Assessment of the Frail Patient With End-Stage Liver Disease: A Practical Overview of Sarcopenia, Physical Function, and Disability

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Frailty has emerged as a powerful predictor of clinical outcomes (e.g., decompensation, hospitalization, mortality) in patients with end-stage liver disease (ESLD). It is therefore of paramount importance that all patients with ESLD undergo an assessment of frailty, to support life and death decision making (i.e., candidacy for critical care, transplantation) and aid with prioritization of evolving prehabilitation services (i.e., nutrition, physiotherapy, psychotherapy). This article aims to provide a practical overview of the recent advances in the clinical, radiological, and remote assessment tools of the frail patient with ESLD. Historically, clinicians have incorporated an assessment of frailty using the "end-of-the-bed test" or "eyeball test" into their clinical decision making. However, over the last decade, numerous nonspecific and specific tools have emerged. The current evidence supports the use of a combination of simple, user-friendly, objective measures to first identify frailty in ESLD (notably Clinical Frailty Scale, Liver Frailty Index), followed by a combination of serial tools to assess specifically sarcopenia (i.e., muscle ultrasound), physical function (i.e., chair stands, hand grip strength), functional capacity (i.e., 6-minute walk test), and physical disability (i.e., activities of daily living). (*Hepatology Communications* 2021;5:923-937).

Over the last decade, frailty has emerged as a powerful predictor of clinical outcomes in patients with cirrhosis and in those requiring liver transplantation. Frailty has become more relevant over time, as patients with cirrhosis are older in age, sicker as assessed by liver-disease severity, and are burdened by comorbidities including obesity and type 2 diabetes.[1] Increasingly, clinicians have recognized the end manifestation of all of these factors in the patient as "frailty," and incorporated an assessment of frailty using the "eyeball test" into their clinical decision making (e.g., candidacy for critical care or transplantation). Even though this subjective clinical assessment of frailty has been shown to predict mortality reasonably well in patients with end-stage liver disease (ESLD), it lacks objectivity, consistency, reproducibility, and meaningful serial variability. Consequently, recent years have seen the emergence of objective measures of frailty, in particular physical frailty, to assist the high-stakes decision making with ESLD. Despite the recent surge of evidence, most hepatology departments do not routinely perform

Abbreviations: ADL, activities of daily living; ASMI, appendicular skeletal muscle index; AT, anaerobic threshold; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CFS, clinical frailty scale; CPET, cardiopulmonary exercise testing; CT, computed tomography; DASI, Duke Activity Status Index; DEXA, dual-energy X-ray absorption; ESLD, end-stage liver disease; FFI, Fried Frailty Index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HGS, hand grip strength; HR, hazard ratio; IADL, instrumental ADL; KPS, Karnofsky Performance Scale; LFI, liver frailty index; LT, liver transplantation; L3, third lumbar vertebrae; MAC, midarm circumference; MAMC, midarm muscle circumference; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OR, odds ratio; PMI, psoas muscle index; SMI, skeletal muscle index; SPPB, short physical performance battery; TSF, triceps skin fold; 6MWD, 6-minute walking distance; 6MWT, 6-minute walk test.

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objective measures of physical frailty. This may be due in part to a lack of clinician awareness of tools available and the benefits/limitations of such in patients with ESLD. Consequently, without a standardized approach to frailty in this patient population, this may result in inconsistent clinical decision making and poor prioritization of available therapies. This review focuses on the recent advances in the clinical, radiological, and remote assessment tools of the frail patient with ESLD, to guide future clinical management (Appendix 1).

Definition of the Frail Patient

Frailty is most commonly defined as a clinical state of decreased physiologic reserve and increased vulnerability to health stressors, which in turn predisposes individuals to adverse clinical outcomes.[2] Frailty was first described in community-dwelling adults over the age of 65, as a multidimensional construct consisting of physical, psychological, social, and other environmental components.[2] Physical frailty is the component that has most frequently been described in ESLD, but there remains a lack of consensus regarding the definition in this patient population. In general, physical frailty is not synonymous with, but encompasses:

1. *Sarcopenia*: generalized loss of skeletal muscle mass. The term was first used in 1989 to describe loss of anatomical skeletal muscle mass in the aging population (primary sarcopenia), and is now widely recognized in a variety of chronic diseases (secondary sarcopenia), including ESLD and cancer. The only validated definition of sarcopenia in ESLD relies solely on computed tomography (CT)–measured skeletal muscle area at the third lumbar vertebrae (L3), which is normalized to the second power of height to form the "skeletal muscle index" (SMI).[3] Sex-specific cutoffs exist to define sarcopenia in ESLD, namely SMI < 50 cm^2/m^2 in men and <39 cm^2/m^2 in women.
2. *Reduced physical function:* progressive decrease in muscle strength (e.g., hand grip strength) and/or function (e.g., chair stands).
3. *Reduced aerobic exercise capacity:* deficient use of oxygen, leading to a reduced capacity to sustain physical work or endure physiological stresses including major surgery. Typically, aerobic exercise capacity is assessed through direct measurement of oxygen consumption by a patient on a treadmill or cycle ergometer, or by indirect measures such as field walking tests.
4. *Physical disability:* deficits in the ability to complete activities necessary to live independently within one's home and in one's community, commonly known as activities of daily living (ADLs) and instrumental ADLs (IADLs), respectively.[4]

