Duke Activity Status Index and Liver Frailty Index predict mortality in ambulatory patients with advanced chronic liver disease

Williams, Felicity R; Quinlan, Jonathan; Freer, Alice; Morrison, Breanna; Sitch, Alice; Hockey, Florence; Klas, Natasza; Towey, Jennifer; Perera, Thamara P R; Rajoriya, Neil; Lord, Janet M; Armstrong, Matthew J

DOI:
10.1111/apt.17834

Received: 7 June 2023 | First decision: 8 July 2023 | Accepted: 2 December 2023

DOI: 10.1111/apt.17834

AP&T Alimentary Pharmacology & Therapeutics WILEY

Duke Activity Status Index and Liver Frailty Index predict mortality in ambulatory patients with advanced chronic liver disease: A prospective, observational study

Felicity R. Williams[1,2,3] | Jonathan Quinlan[1,2] | Alice Freer[4] | Breanna Morrison[5] | Alice Sitch[1,5] | Florence Hockey[6] | Natasza Klas[6] | Jennifer Towey[4] | Thamara P. R. Perera[3] | Neil Rajoriya[1,3] | Janet M. Lord[1,7] | Matthew J. Armstrong[1,3]

[1]NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK

[2]School of Sports, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

[3]Liver Transplant Unit, Queen Elizabeth University Hospitals Birmingham, Birmingham, UK

[4]Therapies Department, Queen Elizabeth University Hospitals Birmingham, Birmingham, UK

[5]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[6]Medical and Dental School, University of Birmingham, Birmingham, UK

[7]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

Correspondence
Felicity R. Williams and Matthew J. Armstrong, Liver Transplant Unit, Queen Elizabeth University Hospitals Birmingham, 3rd Floor Nuffield House, Mindelsohn Way, Birmingham B15 2TH, UK.
Email: f.williams@bham.ac.uk; mattyarm2010@googlemail.com

Summary

Background: There remains a lack of consensus on how to assess functional exercise capacity and physical frailty in patients with advanced chronic liver disease (CLD) being assessed for liver transplantation (LT). Aim To investigate prospectively the utility of the Duke Activity Status Index (DASI) and Liver Frailty Index (LFI) in ambulatory patients with CLD.

Aim: To investigate prospectively the utility of the Duke Activity Status Index (DASI) and Liver Frailty Index (LFI) in ambulatory patients with CLD.

Methods: We recruited patients from outpatient clinics at University Hospitals Birmingham, UK (2018–2019). We prospectively collated the DASI and LFI to identify the prevalence of, respectively, functional capacity and physical frailty, and to evaluate their accuracy in predicting overall and pre-LT mortality.

Results: We studied 307 patients (57% male; median age 54 years; UKELD 52). Median DASI score was 28.7 (IQR 16.2–50.2), mean LFI was 3.82 (SD = 0.72), and 81% were defined either 'pre-frail' or 'frail'. Female sex and hyponatraemia were significant independent predictors of both DASI and LFI. Age and encephalopathy were significant independent predictors of LFI, while BMI significantly predicted DASI. DASI and LFI were significantly related to overall (HR 0.97, $p = 0.001$ [DASI], HR 2.04, $p = 0.001$ [LFI]) and pre-LT mortality (HR 0.96, $p = 0.02$ [DASI], HR 1.94, $p = 0.04$ [LFI]).

Conclusions: Poor functional exercise capacity and physical frailty are highly prevalent among ambulatory patients with CLD who are being assessed for LT. The DASI and LFI are simple, low-cost tools that predict overall and pre-LT mortality. Implementation of both should be considered in all outpatients with CLD to highlight those who may benefit from targeted nutritional and exercise interventions.

The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Patients with advanced chronic liver disease (CLD) and assessed for liver transplantation (LT) in the current era tend to be sicker, medically more complex and are more often described as 'frail'.[1] This is largely due to an ageing population, increased prevalence of metabolic-related liver disease (i.e., diabetes and obesity) and worsening degree of liver disease severity at the time of presentation. Frailty is a multidimensional clinical state of decreased physiological reserve and increased vulnerability to health stressors.[2] More specifically, physical frailty refers to the functional ability (i.e., functional performance, capacity and disability) of a patient,[1] It is highly prevalent in CLD and is an independent predictor of adverse clinical outcomes in the United States (US).[3] Despite this, objective and reproducible assessments of physical frailty are scarce in Europe, with many clinicians adopting the subjective 'eyeball test' for assessing frailty in LT listing candidates.[4] Consequently, the prevalence of physical frailty remains unknown in non-US countries and still the majority of US states.

The Liver Frailty Index (LFI), by Lai and colleagues,[5] is the most studied tool for physical frailty to date, consisting of three performance-based measures of physical function and strength (hand grip strength, balance and chair stands). LFI is simple, quick (3–5 min), can be carried out in any clinical setting (including outpatient clinic) and is reproducible.[6] In several centres in the United States, the LFI has been shown to predict waiting list mortality, hospitalisation and outcomes post-LT.[7–9] However, it has not been studied or validated outside of the United States. Despite the positive contribution of the LFI to physical frailty assessments, it does not incorporate all aspects of physical frailty, including functional 'exercise' capacity (also referred to as 'aerobic exercise capacity'—the ability to sustain physical activity or endure physiological stress). Measures of functional 'exercise' capacity, such as the six-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET), have proved useful in predicting LT waiting list mortality.[10–12] However, 6MWT is limited in accuracy, practicability and the 'learning effect'. Although more accurate, CPET requires costly equipment, specifically trained staff and can be uncomfortable for patients with CLD, especially those with ascites. The Duke Activity Status Index (DASI) is a quick, self-reported 12-item physical activity questionnaire which correlates well with gold-standard assessments of functional capacity (CPET) in patients with chronic cardiorespiratory diseases.[13–16] Furthermore, the DASI was able to predict adverse outcomes (30-day mortality, myocardial infarction and one-year new disability) over and above that of CPET and serological tests in 1401 patients undergoing major non-cardiac surgery.[17] In view of these results, the ease of assessment and the cost-savings of completion; the investigation of the validity of DASI, alongside the LFI, warrants investigation in patients with CLD.

Simple and accurate assessment of a patient's physiological reserve and ability to cope with the physical stressors (i.e., LT, radiological interventions) remain key in CLD. Therefore, the aim of this prospective, observational UK study was to determine the prevalence, severity and predictors of physical frailty in outpatients with CLD and assessed for LT, in addition to investigating the ability of the DASI (functional exercise capacity) and LFI (physical frailty) to predict all-cause mortality, pre-LT list mortality and intensive care unit (ICU) length of stay.

