, who have traditionally been considered at higher risk for vitamin deficiencies and low bone mineral density, did not display the highest rates of frailty in our cohort, because of the counter-balancing factors of younger ages and lower rates of portal hypertensive complications and non-hepatic co-morbidities. Such findings strengthen the value of objective frailty indices in the assessment of patients with cirrhosis: they offer clinicians the ability to 'sum up' the effects of all of the risk factors that we know are important in patients with cirrhosis (eg older age, chronic renal disease, malnutrition, medical co-morbidities) but present at varying rates in individual patients.

We acknowledge the following limitations to this study. Our study is limited by the retrospective nature of the investigation, which is vulnerable to selection biases and potential confounding despite efforts to control for these factors. While multi-centre enrollment in our cohort is a strength of this study, we acknowledge that there is variation between centres with respect to clinical management and waitlist practices. While this leads to heterogeneity in the cohort, we also believe that this can strengthen the generalizability and applicability of our results to other transplant centers that are seeking to assess frailty in their practice. We also have shown in our prior studies that centre variation has not changed the qualitative interpretation of our results.[6,14] Lastly, as the Liver Frailty Index has only been validated in the ambulatory setting, we restricted our cohort to those seen as outpatients. Therefore, these findings are not generalizable to the inpatient liver transplant population.

Despite these limitations, our study fills a discrete knowledge gap in our understanding of frailty in cirrhosis that is essential for its application in clinical practice. While rates of frailty may be higher in those with cirrhosis from ALD, NAFLD or 'other" cirrhosis aetiologies, frailty is a construct that applies to all patients with cirrhosis and is prognostic regardless of disease aetiology. In clinical practice, the assessment of frailty may be as important among those who are not frail as it is in those who are frail, as a patient with NAFLD or ALD who is *not* frail, for example may have a lower risk of waitlist mortality despite the presence of other risk factors such as older age, diabetes or malnutrition. Our data support the integration of objective assessment of frailty in all patients with cirrhosis and lay the foundation for development of effective interventions targeting this potentially modifiable risk factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations:

AI/CD	autoimmune/cholestatic diseases
ALD	alcohol-associated liver disease
CI	confidence interval
HCV	hepatitis C
IQR	interquartile range
LFI	Liver Frailty Index
MELDNa	Model for End-Stage Liver Disease-Sodium
NAFLD	non-alcoholic fatty liver disease
sHR	subhazard ratio

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Lay summary/Key points

Among adult patients with cirrhosis awaiting liver transplant, frailty is more common in those with alcohol-associated liver disease, non-alcoholic fatty liver disease, and ‘other’ aetiologies. We found that frailty was prognostic of mortality on the transplant waitlist regardless of disease aetiology, meaning that it can be applied to all patients with cirrhosis.

TABLE 1

Baseline characteristics of n = 451 frail (Liver Frailty Index ≥ 4.4) liver transplant candidates based on aetiology

		Aetiology					
Characteristics	**All n = 451**	**HCV n = 83 (18%)**	**ALD n = 144 (32%)**	**NAFLD n = 112 (25%)**	**AI/CD n = 55 (12%)**	**Other n = 57 (13%)**	***P*-value**
Age, year	59 (53-64)	59 (54-62)	58 (49-64)	61 (57-65)	57 (44-66)	57 (51-64)	.01
Female	44	43	26	54	78	35	<.001
Race/ethnicity							
Non-Hispanic White	70	62	75	76	55	74	.01
Black	6	7	2	3	15	10	
Hispanic White	19	28	17	15	25	10	
Asian	3	2	4	3	5	4	
Other	2	1	2	3	0	2	
BMI, kg/m^2	28 (25-33)	28 (25-35)	27 (24-31)	31 (27-37)	25 (21-27)	28 (25-33)	<.001
Laboratory tests							
MELDNa	21 (16-25)	22 (16-25)	21 (16-24)	21 (17-24)	19 (15-23)	23 (16-28)	.42
Total Bilirubin, mg/dl	2.5 (1.5-4.7)	2.4 (1.2-4.2)	2.6 (1.5-4.3)	2.5 (1.5-3.9)	3.6 (1.8-8.0)	2.7 (1.2-6.2)	.01
INR	1.4 (1.3-1.7)	1.4 (1.2-1.7)	1.5 (1.3-1.8)	1.4 (1.2-1.6)	1.3 (1.1-1.6)	1.5 (1.4-2.0)	<.001
Creatinine, mg/dl	1.07 (0.8-1.5)	1.1 (0.8-1.9)	1.1 (0.9-1.5)	1.1 (0.8-1.6)	0.9 (0.7-1.2)	1.1 (0.9-1.4)	.004
Sodium, mEq/L	136 (132-139)	136 (132-139)	136 (132-139)	136 (133-139)	137 (133-139)	136 (134-139)	.91
Child Pugh Score	9 (7-10)	8 (7-10)	9 (7-10)	8 (7-10)	8 (8-10)	9 (7-10)	.40
Ascites							
Absent	46	57	40	42	62	42	.02
Mild/moderate	39	35	39	41	33	46	
Severe	15	8	21	17	5	12	
Hepatic encephalopathy							
Absent	67	63	63	71	69	70	.50
Grade ≥ 1	33	37	37	29	31	30	
Albumin, g/dl	3.1 (2.6-3.5)	3.0 (2.6-3.4)	3.1 (2.8-3.6)	3.1 (2.6-3.5)	2.9 (2.5-3.4)	3.0 (2.5-3.4)	.08