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In addition, sarcopenic obesity (defined as reduced muscle mass/strength with obesity [body mass index (BMI) > 30 kg/m^2]) is an emerging challenge, primarily as a result of the rising prevalence of nonalcoholic fatty liver disease. Obesity can mask muscle wasting in patients with ESLD, and as such, sarcopenia can go underrecognized in the absence of measures of physical function. It is also important to acknowledge that a patient's current frailty status is only a snapshot of a dynamic clinical picture in patients with ESLD. ESLD is characterized by marked fluctuations in liver-disease severity (e.g., acute exacerbations of hepatic encephalopathy (HE), ascites, variceal bleeding)—all of which likely contribute to worsening frailty.

Is the Patient Frail?

To date, three indices have been used to assess physical frailty in patients with ESLD, namely the Fried Frailty Index (FFI) and more recently the Clinical Frailty Scale (CFS) and the Liver Frailty Index (LFI) (Table 1).

FRIED FRAILTY INDEX

The FFI is a single 5-point score based on a combination of subjective reports (exhaustion, unintentional weight loss, and low physical activity) and objective measurements (walk speed and hand grip),[2] in which patients are scored on a scale of 0 (no frailty) to 5 (most frail). The FFI is a reliable and well-validated assessment tool (<10 minutes to complete) and is frequently used world-wide across all solid-organ transplantation.[5]

Within the field of liver transplantation, every one unit increase in FFI results in a 50% increase in wait-list mortality (hazard ratio [HR] 1.50, P = 0.01).[6] Indeed, those who are deemed frail (FFI ≥ 3) are less likely to be independent with activities of daily living (8 vs. 7, P = 0.003) and are more likely to fall (50% [n = 10] vs. 23% [n = 30]).[7] The FFI therefore provides clinicians with a good overview of frailty and may be used to predict outcomes, as well as risk stratify those who may need additional therapeutic intervention, such as nutrition and/or tailored exercise. It is important to acknowledge that the FFI was originally developed to predict mortality in community-dwelling

TABLE 1. COMPARISON OF FRAILTY MEASURES

Test	Description	Time (Minutes)	Limitations	Predictors of Outcome	Predictors of Survival
FFI	Single 5-point score based on subjective (exhaustion, unintentional weight loss, low physical activity) and objective (walk speed, HGS) measures	<10	Complex and time-consuming compared with other frailty measures; omits other consideration such as comorbidities, age, malnutrition, and HE; limited use in measuring change to interventions such as prehabilitation	FFI ≥ 3 = decreased independent ADLs and increased risk of falls[7]	1-unit increase in FFS = 50% increase in wait-list mortality[6]
CFS	Subjective clinical assessment of stability/presence of comorbidities, level of daily physical activity, dependence on ADLs, and presence of terminal illness*	<1	Only a snapshot of frailty and not able to identify specific areas of frailty; not specific enough to monitor change in therapeutic intervention	CFS > 4 associated with 6-month hospitalization or death[9]	CFS > 3 associated with higher mortality or need for LT[8]
LFI	Composite metric of three performance-based measures (HGS, balance, chair stands)	<5	Not validated outside of the United States; not validated in hospitalized inpatients or acutely unwell	Higher LFI = longer LOS after LT[14] pre-LT = less likely to return to a "robust" state within 12/12 of LT[14]	LFI > 4.4 = predictor of 3/12 wait-list mortality[11] LFI > 4.2 = predictor of 6/12 wait-list mortality[11]

*Life expectancy less than 6 months.
Abbreviation: LT, liver transplant.

older adults (>65 years) and lacks applicability to the multidimensional causes of frailty in ESLD, by omitting factors such as comorbidities, age, malnutrition, severe liver failure, and HE. It is also limited by its strong ceiling/floor effects and its complexity, which is time-consuming and not always convenient in a busy clinical environment. Furthermore, the FFI may not be useful when measuring change in response to interventions (i.e., prehabilitation), as components of the FFI, such as weight loss and exhaustion, are unlikely to be influenced.

CLINICAL FRAILTY SCALE

The CFS is based on clinical assessment performed in person (i.e., in clinic) or by questioning the patient/care giver/next of kin over the phone. It is divided into nine categories, ranging from "very fit" to "severely frail," depending on how active they are and how dependent they are on others for daily living.[8] A score of 4 indicates that the patient is prefrail, whereas a score of >4 (CFS 5-9) indicates frailty. The CFS is one of the quickest objective frailty measures (<1 minute to complete) and has excellent interobserver reliability (0.87-0.93).[9] In 2016, Tandon et al.[9] highlighted that frailty (CFS > 4) is associated with hospitalization or death (adjusted odds ratio [OR] 3.6, P = 0.0008) in 300 Canadian outpatients with cirrhosis. These findings were supported in a European population, in which patients presenting with prefrailty (>3) were more likely to die or need a liver transplant (P < 0.001).[8] Furthermore, in multiple Cox regression analysis, a CFS score of >3 was independently associated with higher mortality (HR = 2.7, P = 0.007), which was maintained after controlling for muscle mass (HR = 1.7, P = 0.002).[8]

The CFS can also be used as a continuous measure, as for every one-point increase there is an increased risk for unplanned hospitalization or death within 6 months (adjusted OR 1.9, P < 0.0001).[9] Furthermore, despite its snap-shot view of frailty, the CFS has higher calibration and greater discrimination for predicting outcome than other, more time-consuming, measures such as FFI and the short physical performance battery (SPPB).[9] Therefore, the CFS is a useful tool to identify frailty quickly and may be able to help risk-stratify patients toward a referral for a more in-depth assessment and/or prehabilitation.