2 | METHODS

2.1 | Study overview and population

A single-centre, prospective observational cohort study was conducted at the LT Unit, Queen Elizabeth University Hospital Birmingham (QEUHB), UK. A service quality improvement audit code (ID: 15209) was obtained from QEUHB clinical governance and ethics department in 2018. Between 1 September 2018 and 1 September 2019, adult patients (≥18 years) with CLD were consecutively recruited from the liver outpatient assessment clinic at QEUHB. The term CLD incorporated all UK indications for LT, including decompensated cirrhosis (all aetiologies), >2 cm single and/or multiple hepatocellular carcinoma (HCC) with cirrhosis/portal hypertension (Milan criteria), non-cirrhotic portal hypertension (i.e., refractory ascites, varices) and other 'variant' indications (refractory recurrent cholangitis, polycystic liver disease). Outpatients were excluded if they were unable to give written consent or unable to complete one or more of the tests, because they required urgent hospital admission for acute illness, severe hepatic encephalopathy (grade ≥3 or 4) or an acute musculoskeletal injury impeding completion of one or more elements of the tests. All patients with grade 1 or 2 hepatic encephalopathy underwent two independent capacity assessments (MA, NR) prior to written informed consent. Those who lacked capacity to consent were excluded from the study.

2.2 | Study procedures

In addition to the routine outpatient clinic visit procedures, study participants were asked to complete the DASI questionnaire and the LFI under the supervision of trained personnel (e.g., physiotherapist [F.W., A.F.] or an exercise physiologist [JQ]). The DASI and LFI results were concealed from the participants and clinicians in order to avoid study potential influence on intervention, donor organ allocation and/or LT waiting list status. Assistance in the form of reading the DASI questions and circling the answer, from either study personnel or the caregiver/translator, was given for those who were unable to independently complete the questionnaire (i.e., English was not their first language). Study personnel, patients and caregivers were encouraged to ensure that the answers were provided by the patient alone. The self-reported DASI questionnaire consists of 12 questions related to functional capacity (i.e., can you climb a flight of stairs?) and is scored from 0 to 58.2, with the latter representing the highest functional status (Figure S1). The DASI score was converted into an estimated VO_2 peak using the following equation: VO_2 peak (mL/kg) = 0.43

x DASI +9.6.[17] Physical frailty was measured using the LFI,[5] whereby every patient was asked to complete the following three performance-based measures:

1. *Gender-adjusted hand grip strength (HGS)*: The participant was asked to stand up straight with their dominant arm straight down by their side holding the hand dynamometer (Takei, 5401 GRIP-D). The participant was instructed to squeeze the dynamometer as hard as they could for 5 s. HGS was repeated three times (1-min rest between each test) and the average recorded. The HGS was adjusted for gender, as per LFI recommendations.
2. *Timed 5 × chair stands*: Using the same chair and with the patient folding their arms across their chest, the number of seconds required to complete 5 chair stands was recorded.
3. *Balance testing*: The participant was asked to adopt three balance positions (feet together, semi tandem and tandem), and the time that each three positions were held was recorded, up to a maximum of 10 s for each position.

The results of each test were inputted into the online LFI calculator available at http://liverfrailtyindex.ucsf.edu, where a continuous score was provided and the patient categorised as robust (score < 3.2), pre-frail (score = 3.2–4.5) or frail (score > 4.5). The LFI scores for all participants were plotted against the scores provided by the US cohort[5] for comparison of levels of physical frailty between the continents.

2.3 | Data collection

Demographic data were prospectively collected from the patient's electronic health records and laboratory blood sampling (full blood count, urea and electrolytes, liver function tests, international normalised ratio [INR]) on the same day of their clinic visit and completion of the DASI and LFI. Disease aetiology, severity (Model for End-stage Liver Disease [MELD], UK Model for End-stage Liver Disease [UKELD], history of variceal bleed, hepatic encephalopathy, ascites) and key medical comorbidities (i.e., ischaemic heart disease, atrial fibrillation, type 2 diabetes, hypertension and smoking history) were recorded. Body mass index (BMI) was calculated based on the participants estimated dry total body weight, which was corrected for the presence of ascites (minus 5% for mild, 10% for moderate, and 15% for severe ascites) and peripheral oedema (minus 5% for bilateral oedema).[18] Participants were prospectively followed up until the censor date of the study on 31 May 2020, with regard to overall mortality, pre-LT mortality and post-LT ICU length.

2.4 | Statistical analysis

Participant demographics were presented as mean (SD), median (IQR) and number (%) depending on the variable. Single and multiple regression analysis were run between DASI and LFI with other patient variables (UKELD, MELD, age, sex, BMI, diabetes, variceal bleed, ascites, hepatic encephalopathy, sodium, creatinine, bilirubin, INR, white blood cells and neutrophil-to-lymphocyte ratio). Note UKELD and MELD were omitted from the multiple regression analysis due to a 0.8 correlation between those variables and the involvement of identical variables already in the regression model. Due to skewness of the DASI for the regression analysis, the log of DASI (+1 to account for 0 scores) was used for the outcome variable. Coefficients were then back-transformed for the regression models. Regression analysis was also used to compare LFI (and its individual components) between patients with and without cirrhosis and sex (male vs. female). Of note, balance (one component of LFI) was excluded from the comparison of the above groups due to minimum variability in that measure (89% had a perfect score of 30/30).

Pre-LT mortality was defined as the outcome of 'death' whilst on the waiting list for LT. Follow-up time for those who did not die or receive a LT was censored on 31 May 2020. Survival analysis for those listed for LT was calculated using Cox Proportional Hazards Model. Kaplan Meier curves for the Cox Survival models were looked at for any proportional hazards assumption violations. ICU length of stay was defined as the time (days) from admission to ICU to the time of discharge to the ward for those who underwent a LT. Cox Survival analysis was used to calculate the relationship between LFI and ICU length of stay, as well as DASI and ICU length of stay. There was no need to adjust for competing risks in this model as there were no deaths during an ICU stay. The level of significance for all the tests stated above was set at $p < 0.05$.

3 | RESULTS

3.1 | Patient recruitment

A total of 307 patients with CLD were recruited from the LT outpatient assessment clinic at QEUHB over the 12-month study period. Of the 307 patients who underwent LT assessment, 255 (83.1%) were placed on the LT waiting list and 52 (16.9%) were not listed (Figure 1). Reasons for not being listed for LT included too high risk (i.e., cardiac and risk of alcohol relapse; 75%), no active/current LT indication (19%) and progression of HCC outside of criteria (6%).