Characteristics	All n = 451	Aetiology					*P*-value
		HCV n = 83 (18%)	ALD n = 144 (32%)	NAFLD n = 112 (25%)	AI/CD n = 55 (12%)	Other n = 57 (13%)	
Dialysis	8	12	8	13	4	2	.07
Hypertension	38	41	33	54	31	25	<.001
Diabetes	38	41	24	63	18	44	<.001
Coronary Artery Disease	8	5	7	12	2	11	.14
Outcome							
Died or delisted for being too sick	25	31	23	26	24	21	.25
Deceased donor liver transplantation	36	33	32	41	31	47	
Other	8	22	9	9	9	7	

Note: All continuous variables expressed as median (IQR) or % unless otherwise stated.

TABLE 2

Liver Frailty Index and individual frailty components categorized by cirrhosis aetiology

Measure	All n = 1623	HCV n = 369	ALD n = 469	NAFLD n = 347	AI/CD n = 257	Other n = 181	*P*-value
Liver Frailty Index	4.0 (3.5-4.5)	3.9 (3.4-4.3)	4.0 (3.6-4.5)	4.1 (3.7-4.6)	3.8 (3.3-4.3)	4.0 (3.6-4.6)	<.001
Frailty categories							
Robust (LFI < 3.2)	14	15	12	8	23	15	<.001
Pre-frail (LFI 3.2-4.3)	58	63	58	60	55	53	
Frail (≥ 4.4)	28	22	31	32	21	31	
Individual components							
Grip strength, kg	27 (20-34)	29 (22-37)	28 (22-35)	24 (18-31)	24 (18-34)	24 (18-32)	<.001
Chair stands, number per second	0.4 (0.2-0.5)	0.4 (0.3-0.5)	0.4 (0.2-0.5)	0.3 (0.2-0.4)	0.4 (0.3-0.5)	0.4 (0.2-0.5)	<.001
Balance, seconds	30 (30-30)	30 (30-30)	30 (30-30)	30 (29-30)	30 (30-30)	30 (30-30)	.14
Able to complete all balance tests, %	98	98	98	98	98	99	.90

Note: All continuous variables expressed as median (IQR) or % unless otherwise stated.

TABLE 3

Associations between cirrhosis aetiology and frailty (Liver Frailty Index ≥ 4.4) using univariable and multivariable logistic regression

	Univariable analysis		Multivariable analysis	
Variable	**Odds Ratio, 95% CI**	***P*-value**	**Odds Ratio, 95% CI**	***P*-value**
Cirrhosis aetiology				
HCV	Reference		Reference	
ALD	1.53 (1.12-2.09)	.008	1.40 (1.01-1.94)	.04
NAFLD	1.64 (1.18-2.29)	.003	1.41 (1.00-1.98)	.05
AI/CD	0.94 (0.64-1.38)	.75	1.16 (0.77-1.73)	.48
Other	1.58 (1.06-2.36)	.02	1.59 (1.05-2.40)	.03
Age, per year	1.02 (1.01-1.03)	.001	1.02 (1.01-1.03)	<.001
MELDNa, per 1 unit	1.08 (1.06-1.10)	<.001	1.07 (1.05-1.09)	<.001
Ascites	2.17 (1.74-2.71)	<.001	1.82 (1.45-2.30)	<.001

TABLE 4

Univariable and multivariable associations between frailty, cirrhosis aetiologies, and waitlist mortality

	Univariable analysis		Multivariable analysis	
Variable	**Sub-HR, 95%CI**	***P*-value**	**Sub-HR, 95%CI**	***P*-value**
LFI, per 0.1 unit	1.05 (1.04-1.07)	<.001	1.05 (CI 1.03-1.06)	<.001
Cirrhosis aetiology				
HCV	Reference	Reference	Reference	Reference
ALD	0.83 (0.61-1.15)	.28	0.90 (0.64-1.26)	.55
NAFLD	1.08 (0.79-1.49)	.62	0.96 (0.69-1.32)	.79
AI/CD	0.84 (0.57-1.24)	.38	1.01 (0.66-1.53)	.97
Other	0.76 (0.49-1.17)	.21	0.85 (0.54-1.35)	.50
MELDNa, per 1 unit	1.04 (1.02-1.07)	<.001	1.01 (0.99-1.04)	.30
Albumin, g/dL	0.62 (0.51-0.76)	<.001	0.70 (0.56-0.87)	.002
Dialysis	2.16 (1.43-3.27)	<.001	–	
Ascites	1.23 (0.97-1.55)	.09	–	
Hepatic encephalopathy	1.73 (1.33-2.52)	<.001	1.35 (1.02-1.80)	.04
Age, per year	1.03 (1.02-1.05)	<.001	1.03 (1.01-1.04)	<.001
Female	1.38 (1.09-1.73)	.007	–	
Hispanic race	1.60 (1.24-2.05)	<.001	1.52 (1.17-1.99)	.002
Hypertension	1.23 (0.98-1.56)	.08	–	
Diabetes	1.24 (0.97-1.60)	.08	–	