LIVER FRAILTY INDEX

The LFI is a composite metric of three performance-based measures: hand grip strength (HGS), time to do five chair stands (seconds), and time holding three balance positions (feet side by side, semitandem, and tandem), to objectively assess physical frailty in ambulatory patients with ESLD.[10] The LFI score can be calculated using an online calculator (available at http://liverfrailtyindex.ucsf.edu), with patient physical frailty categorized as robust, prefrail, and frail according to their index (index < 3.2, robust; 3.2-4.5, prefrail; and >4.5, frail). Most recently, optimal cutoffs of frailty have been developed in a multicenter U.S. study of 1,405 patients to predict mortality on the wait list after 3 months (LFI > 4.4) and 6-12 months (LFI = 4.2).[11] Overall, the LFI is a reliable test (correlation coefficient = 0.93) and is well-validated in cirrhosis,[12] whereas it has been investigated to a lesser extent in patients without cirrhosis.[13] Importantly, it is a liver disease–specific, continuous variable (i.e., no ceiling or floor effect) that is inexpensive, quick to complete (3-5 minutes), and requires minimal space and staff training, making it a useful and practical tool for measuring physical frailty in the clinical setting.

In a study of 529 participants, a higher LFI (i.e., greater degree of frailty) before liver transplant was significantly associated with wait-list mortality (HR = 2.9, P < 0.001) and length of stay following transplant (P = 0.004).[14] Furthermore, LFI was shown to predict physical recovery following transplant, with those who are categorized as frail before transplant being less likely to return to a "robust" state within 12 months of transplantation.[14] LFI is the best-studied outpatient measure to date in the setting of liver transplantation; however, there is a pressing need to validate it outside of the United States, in hospitalized inpatients, and in the acutely unwell (i.e., acute-on-chronic liver failure).

Assessment of Sarcopenia (Muscle Mass)

CROSS-SECTIONAL IMAGING

A robust index of skeletal muscle mass can be obtained using cross-sectional imaging by means of either CT or magnetic resonance imaging (MRI) of the abdominal muscles at L3 (Table 2). The

TABLE 2. MEASURES OF SARCOPENIA (MUSCLE MASS)

Test	Description	Time (Minutes)	Limitations	Predictors of Outcome	Predictors of Survival
CT	Cross-sectional imaging of abdominal muscles at L3 vertebrae; quantification of skeletal muscle is made using body-segmentation analysis software and then normalized to height to calculate the SMI[16]	10-20	Expensive; radiation exposure; specialized equipment/training; should only be used when clinically indicated, limiting longitudinal follow-up; heterogeneity in definition of sarcopenia and method of assessment	Prolonged ITULOS: 12 vs. 6 days, $P = 0.001$[17] prolonged HLOS (40 vs. 25 days; $P = 0.005$)[17]	Wait-list mortality: HR = 1.72; 95% CI 0.99-3.00; $P = 0.05$[17] post-LT survival: HR = 1.84, 95% CI 1.11-3.05, $P = 0.02$[20]
DEXA	A compartmentalized, 3D assessment of body composition that can be stratified into bone mass, fat mass, and lean mass[22]	10-20	Inability to differentiate between muscle and water; total APLM = reduced sensitivity and weak correlation with SMI-CT[22]	None reported	12-month wait-list mortality: Upper limb APLM HR = 0.27 (0.11, 0.66); $P = 0.004$[23] Mortality: Total APLM HR = 0.44 (0.21, 0.92); $P = 0.029$[23]
Ultrasound	Ultrasound waves, produced by a transducer, provide a noninvasive image of a single muscle or muscle group; the iliopsoas and thigh muscles have been investigated in liver cirrhosis	5-10	Detectability of iliopsoas muscle poor in patients with high BMI[24] limited number of studies; reproducibility is unknown	Increased risk of hospitalization: OR = 0.58, 95% CI 0.42-0.81; $P = 0.002$[24]	Mortality: HR = 0.93, 95% CI 0.88-0.99; $P = 0.017$[24]
MAMC	Calculated as MAC – (TSF × 0.314); results are expressed as a percentage of the expected reference values, adjusted for sex and age	<2	Low intra-observer and interobserver reliability; affected by subcutaneous adipose tissue loss	None reported	A significant inverse reaction with mortality for every 1-unit increase in MAMC (HR = 1.05; $P < 0.001$)[27]