3.2 | Patient demographics

Fifty-seven per cent (175/307) participants were male, median age was 54 (inter quartile range [IQR] 45–61) years. and median dry BMI was 27.8 kg/m^2 (IQR 24–33). The median UKELD score was 52 (IQR 49–55), and the most prevalent CLD disease aetiology was alcohol-related liver disease (ArLD) at 34% (103/307). Decompensated cirrhosis was the main indication for LT assessment in 78% (238/307; of whom 103/238 [43%] were ArLD and 52/238 [22%] were NAFLD),

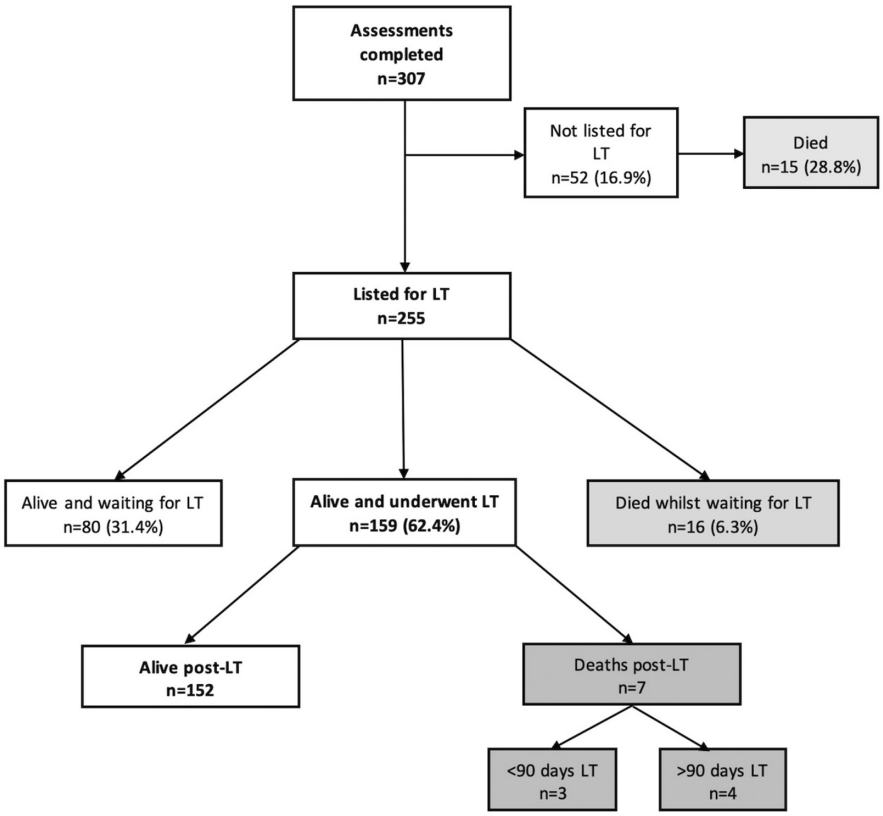

FIGURE 1 Flow diagram of patient journey.

with the remaining 22% assessed for recurrent cholangitis ($n=21$), polycystic liver disease ($n=14$), HCC ($n=9$; compensated viral B or C hepatitis cirrhosis), LT graft failure ($n=5$) and other ($n=15$; i.e., non-cirrhotic portal hypertension, cystic fibrosis and glycogen storage disease). Thirty-eight per cent (117/307) of all participants had grade I-II (west-haven[19]) hepatic encephalopathy and 42% (129/307) had ascites requiring diuretics and/or abdominal paracentesis. The most common medical comorbidities included central obesity (37%), hypertension (26%) and type 2 diabetes (25%), with 27% (81/307) of the cohort having two or more metabolic risk factors (Table 1).

3.3 | Clinical outcomes

The median length of study follow-up from recruitment was 460 (IQR 265–551) days. Of those listed for LT, 159/255 (62.4%) underwent LT in the study time frame, whilst 80/255 (31.4%) were alive and still on the LT waiting list (Figure 1). Sixteen (6.3%) patients died on the LT waiting list (pre-LT), with the cause of deaths being primarily liver-related ($n=6$) and non-liver-related ($n=10$, including; COVID-19, infection/sepsis, other organ failure). The median length of follow-up post-LT was 354 (IQR 247–453) days, with a median length of stay in ICU, and in hospital, post-LT was 2 (IQR 1–5) and 12 (IQR 9–18) days, respectively. There was a total of seven (4.4%) deaths post-LT, two within 30 days (1× intraoperative haemorrhage, 1× sepsis and multi-organ failure), one within 90 days (cause unknown) and four post-90 days ($n=2$ COVID-19, $n=2$ cancer). Thirty-day and 90-day post-LT mortality were 1.3% (2/159) and 1.9% (3/159), respectively.

3.4 | Prevalence and predictors of poor functional 'exercise' capacity (DASI)

At the study baseline, the median DASI score and estimated VO_2 Peak were 28.7 (IQR 16.2–50.2) and 21.9 mL/kg/min (IQR 16.6–31.2), respectively. The DASI significantly correlated with LFI ($r=-0.62$; $p<0.001$), in that the lower the DASI (lower functional capacity) the higher the LFI (frailer; Figure S2). In single regression analysis, female sex ($B=0.811$, 95% CI = 0.694 to 0.946, $p=0.008$), dry BMI ($B=0.984$, 95% CI = 0.972–0.996, $p=0.008$), ascites ($B=0.807$, 95% CI = 0.690–0.943, $p=0.007$), hepatic encephalopathy (B = 0.834, 95% CI = 0.710–0.979, $p=0.027$) and sodium ($B=1.028$, 95% CI = 1.009–1.047, $p=0.004$) were significantly associated with lower DASI scores (lower functional capacity). However, in multiple regression analysis only female sex ($B=0.739$, 95% CI = 0.63–0.868, $p<0.001$), BMI ($B=0.981$, 95% CI = 0.969–0.995, $p=0.006$) and sodium ($B=1.025$, 95% CI = 1.005–1.047, $p=0.017$) were independent predictors of low DASI scores (adjusted $R^2=0.09$; Table 2).

3.5 | Prevalence and predictors of physical frailty

At the study baseline, the mean LFI score was 3.82 (SD = 0.72), with 19% (59/307) classified as robust, 65% (201/307) pre-frail and 15% (47/307) frail, which was similar to that presented by the US group in 2017[5] (Figure 2). Single regression analysis showed that age (regression coefficient, $B=0.012$, 95% CI = 0.006–0.018,

TABLE 1 Characteristics of study cohort overall and by level of physical frailty (based on LFI).