Abbreviations: APLM, appendicular lean mass; CI, confidence interval; HLOS, hospital length of stay; ITULOS, intensive care length of stay.

cross-sectional area of the skeletal muscle is quantified using body segmentation analysis software and then normalized to the second power of height to calculate the SMI (cm^2/m^2).[15] Although MRI and CT can be used, there are a paucity of MRI data in patients with cirrhosis, and normal values are still required.[15] The most commonly discussed muscle indexes in the literature are total SMI and, more specifically, the psoas muscle index (PMI). PMI is quick and easier to assess than SMI; however, it is not as accurate at predicting mortality in patients (especially men) with ESLD.[16]

A large systematic review of 19 studies (n = 3,803) by Van Vugt et al. (2016) showed that low muscle mass on CT imaging was prevalent in 22%-70% of patients selected for liver transplantation and was associated with greater risk of death on the wait list (HR = 1.72, P = 0.05).[17] Furthermore, low muscle mass resulted in increased critical care (12 vs. 6 days, P = 0.001) and inpatient ward (40 vs. 25 days, P = 0.005) length of stay, and to a lesser extent complications, including infection.[17] However, due to a lack of standardized definition of sarcopenia, sex-defined cutoffs and heterogenous methods of assessment (e.g., SMI, PMI) in these studies, widespread clinical application has been challenging. Moreover, 13 of the 19 studies included patients from the same four North American liver centers, thereby limiting their generalizability. Traditionally, SMI-CT cutoffs were taken from oncological data sets; however, the recent formation of the North American FLEXIT (Fitness, Life Enhancement, and Exercise in Liver Transplantation) Consortium has resulted in validated cutoffs for SMI at L3 to define sarcopenia in ESLD, namely, <50 cm^2/m^2 in men and <39 cm^2/m^2 in women.[18] These sex-specific cutoffs of SMI correlated with liver transplant wait-list mortality,[18,19] but it is important to recognize both the sex and the severity of the underlying illness when applying SMI. For example, in male patients with high Model for End-Stage Liver Disease (MELD > 30) scores admitted with an acute deterioration that required liver transplantation, an SMI under 48 cm^2/m^2 resulted in a four-fold increase in posttransplant mortality.[20] In a separate cohort of over 600 patients with cirrhosis, the addition of SMI into the MELD (termed "MELD-sarcopenia") improved the predictive value of mortality, particularly in those with a MELD < 20.[19]

The most recent European Association for the Study of the Liver (EASL) Clinical Practice Guidelines in Nutrition (2019)[15] advise the use of CT to assess for low muscle mass in patients with cirrhosis and ESLD. This is achieved relatively easily for those patients being assessed for liver transplantation, as CT is reproducible, accurate, and frequently used to evaluate hepatocellular carcinoma (HCC), vasculature, and biliary anatomy. However, CT is expensive, time-consuming, and the repeated radiation exposure restricts its use for routine and longitudinal assessment of muscle mass.

DUAL-ENERGY X-RAY ABSORPTION

Dual-energy X-ray absorption (DEXA) is an easy, reproducible, and accurate method in the general population to analyze body composition (fat and fat-free mass), with minimal radiation exposure.[21] However, the analysis of muscle mass using fat-free mass index (kg/m^2) in DEXA can be overestimated due to its inability to distinguish water from muscle, which is particularly problematic in patients with ascites, hydrothorax, and/or peripheral fluid retention.[22] Belarmino et al. aimed to overcome this limitation by using appendicular (arm or leg) skeletal muscle index (ASMI) (kg/m^2), and demonstrated no change in DEXA-ASMI before and after abdominal paracentesis.[22] However, Giusto et al. still highlighted that DEXA-ASMI only weakly correlated with SMI-CT, albeit in only 59 patients.[21] This discrepancy may be explained by the fact that DEXA-ASMI may have detected fluid retention in the lower limbs, as more recent studies have highlighted differences in the predictive accuracy of DEXA in the upper versus the lower limbs in cirrhosis. In a recent study of 429 men with cirrhosis, DEXA measures of appendicular lean mass of the upper limb were strongly associated with mortality (HR = 0.27, P = 0.004), whereas measures of lower limb were not (HR = 1.02, P = 0.71).[23] Targeted DEXA measures of upper limb lean muscle mass may provide a safer, more accessible, and quicker tool in the clinical setting of ESLD; however, larger studies are needed to validate these findings (especially in women).

ULTRASOUND IMAGING

Ultrasound imaging is a simple, cheap, safe, and feasible method to measure muscle mass in patients with ESLD; however, only three studies have

investigated its use to date.[24-26] Two studies highlighted that the iliopsoas muscle was easily detectable in 80%-100% of cases, with good diagnostic accuracy for sarcopenia (area under the receiver operating characteristic curve [AUROC] = 0.835) and acceptable intra-operator and interoperator variability.[24,25] Furthermore, ultrasound-defined iliopsoas muscle index (muscle area to patient height^2 ratio) significantly correlated with CT in both sexes (correlation > 0.90, $P < 0.0001$)[25] and was associated with increased risk of hospitalization and mortality (HR = 0.91 and 0.93, respectively) in 75 patients with decompensated cirrhosis.[24] Identification of the Iliopsoas muscle was limited primarily in patients with high abdominal circumferences,[24] calling into question its accuracy in patients with ESLD and morbid obesity. Alternatively, Tandon et al. evaluated ultrasound to measure thigh (quadricep) muscle thickness in 159 patients with cirrhosis (60% Childs-Pugh A) compared with CT-SMI or MRI.[26] Targeting the quadriceps demonstrated excellent interobserver reliability (correlation = 0.97), and when combined with BMI it identified sarcopenia in male and female patients almost as well as cross-sectional imaging (AUROC = 0.78 and 0.89, respectively). Despite the fact that larger prospective longitudinal studies are needed, ultrasound shows promise and may play a unique future role in monitoring and assessing response to nutrition in bed-bound inpatients and those who are critically unwell.

ANTHROPOMETRY

Midarm muscle circumference (MAMC) (cm) is obtained by measuring the midarm circumference (MAC, cm) and triceps skin fold (TSF, mm): calculated MAMC = MAC − (3.14 × TSF). These measures are the quickest, simplest, and most inexpensive way to assess muscle mass at the bedside or in the outpatient clinic. When performed by trained personnel, both methods have good intra-observer and interobserver agreement (correlation coefficient = 0.8 and 0.9, respectively). MAMC is a better predictor of mortality when comparing patients who are below the fifth percentile for muscle mass with those above ($P = 0.001$).[27] Furthermore, in one study, MAMC was a good predictor of low muscle mass when CT was used as the gold standard (AUROC = 0.75 in men and 0.84 in women).[26] Therefore, MAMC can be used as a screening tool to highlight those patients with potential sarcopenia who require assessment of their physical function and targeted prehabilitation.

ASSESSMENT OF PHYSICAL FUNCTION (MUSCLE STRENGTH/ FUNCTION)

Hand Grip Strength

Recent International Clinical Practice Guidelines (EASL, ESPEN 2019) recommend that all patients with ESLD undergo assessment of muscle mass and strength with MAMC and HGS, respectively.[15,28] Measurement of HGS is a quick, simple, and inexpensive method of measuring upper-limb muscle strength (Table 3). It is recommended that it be performed three times in the "nondominant" hand, and the mean value compared with historical "normal" values for women (29 kg) and men (40 kg). HGS is significantly lower in transplant wait-list cohorts when compared with normative data for older adults (60-69 years) (median 28 kg, interquartile range [IQR] 21-27 (n = 536) versus 40 kg/24 kg (males/females) ($P < 0.001$).[10] Low HGS is associated with hospitalization (median 27.7 kg [hospitalized] vs. 32.7 kg [not hospitalized]),[29] low physical activity, malnutrition, HE, and severe liver disease.[5,10,30] In a multivariate analysis, Hanai et al. showed that HGS is also associated with all-cause and liver-related mortality, independent of age, etiology of cirrhosis, development of HCC, and serum sodium level (HR = 0.96, $P < 0.001$).[31] Although this study has its limitations (older adults [>70 years]; 49% hepatitis C), it is supported by another recent study by Sinclair et al.[32] (n = 145, mixed etiology of liver cirrhosis), who showed that with every 1-kg increase in HGS, survival was increased by 6%.[32] However, this study investigated male patients with liver cirrhosis only, and further research is needed to establish the mortality risk as well as cutoff points in females and all liver etiologies.

Chair Stands

Chair stands are a bedside measure of muscle function and strength. The number of chair stands

TABLE 3. MEASURES OF PHYSICAL FUNCTION

Test	Description	Time (Minutes)	Limitations	Predictors of Outcome	Predictors of Survival
HGS	Three consecutive measurements of static force (kg) produced by the nondominant hand around a dynamometer; mean value is used for analysis[16]	3-5	Further research needed to establish mortality risk and cutoff points for females of mixed liver-disease etiologies	Low HGS associated with hospitalization[29], low physical activity, malnutrition, and severe liver disease[5,10,30]	Mortality: HR = 0.96, 95% CI 0.94-0.98; $P < 0.001$[31] 6% survival increase with every 1-kg increase in HGS[32]
Chair stands	The number of chair stands (defined as rising from a seated position and returning to a seated position) completed in a set time period	<2	No data outside the United States; limited in those with lower-limb musculoskeletal problems	<10 chair stands within 30 seconds = 73% sensitivity for falls[33] >5 chair stands within 10 seconds = reduced risk of infection ($P = 0.046$)[29]	Wait-list mortality: HR = 0.02 (0.01-0.07), $P < 0.001$[10]
SPPB	Functional status and physical performance are measured from three components: time to complete five chair stands, timed 4-m walk, and balance testing[35]	3-5	Ceiling effect[36]		Score ≤9/12 = higher wait-list mortality, independent of age (young impaired [≤9] HR = 1.77, $P = 0.03$; old impaired [≤9] HR = 2.70, $P = 0.03$; old robust [≥10] HR = 1.38, $P = 0.03$)[35]
Gait speed	A self-selected gait speed is measured over a set distance (usually 2.44-5.00 m)	<2	Clinical use limited by minimal clinical difference between scores; no influence on prediction of wait-list mortality when used in combination with other functional assessments	Slow speed associated with higher rate of hospital days/100 days (RR = 0.78, $P < 0.001$, 95% CI 0.68-0.89) and wait-list removal (RR = 0.82, $P = 0.02$, 95% CI 0.70-0.97)[29]	None reported
6MWT	Self-paced field-walking test; patient instructed to walk as far as possible in 6 minutes along set course	20	Requires 30-m level indoor walking course; significant learning effect[44]	Presence of cirrhosis and severity of cirrhosis (Child-Pugh) associated with reduced 6MWD[40]	Reduced 6MWD (<250 m; HR = 2.1) predicts mortality among LT candidates [38-42]