Characteristic	Overall (*n* = 307)	Frail (*n* = 47)	Pre-frail (*n* = 201)	Robust (*n* = 59)
Sex (male)	175 (57%)	26 (55%)	107 (53%)	42 (71%)
Age (years)	54 (45, 61)	57 (52, 61)	55 (45, 62)	48 (36, 56)
BMI kg/m^2	27.8 (24, 33)	31 (26, 34)	28 (24, 34)	26 (24, 30)
BMI >30 kg/m^2	114 (37%)	24 (51%)	74 (37%)	16 (27%)
Aetiology				
ArLD	103 (34%)	25 (53%)	67 (33%)	11 (19%)
NAFLD	52 (17%)	10 (21%)	31 (15%)	11 (19%)
Immune (AIH, PSC, PBC)	69 (22%)	7 (15%)	45 (22%)	17 (29%)
HCC	19 (6%)	0 (0%)	13 (7%)	6 (10%)
Other	64 (21%)	5 (11%)	45 (22%)	14 (24%)
Severity of liver disease				
Cirrhosis	239 (78%)	42 (89%)	160 (80%)	37 (63%)
UKELD	52 (49, 55)	52 (50, 55)	52 (49, 55)	51 (47, 54)
MELD	13 (9, 16)	11 (10, 16)	13 (9, 16)	13 (9, 15)
Variceal haemorrhage	48 (16%)	6 (13%)	33 (16%)	9 (15%)
Hepatic encephalopathy	117 (38%)	26 (55%)	77 (38%)	14 (24%)
Ascites	129 (42%)	27 (57%)	90 (48%)	12 (20%)
Comorbidities				
Hypertension	79 (26%)	9 (19%)	61 (30%)	9 (15%)
Type 2 diabetes	78 (25%)	11 (23%)	57 (28%)	11 (19%)
Atrial Fibrillation	8 (3%)	2 (4%)	6 (3%)	0 (0%)
Ischaemic heart disease	4 (1%)	1 (2%)	3 (2%)	0 (0%)
≥2 metabolic components	82 (27%)	11 (23%)	63 (31%)	8 (14%)
Smoking history				
Non-smoker	184 (60%)	26 (55%)	117 (58%)	41 (69%)
Ex-smoker	107 (35%)	18 (38%)	74 (37%)	15 (25%)
Current smoker	16 (5%)	3 (6%)	10 (5%)	3 (5%)
Physical frailty				
LFI[a]	3.82 (0.72)	4.95 (0.39)	3.85 (0.36)	2.83 (0.37)
DASI (scale 0–58)[b]	28.7 (16.2, 50.2)	15 (10, 21)	29 (18, 43)	51 (38, 58)
Outcomes				
Overall death	38 (12%)	7 (15%)	29 (14%)	2 (3%)
Underwent LT	159 (52%)	15 (32%)	111 (55%)	33 (56%)
ICU length of stay (days)	2.0 (1.0, 5.0)	3.0 (2.5, 5.0)	2.0 (2.0, 5.0)	2.0 (1.0, 5.0)
Hospital length of stay (days)	12 (9, 18)	9 (8, 16)	12 (9, 18)	11 (9, 19)

Note: Data expressed as *n* (%), mean (SD) or median (interquartile range).

Abbreviations: AIH, autoimmune hepatitis; ArLD, alcohol-related liver disease; BMI, body mass index; DASI, Duke Activity Status Index; HCC, hepatocellular carcinoma; ICU, intensive care unit; LFI, Liver Frailty Index; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcohol-related liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

[a]High = more frail.

[b]Low = worse functional capacity.

$p < 0.001$), hepatic encephalopathy ($B = 0.386$, 95% CI = 0.224–0.548, $p < 0.001$), ascites ($B = 0.274$, 95% CI 0.112–0.435, $p = 0.001$), sodium ($B = -0.047$, 95% CI −0.066 to −0.027, $p < 0.001$), INR ($B = 0.306$, 95% CI = 0.069–0.543, $p = 0.012$), UKELD ($B = 0.023$, 95% CI 0.005–0.04, $p = 0.01$) and the presence of cirrhosis ($B = 0.279$, 95% CI = 0.086–0.473, $p = 0.005$)

TABLE 2 Unadjusted and adjusted regressions of LFI in patients assessed for a LT.

Variable	Univariate coefficient (95% CI)	*p*-value	Multivariate coefficient (95% CI)	*p*-value
Age	0.012 (0.006–0.018)	<0.001[a]	0.009 (0.002–0.015)	0.008[a]
Female sex	0.154 (−0.01–0.318)	0.065	0.275 (0.114–0.437)	0.001[a]
Dry BMI	0.01 (−0.003–0.023)	0.116	0.001 (−0.012–0.014)	0.871
UKELD	0.023 (0.005–0.04)	0.01[a]	–	–
MELD	0.008 (−0.01 to 0.027)	0.373	–	–
Cirrhosis	0.279 (0.086–0.473)	0.005[a]	0 (−0.224 to 0.224)	1.00
Ascites	0.274 (−0.112–0.435)	0.001[a]	0.038 (−0.144 to 0.219)	0.683
Hepatic encephalopathy	0.386 (0.224–0.548)	<0.001[a]	0.275 (0.094–0.456)	0.003[a]
Diabetes	0.128 (−0.06 to 0.317)	0.188	−0.011 (−0.197 to 0.175)	0.907
Significant varices	0.025 (−0.197–0.248)	0.823	−0.047 (−0.261 to 0.167)	0.667
Sodium	−0.047 (−0.066 to −0.027)	<0.001[a]	−0.041 (−0.063 to −0.02)	<0.001[a]
Creatinine	0 (−0.001–0.001)	0.359	0 (−0.001–0.001)	0.664
Bilirubin	0 (−0.001 to 0.001)	0.89	−0.001 (−0.003 to 0)	0.077
INR	0.306 (0.069–0.543)	0.012[a]	0.221 (−0.033 to 0.475)	0.088
WBC	0.013 (−0.021 to 0.047)	0.456	0.011 (−0.024 to 0.046)	0.528
NLR	0.005 (−0.013–0.023)	0.578	−0.001 (−0.019 to 0.016)	0.865

Note: Due to the inclusion of identical variables, MELD and UKELD were not included in the multivariate analysis.

Shaded area represent statistical significance.

[a]Significant variable.

Abbreviations: BMI, body mass index; CI, confidence interval; INR, international normalised ration; LFI, Liver Frailty Index; MELD, model for end-stage liver disease; NLR, neutrophil-to-lymphocyte ratio; UKELD, UK model for end-stage liver disease; WBC, white blood cell count.