Abbreviations: CI, confidence interval; RR, rate ratio.

(defined as rising from a seated position and returning to a seated position) completed in a set time period is recorded. Lai et al.[10] found chair stands to be one of the strongest predictors of wait-list mortality when used in combination with HGS (AUROC = 0.72). For example, those who completed fewer than 10 chair stands within 30 seconds had a sensitivity/specificity of 73%/54% for falls,[33] and those who completed five chair stands within 10 seconds had less chance of developing an infection (P = 0.046).[29] Nevertheless, further research is needed to validate chair stands as a measure of frailty in ESLD, as well as to determine specific cut-off points for predicting clinical outcome.

Short Physical Performance Battery

The SPPB is an inexpensive and efficient assessment tool designed to measure functional status and physical performance. It is calculated from three components: time to complete five chair stands, time to walk 4 m, and balance testing. Each component is scored with a possible 4 points, with the scores combined to give a total possible score of 12 (range 0-12)[34]; the higher scores represent the best physical status (Table 3).

SPPB scores are significantly lower in older compared with younger transplant candidates (median 10 [9-11] vs. 11 [9-12]; P = 0.01).[35] An SPPB score of ≤9 predicts a higher risk of wait-list mortality in both young (HR = 1.77, P = 0.03) and older (HR = 2.70; P = 0.03) patients.[35] However, studies have highlighted that most (68%) liver-transplant wait-list patients score ≥10,[35] and while these patients may have a lower risk of wait-list mortality, functional decline on the wait list occurs at a median rate of 0.16 SPPB points every 3 months.[7] This implies that a significant proportion of patients may deteriorate below a SPPB of 10 while on the wait list—especially those with the longer wait times. Early identification of those at risk of functional decline remains a challenge, but the functional assessment in liver transplantation (FrAILT) data highlight that tools such as SPPB may be useful in identifying those most in need of prehabilitation. Whether SPPB can be used reliably as a serial measure of response to prehabilitation remains to be seen. Williams et al.[36] found a ceiling effect of SPPB scores (i.e., maximized to 12/12) in 18 patients who received 12 weeks of home-based exercise while on the liver-transplant wait list. Although a small sample size, this study highlights that additional functional gains with prehabilitation may be missed using SPPB alone—especially in those who have a high score at baseline.

Gait Speed

Gait speed is a reproducible way of measuring physical function in patients awaiting liver transplant.[37] The participant uses a self-selected (usual pace) gait speed over a set distance (usually 2.4 m to 5 m). It can be used as a stand-alone test or as part of a battery of tests such as SPPB. Gait speed is slower in patients listed for liver transplantation (n = 350) when compared with normative data for older adults (mean gait speed: males 0.90 m/s vs. 1.3 m/s; females 0.98 m/s vs. 1.2 m/s).[37] Overall, it is significantly associated with poorer outcomes such as higher rates of hospitalization (P < 0.001) and risk of wait-list removal (P = 0.02).[29] Indeed, patients removed from the transplant wait list at the University of Pittsburgh Medical Center had significantly slower gait speeds than those who remained active on the list (0.92 m/s vs. 1.03 m/s; P < 0.05). Even though statistically significant, a clinical difference of as little as 0.11 m/s between these patient groups leads to questions about the relevance of gait speed in isolation.

Six-Minute Walk Test

The 6-minute walk test (6MWT) is a self-paced field-walking test conducted under controlled conditions and is a reliable and valid measure of exercise tolerance in various patient populations.[38,39] The distance walked in 6 minutes (6MWD) is 27% shorter in patients with cirrhosis than in healthy controls, and is further reduced in patients with ESLD and advancing Child-Pugh classification.[40] A reduced 6MWD predicts wait-list mortality,[38-42] with those scoring under 250 m two times more likely to die before liver transplantation.[42] Every 100-m decrease in the 6MWD represents an almost 50% increase in wait-list mortality, independent of liver disease severity (based on MELD).

The test is inexpensive and simple to administer; however, a number of issues may limit its practical application. It requires a 30-m level indoor walking course, and the course layout and degree of patient encouragement must be standardized, as they

significantly affect the distance walked.[43] Strong evidence of a learning effect (i.e., patient becomes more familiar with the test) has been seen in studies using repeated 6MWT, and this may complicate the clinical interpretation of changes in test results over time.[44] The learning effect may be reduced by performing two tests and recording the best result at each clinical/study time point.