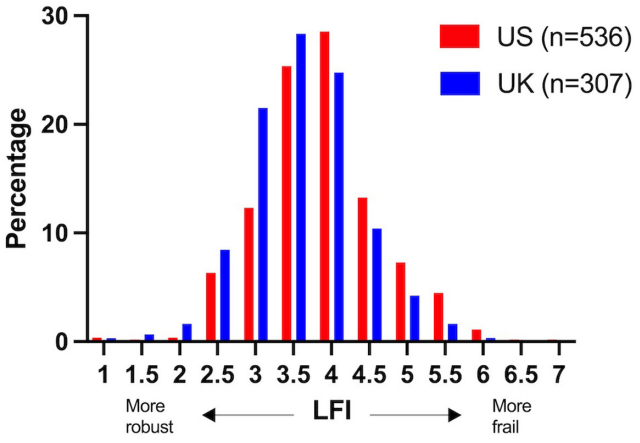

FIGURE 2 Comparison of Liver Frailty Index (LFI) scores from a UK and US dataset*. *US dataset taken from Lai et al. ([5]).

were all significantly associated with a higher LFI (i.e., increased physical frailty). In multiple regression analysis, age ($B=0.009$, 95% CI = 0.002–0.015, $p=0.008$), female sex ($B=0.275$, 95% CI = 0.114–0.437, $p=0.001$), hepatic encephalopathy ($B=0.275$, 95% CI = 0.094–0.456, $p=0.003$) and sodium ($B=-0.041$, 95% CI = −0.063 to −0.02, $p<0.001$) were independent predictors of high LFI (adjusted $R^2=0.15$; Table 3). Additionally, individual components of the LFI (chair stands and hand grip strength) were analysed against variables of interest including sex and the presence or absence of cirrhosis. Females and those with cirrhosis were significantly slower at performing five chair stands than males and those without cirrhosis (0.38 vs. 0.43 chair stands per second (cs/s), $p=0.046$ and 0.39 vs. 0.47 cs/s, $p=0.005$), respectively. Not surprisingly, females had significant lower hand grip strength than males (20.8 vs. 34.2 kg, $p<0.001$), which were subsequently gender-adjusted for LFI calculation. Analysis for balance was not reasonable as 89% of all participants scored the maximal 30/30 (i.e., 30 s total balance).

3.6 | Predictors of overall and pre-LT mortality

The overall mortality for the study population was 12.4% (38/307). Both DASI (HR = 0.97, 95% CI 0.95–0.99, $p=0.001$) and LFI (HR = 2.04, 95% CI 1.31–3.16, $p=0.001$) were significantly related to overall mortality (concordance = 0.68 [DASI], 0.64 [LFI]; Figure 3). When UKELD is added to the models, both DASI (HR = 0.97, 95% CI 0.95–0.99, $p=0.002$) and LFI (HR = 1.94, 95% CI 1.24–3.03, $p=0.004$) and remained significant predictors of all-cause mortality, with marginal improvements in concordance (0.73 for DASI + UKELD and 0.70 for LFI + UKELD; Table 4).

6.3% (16/255) of participants died pre-LT. Again, both DASI (HR = 0.96, 95% CI = 0.93–0.99, $p=0.020$) and LFI (HR = 1.94, 95% CI = 1.03–3.68, $p=0.04$) predicted pre-LT mortality (Table 4, Figure 4). When the UKELD was added to the models the DASI (HR = 0.96, 95% CI = 0.93–1.00, $p=0.037$) remained significant, with a concordance of 0.85, whilst the LFI (HR = 1.68, 95% CI = 0.93–3.05, $p=0.088$) was insignificant (concordance 0.80).

TABLE 3 Unadjusted and adjusted regression of DASI in patients assessed for a LT.

Variable	Univariate coefficient (95% CI)	*p*-value	Multivariate coefficient (95% CI)	*p*-value
Age	0.996 (0.99–1.002)	0.185	1 (0.993–1.006)	0.945
Female sex	0.811 (0.694–0.946)	0.008[a]	0.739 (0.63–0.868)	<0.001[a]
BMI	0.984 (0.972–0.996)	0.008[a]	0.981 (0.969–0.995)	0.006[a]
UKELD	0.988 (0.972–1.005)	0.165	—	—
MELD	0.995 (0.977–1.012)	0.556	—	—
Cirrhosis	0.888 (0.735–1.012)	0.212	1.025 (0.822–1.279)	0.824
Ascites	0.807 (0.69–0.943)	0.007[a]	0.879 (0.735–1.052)	0.159
Hepatic encephalopathy	0.834 (0.71–0.979)	0.027[a]	0.942 (0.787–1.125)	0.507
Diabetes	0.944 (0.787–1.132)	0.531	1.033 (0.857–1.244)	0.732
Significant varices	0.906 (0.732–1.12)	0.357	0.891 (0.722–1.102)	0.288
Sodium	1.028 (1.009–1.047)	0.004[a]	1.025 (1.005–1.047)	0.017[a]
Creatinine	1 (0.999–1.001)	0.903	1 (0.999–1.001)	0.711
Bilirubin	1 (0.998–1.001)	0.583	1.001 (0.999–1.002)	0.256
INR	0.874 (0.689–1.108)	0.266	0.943 (0.734–1.23)	0.662
WBC	0.968 (0.936–1)	0.05	0.967 (0.933–1.002)	0.063
NLR	0.988 (0.972–1.005)	0.166	0.997 (0.98–1.014)	0.721

Note: Due to the inclusion of identical variables, MELD and UKELD were not included in the multivariate analysis. Also, since DASI was log transformed and the coefficients above have been transformed back these represent a per cent increase rather than a point increase.

Abbreviations: BMI, body mass index; DASI, Duke Activity Status Index; INR, international normalised ratio; MELD, model for end-stage liver disease; NLR, neutrophil-to-lymphocyte ratio; UKELD, UK model for end-stage liver disease; WBC, white blood cell count.

Shaded area represent statistical significance.

[a]Significant variable.

3.7 | Predictors of ICU length of stay

Neither LFI (HR = 0.84, 95% CI = 0.66–1.07, $p = 0.157$) nor DASI (HR = 1.00, 95% CI = 1.00–1.01, $p = 0.405$) were significantly related to ICU length of stay, which remained insignificant when UKELD was added to the model (HR 0.85 [LFI] and 1.00 [DASI], $p > 0.05$ in both models; Table 4).

4 | DISCUSSION

Our prospective, single-centre UK study highlights that both poor functional exercise capacity and physical frailty, as determined by simple easy-to-use tools of the DASI and LFI, are common in ambulatory patients with CLD; with only 19% of patients defined as 'robust' in a tertiary liver outpatient unit. Furthermore, both DASI and LFI predicted both pre-LT and overall 'all-cause' mortality. Both female sex and hyponatraemia were independent predictors of both poor functional capacity (low DASI) and physical frailty (high LFI). In addition, older age and hepatic encephalopathy predicted physical frailty, whilst high BMI predicted poor functional capacity. Understanding and identifying those patients with CLD who are at higher risk of poor functional capacity, physical frailty and subsequent mortality, will aid with targeting and tailoring future prehabilitation programmes (nutrition, exercise, psychology).

In outpatient liver departments, in which time and space can be limited, evaluation of functional exercise capacity has remained a challenge in patients with CLD. Our study is the first to investigate the utility of the DASI questionnaire in this patient population. Not only is the DASI questionnaire user-friendly, cost-effective, time-efficient (<2 min), but also it provides a simpler alternative to either the 6MWT or CPET, in predicting all-cause and pre-LT mortality. Whilst the DASI questionnaire is limited by its patient subjectivity, it has previously been shown to correlate well with the gold-standard measure of CPET, in patients with chronic cardiorespiratory diseases and those undergoing non-cardiac surgery.[13–16] Similar to our findings in patients with CLD, Wijeysundera et al.[17] highlighted in 1401 patients undergoing major non-cardiac surgery (excluding LT surgery) that the DASI was able to predict 30-day and 1-year survival. Similarly, Ney and colleagues (2016) performed a meta-analysis of CPET in 1107 patients and highlighted that functional capacity (i.e., weighted mean VO_2 peak) was below the threshold required for independent living in CLD and was associated with pre-and post-LT survival.[12] Despite these significant findings, the use of CPET in CLD and the LT setting is not uniform throughout Europe and the United States, largely as a result of cost, specialist equipment, workforce requirement and perception that the logistical burden of CPET outweighs the additional information provided to guide patient care.[4] Based on our findings, the DASI may be utilised as a quick, cheap screening tool in liver outpatients to determine which patients with

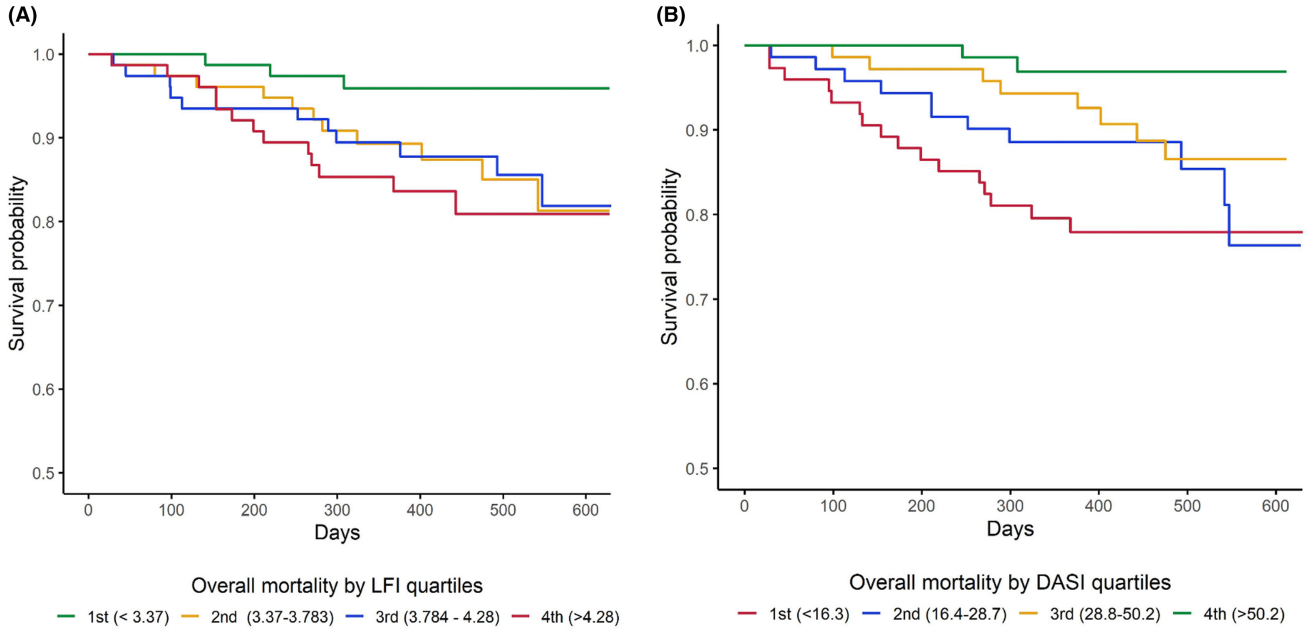

FIGURE 3 Overall mortality (A) Overall mortality by Liver Frailty Index (LFI) quartiles. The lower the LFI the more 'robust' and the higher the LFI the more 'frail'. (B) Overall mortality by Duke Activity Status Index (DASI) quartile. The lower the DASI score the lower the functional capacity and the higher the DASI the greater the functional capacity.

TABLE 4 Cox survival models with LFI or DASI: Overall mortality, waiting list mortality and ICU length of stay.

	Overall mortality			Waiting list mortality			ICU length of stay		
Variable	HR (95% CI)	*p*-value	Concordance	HR (95% CI)	*p*-value	Concordance	HR (95% CI)	*p*-value	Concordance
LFI	2.04 (1.31–3.16)	0.001	0.64	1.94 (1.03–3.68)	0.042	0.63	0.84 (0.66–1.07)	0.157	0.59
LFI + UKELD	1.94 (1.24–3.03) (LFI)	0.004	0.70	1.68 (0.93–3.05) (LFI)	0.088	0.80	0.85 (0.66–1.09) (LFI)	0.193	0.60
	1.1 (1.03–1.18) (UKELD)	0.004	—	1.31 (1.17–1.47) (UKELD)	<0.001	—	0.99 (0.96–1.03) (UKELD)	0.71	—
DASI	0.97 (0.95–0.99)	0.001	0.68	0.96 (0.93–0.99)	0.020	0.73	1.00 (1.00–1.01)	0.405	0.56
DASI+UKELD	0.97 (0.95–0.99) (DASI)	0.002	0.73	0.96 (0.93–1.00) (DASI)	0.037	0.85	1.00 (0.99–1.01) (DASI)	0.446	0.59
	1.09 (1.03–1.17) (UKELD)	0.005	—	1.29 (1.16–1.44) (UKELD)	<0.001	—	0.99 (0.96–1.02) (UKELD)	0.554	—

Abbreviations: CI, confidence interval; DASI, Duke Activity Status Index; HR, hazard ratio; ICU, intensive care unit; LFI, Liver Frailty Index; UKELD = UK model for end-stage liver disease.

CLD need more intricate analysis and individualised prehabilitation prior to radiological procedures and/or LT. In the era of virtual 'clinic' monitoring, the DASI could be completed by the patient at home and reported back to the specialist hospital team.