ASSESSMENT OF AEROBIC EXERCISE CAPACITY AND PHYSICAL ACTIVITY

Reduced aerobic capacity is a fundamental component of frailty, reflecting limited reserve capacity of multiple organ systems and contributing to low habitual activity levels and slow walking speed.[2,45-47] In patients with ESLD, aerobic exercise capacity is substantially poorer than general population norms, and in turn is associated with poorer overall survival[41,48] (Table 4).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is the gold-standard assessment of aerobic exercise capacity. It directly assesses gas exchange, work, heart rate and rhythm, and blood pressure during intense exercise. In a small prospective U.K. study of patients undergoing assessment for liver transplantation, Prentis et al. demonstrated that an oxygen consumption at the anaerobic threshold (AT) of less than 9 mL/kg/min was a good discriminator of 90-day postoperative mortality, with 90.7% sensitivity and 83.3% specificity.[49] It is important to not overinterpret the AT cutoff in this study, due to the small sample size of 60 patients and the fact there were only six reported deaths. In the largest retrospective study to date (n = 399), Bernal et al. demonstrated that low AT was associated with reduced survival and increased postoperative hospitalization for patients undergoing liver transplantation.[48] Furthermore, they found that low AT and low peak oxygen consumption were associated with reduced 1-year survival among patients who were assessed for, but did not undergo, transplantation.

In 2016, Ney et al. performed a seven-study (1,107-patient) meta-analysis in patients awaiting (three studies) or following liver transplantation (four studies).[50] Most of these studies were retrospective and only included those deemed fit enough for liver transplantation (i.e., selection bias). Overall, they found that AT was the CPET variable most consistently associated with liver transplant outcomes, with mean differences of 2.0 mL/kg/min between survivors and nonsurvivors. In contrast with field-walking tests, measurement of the AT does not require maximal patient effort and is less likely to be confounded by volitional factors. CPET may also provide data to support a diagnosis of cardiovascular, respiratory, or

TABLE 4. MEASURES OF PHYSICAL ACTIVITY/AEROBIC EXERCISE CAPACITY

Test	Description	Limitations	Predictors of Poor Test Outcome	Predictors of Survival
Habitual physical activity	Free-living activity levels measured over a period of days by wrist-worn or body-worn accelerometry	Patient must wear accelerometer continuously	Patients awaiting LT are significantly less physically active than the general population[62]	Moderate to vigorous activity predicts long-term survival in liver disease of any etiology/severity[61]
CPET	Direct assessment of integrated cardiorespiratory and musculoskeletal function under increasing workload	Requires significant investment in equipment and staff training; expensive	VO_2 peak, AT, and maximum workload are lower among LT candidates than predicted for healthy population[48]	AT < 9 mL/kg/min predicts 90-day mortality after LT (small sample size, n = 60)[49] low AT associated with increased hospitalization and reduced survival after LT[48] low AT and low VO_2 peak associated with reduced 1-year survival among LT candidates who were not transplanted[48]

Abbreviation: VO_2 peak, peak oxygen uptake.

metabolic disease in patients with limited exercise capacity. However, the use of CPET in ESLD is limited by the requirement for costly equipment, specifically trained staff, and the lack of robust AT cutoffs for predicting mortality due to study heterogeneity.[50] Interestingly, the Duke Activity Status Index (DASI) has been shown to be a useful predictor of adverse outcomes (e.g., death, myocardial infarction) after major noncardiac surgery[51]—over and above that of CPET and serological tests (i.e., N-terminal–pro hormone BNP). This 12-item self-reported assessment of functional capacity requires minimal time to complete.[52] It provides prognostic information in a variety of chronic diseases and can be used as an index of disease progression over time.[53-55] There are no published data of DASI in patients with ESLD or liver transplantation, but based on the recent findings in major noncardiac surgery and its ease/cost savings of completion, validation of DASI should be sought.

Physical Activity Measured by Accelerometry

Among the general population, a higher volume of habitual moderate to vigorous physical activity, as detected by wrist-worn or body-worn accelerometer, appears to be protective against mortality.[56-58] As few as 3 days of accelerometry provide a valid estimate of habitual physical activity, and there appears to be good agreement between wrist-worn and hip-worn devices.[59,60] In a prospective study of patients with self-reported liver disease of any etiology and severity, moderate to vigorous physical activity was strongly protective against mortality over an average 80-month follow-up (adjusted HR = 0.11, P = 0.004).[61] Activity levels observed in patients awaiting liver transplantation are among the lowest seen in chronic disease populations: 3,164 ± 2,842 steps per day compared with 7,000 to 13,000 steps in healthy adults.[62] Interestingly, this objectively measured activity does not appear to correlate well with clinically assessed activity levels, supporting the value of accelerometry in this population. In light of the fact that travel distance from liver transplant centers in the United Kingdom and United States has been shown to correlate with worse outcomes,[63] there is a pressing need to use virtual monitoring of patients in their local community and homes. In light of rapidly increasing world-wide popularity of wearable physical activity monitors,[64] future research should focus on the use of these devices (i.e., compliance, response to interventions) in ESLD.