The prevalence of physical frailty within our UK-based study and its ability to predict mortality is similar to that reported by Lai and colleagues in the United States (Figure 2),[5,7] thereby further validating the use of LFI in ambulatory patients with CLD. Most notably, in our study, female sex was a predictor of both poor functional capacity and physical frailty. In particular, females performed significantly worse on the gender-adjusted hand grip strength and chair stand components of the LFI. This finding is supported by a multicentre cohort US study (2020) of 1405 patients with cirrhosis waiting for LT, in which females presented with worse physical frailty scores despite similar liver disease severity. Moreover in the US study, physical frailty accounted for 13% of the known gender gap in pre-LT mortality.[20] Socioeconomic status and/or sociocultural experiences may contribute to the gender variations seen in physical frailty, in addition to the more widely recognised physical differences, such as biological or genetic factors.[21] These findings are important, because unlike factors such as liver disease severity and age, physical frailty is a potentially modifiable contributor of pre-LT mortality.[22] In addition to female sex and age, key clinical determinants of the severity of liver failure (including hyponatraemia, hepatic encephalopathy, ascites and UKELD) were all significant predictors of increased physical frailty in our cohort. In addition, patients with cirrhosis performed

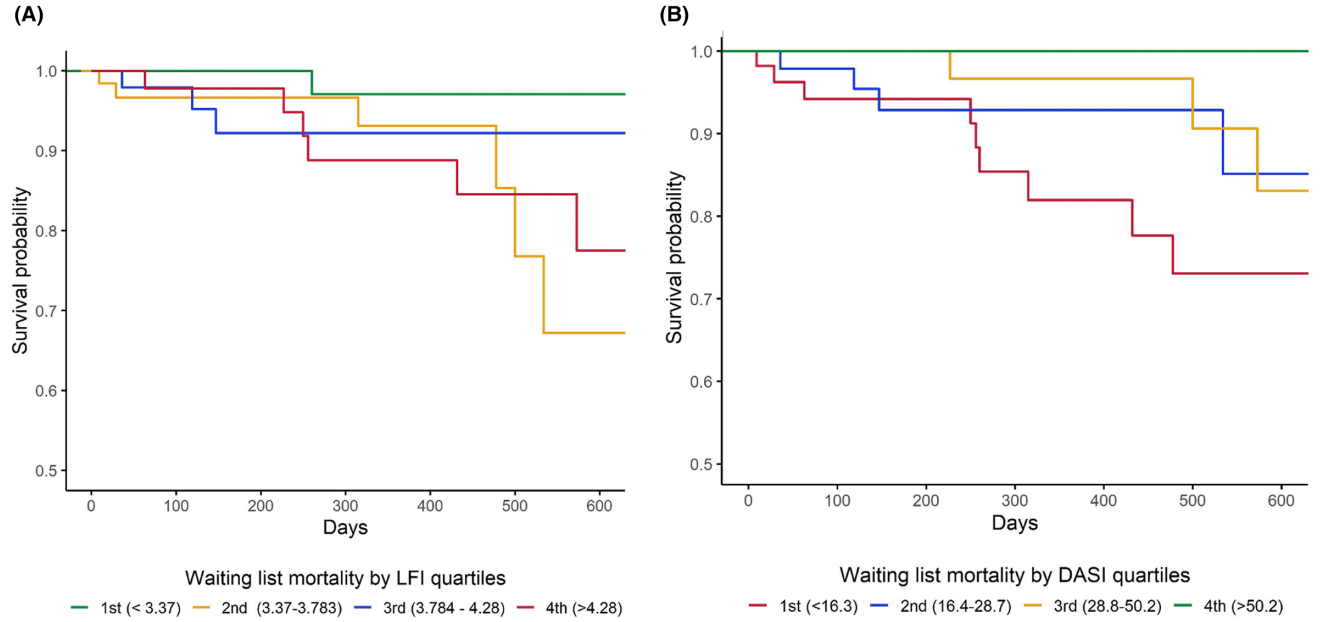

FIGURE 4 Pre-LT mortality (A) Pre-LT mortality by Liver Frailty Index (LFI) quartiles. The lower the LFI the more 'robust' and the higher the LFI the 'frailer'. (B) Pre-LT mortality by Duke Activity Status Index (DASI) quartile. The lower the DASI score the lower the functional capacity.

significantly worse in the physical frailty subscale chair stands than those with non-cirrhotic disease aetiologies, such as severe recurrent cholangitis (e.g., PSC). These findings may be explained by the multiple mechanisms driving physical frailty in cirrhosis (i.e., chronic inflammation, 'accelerated starvation' state/malnutrition and hyperammonaemia),[23] which ultimately result in disruption of the maintenance of muscle health.

Hepatic encephalopathy and ascites are the two most common debilitating complications of CLD,[24,25] with both being strongly associated with poor functional capacity and frailty in our study. Due to reduced hepatic function and/or portal systemic shunting those with hepatic encephalopathy have higher levels of circulating ammonia,[19] which directly upregulates myostatin (i.e., increases muscle protein breakdown)[26,27] and increases mitochondrial dysfunction.[28] Patients with ascites, as highlighted by our study, are particular susceptible to physical frailty due to reduced appetite, early satiety, delayed gut motility[29] and subsequent decreased calorie intake; all of which exacerbate the state of 'accelerated starvation' (impaired hepatic glycogen stores) found in cirrhosis.[23] Both hepatic encephalopathy and ascites should therefore be optimised in the ambulatory setting (i.e., medications and easy-to-access paracentesis), in parallel to prehabilitation programmes (nutrition/exercise), in order to minimise physical frailty and functional decline in patients with CLD.

Our study has several strengths and limitations. Primarily, this is the first study to investigate the predictive ability of the DASI questionnaire on overall and pre-LT mortality in patients with CLD and assessed for LT. Subsequently, the DASI provides clinicians with a time and cost-effective alternative to CPET to identify those most at risk and/or potentially require further in-depth investigation of their functional status. In addition, even though LFI has been assessed in several states in the United States, this is the first non-US study to validate its utility in European outpatient units. The findings highlight the pressing need for other liver centres to validate and consider incorporating these simple and cheap measures within outpatient clinics that manage CLD and assess for LT. Another strength is that in 2018–2020, both DASI and LFI were not part of the routine outpatient assessment or monitoring of CLD at our study centre. Therefore, by *blinding* the patient's clinician/multidisciplinary teams to the DASI and LFI findings, it mitigated any potential selection bias pre-LT.

The limitations are largely due to the fact that the data collection ran in parallel to routine 'real-world' clinical practice. Firstly, our findings are only applicable to patients in the ambulatory setting and can't be extrapolated to hospitalised patients with CLD. Secondly, the functional/frailty assessments only represent a cross-sectional 'snapshot' of the patient, rather than serial measures overtime to enable observation of dynamic changes. Thirdly, our study recruitment likely underrepresents patients with HCC (6% of study cohort), as 19% of all UK registrations for liver transplantation had HCC during the same time period (NHSBT 2018/2019 annual report). Fourthly, patients with CLD were recruited from a tertiary care LT assessment unit and may not be a true reflection of patients with CLD in the community or non-specialist centres, as a result of referrers' selection bias. Interestingly, both DASI and LFI remained significant in predicting pre-LT waiting list mortality, despite the limitation that subjectively the 'frailest' may have been deemed ('eyeball test') too high risk at the time of LT assessment. Concerns regarding selection bias were mitigated with overall mortality, which included all patients who died after LT assessment, on the pre-LT waiting list,

or post-LT. Throughout the study, patients continued to receive the standard of care guidance for nutrition and physical activity[18]; however, the study was unable to control for potential varying degrees of healthcare intervention. If anything, those who were subjectively perceived to be the frailest or functionally dependent would likely have received the most healthcare intervention, yet still the baseline DASI and LFI predicted poor clinical outcomes.

5 | CONCLUSION

In conclusion, poor functional exercise capacity and physical frailty are highly prevalent in UK ambulatory patients with CLD, assessed for LT. Both DASI and LFI predict pre-LT and overall mortality. Female sex and hyponatraemia, in particular, are significant predictors for both poor functional capacity and physical frailty. Both the DASI and LFI, which measure different aspects of physiological reserve, should be utilised in ambulatory patients with CLD, in order to target and individualise exercise/nutritional interventions.

AUTHOR CONTRIBUTIONS

Felicity R. Williams: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Jonathan Quinlan:** Data curation; investigation; writing – review and editing. **Alice Freer:** Data curation; investigation; writing – review and editing. **Jennifer Towey:** Data curation; investigation; writing – review and editing. **Breanna Morrison:** Formal analysis; writing – review and editing. **Alice Sitch:** Formal analysis; writing – review and editing. **Thamara P. R. Perera:** Methodology; supervision; writing – review and editing. **Neil Rajoriya:** Supervision; writing – review and editing. **Janet M. Lord:** Supervision; writing – original draft; writing – review and editing. **Matthew J. Armstrong:** Conceptualization; data curation; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing.

ACKNOWLEDGEMENTS

Declaration of personal interests: The authors of this paper have no conflicts of interest to declare.

AUTHORSHIP

Guarantor of the article: Matthew J. Armstrong.

ORCID

Felicity R. Williams https://orcid.org/0000-0001-5189-4073
Jonathan Quinlan https://orcid.org/0000-0002-1205-7069
Matthew J. Armstrong https://orcid.org/0000-0002-3425-1161

REFERENCES

1. Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, et al. Frailty in liver transplantation: an expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. Am J Transplant. 2019;19(7):1896–906.
2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
3. Kardashian A, Ge J, McCulloch CE, Kappus MR, Dunn MA, Duarte-Rojo A, et al. Identifying an optimal liver frailty index cutoff to predict waitlist mortality in liver transplant candidates. Hepatology. 2020;73:1132–9.
4. Williams FR, Milliken D, Lai JC, Armstrong MJ. Assessment of the frail patient with end-stage liver disease: a practical overview of sarcopenia, physical function, and disability. Hepatol Commun. 2021;5(6):923–37.
5. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66(2):564–74.
6. Wang CW, Lebsack A, Chau S, Lai JC. The range and reproducibility of the Liver Frailty Index. Liver Transpl. 2019;25(6):841–7.
7. Lai JC, Covinsky KE, McCulloch CE, Feng S. The Liver Frailty Index improves mortality prediction of the subjective clinician assessment in patients with cirrhosis. Am J Gastroenterol. 2018;113(2):235–42.
8. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. World J Gastroenterol. 2017;23(5):899–905.
9. Lai JC, Segev DL, McCulloch CE, Covinsky KE, Dodge JL, Feng S. Physical frailty after liver transplantation. Am J Transplant. 2018;18(8):1986–94.
10. Carey EJ, Steidley DE, Aqel BA, Byrne TJ, Mekeel KL, Rakela J, et al. Six-minute walk distance predicts mortality in liver transplant candidates. Liver Transpl. 2010;16(12):1373–8.
11. Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transpl. 2014;20(1):54–62.
12. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. Aliment Pharmacol Ther. 2016;44(8):796–806.
13. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989;64(10):651–4.
14. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B. Criterion validity of the Duke Activity Status Index for assessing functional capacity in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2002;22(4):298–308.
15. Tang WH, Topol EJ, Fan Y, Wu Y, Cho L, Stevenson C, et al. Prognostic value of estimated functional capacity incremental to cardiac biomarkers in stable cardiac patients. J Am Heart Assoc. 2014;3(5):e000960.
16. Wu JR, Lennie TA, Frazier SK, Moser DK. Health-related quality of life, functional status, and cardiac event-free survival in patients with heart failure. J Cardiovasc Nurs. 2016;31(3):236–44.
17. Wijeysundera DN, Pearse RM, Shulman MA, Abbott TEF, Torres E, Ambosta A, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet. 2018;391(10140):2631–40.
18. Merli MBA, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, Plauth M, et al. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70(1):172–93.
19. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the liver. Hepatology. 2014;60(2):715–35.

20. Lai JC, Ganger DR, Volk ML, Dodge JL, Dunn MA, Duarte-Rojo A, et al. Association of Frailty and sex with Wait List Mortality in liver transplant candidates in the multicenter functional assessment in liver transplantation (FrAILT) study. JAMA Surg. 2021;156(3):256–62.
21. Corbi G, Cacciatore F, Komici K, Rengo G, Vitale DF, Furgi G, et al. Inter-relationships between gender, frailty and 10-year survival in older Italian adults: an observational longitudinal study. Sci Rep. 2019;9(1):18416.
22. Williams FR, Vallance A, Faulkner T, Towey J, Durman S, Kyte D, et al. Home-based exercise in patients awaiting liver transplantation: a feasibility study. Liver Transpl. 2019;25(7):995–1006.
23. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65(6):1232–44.
24. Dharel N, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. J Clin Exp Hepatol. 2015;5:S37–41.
25. Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol. 2001;96(9):2718–23.
26. Dasarathy S, Muc S, Hisamuddin K, Edmison JM, Dodig M, McCullough AJ, et al. Altered expression of genes regulating skeletal muscle mass in the portacaval anastamosis rat. Am J Physiol gastrointest Liver Phys Ther. 2007;292(4):G1105–13.
27. Qiu J, Tsien C, Thapalaya S, Narayanan A, Weihl CC, Ching JK, et al. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. Am J Physiol Endocrinol Metabol. 2012;303(8):E983–93.
28. Davuluri G, Allawy A, Thapaliya S, Rennison JH, Singh D, Kumar A, et al. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. J Physiol. 2016;594(24):7341–60.
29. Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. J Gastroenterol. 2019;54(10):845–59.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Williams FR, Quinlan J, Freer A, Morrison B, Sitch A, Hockey F, et al. Duke Activity Status Index and Liver Frailty Index predict mortality in ambulatory patients with advanced chronic liver disease: A prospective, observational study. Aliment Pharmacol Ther. 2024;59:547–557. https://doi.org/10.1111/apt.17834