SUBJECTIVE ASSESSMENT OF PHYSICAL DISABILITY

Activities of daily living

Physical disability, as indicated by impaired ADLs (i.e., bathing, dressing, toileting, transferring, continence, and feeding) or IADLs (i.e., using a telephone, shopping, food preparation, housekeeping, doing laundry, transportation, managing finances, and managing medications), is more prevalent among elderly people with cirrhosis than in those without liver disease.[65] Forty percent of patients with ESLD have impairment of at least one IADL, and in this group physical disability is associated with adverse outcomes. Specifically, impairments of toileting, transferring, housekeeping, and laundry have been found to be associated with mortality on the liver-transplant wait list.[66] Liver transplantation appears to reduce disability among recipients, with an improvement in ADLs seen at 6 and 12 months following transplant.[67]

Karnofsky Performance Scale

Reduced performance status and low levels of habitual activity are key components of the frailty construct. A number of scales have been developed to quantify patient and clinician assessment of performance status, but only the Karnofsky Performance Scale (KPS) has been used in the setting of ESLD and transplantation. Developed more than 70 years ago as a measure of functional independence for patients with cancer, the KPS is a unidimensional clinician-reported measure ranging from zero (death) to 100 (no limitation). It may aid prognosis in a variety of chronic disease states, following acute medical admission and predicting decline in elderly outpatients.[68-70] A large retrospective U.S. transplant registration series (>70,000 patients) has demonstrated an association between a low KPS and death among patients awaiting liver transplantation.[71] KPS tends to decline over time as patients await liver transplant, and then improves in the posttransplant period. Furthermore, recipients with lower KPS or a failure to

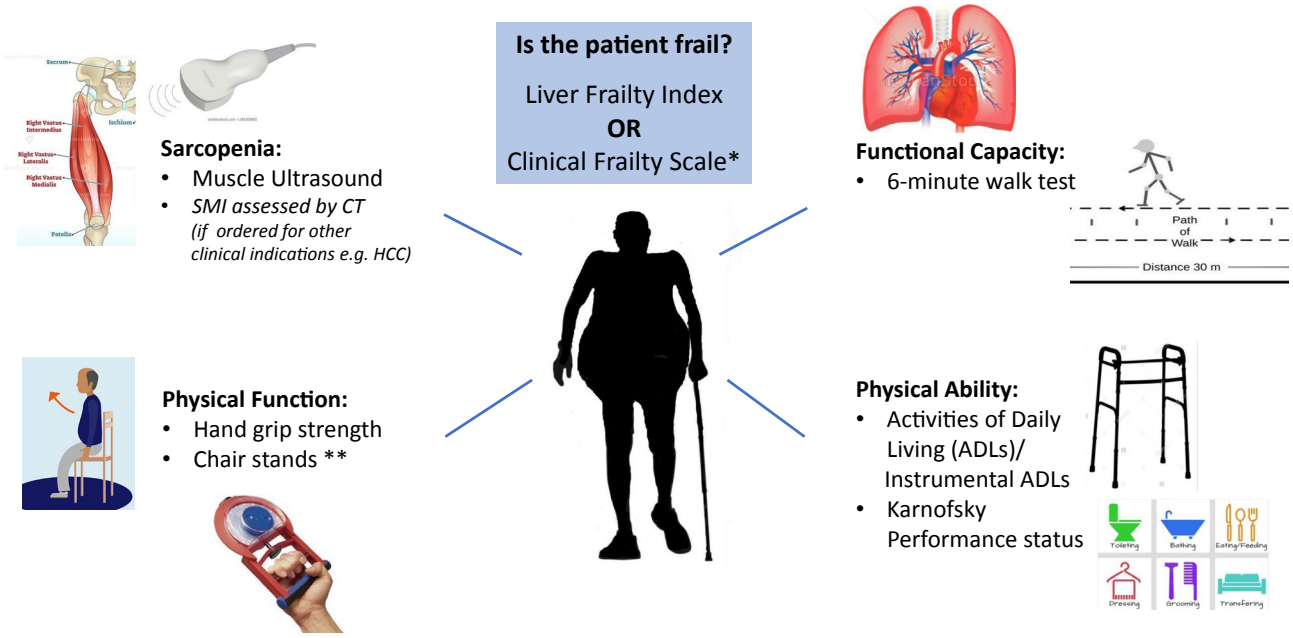

FIG. 1. Clinic assessment and monitoring of a frail patient with ESLD (authors' views only). *Rapid assessment in clinic or virtual assessment. **LFI contains muscle strength/function (HGS for upper limb; chair stands for core/lower limb) and balance; serial LFI measurements correlate with clinical outcomes (Lai, J Hepatol 2020).

improve KPS after transplant have poorer graft and patient survival.[72] The KPS also improves prediction of death in patients with ESLD and who are within 3 months of discharge from hospital.[73] The effect on clinical outcomes of using the KPS to prioritize those patients most in need of early follow-up, closer monitoring, and targeted prehabilitation has not been studied.

Author Recommendations

In current outpatient settings, health care professionals often have limited time, space, and resources to undertake a thorough assessment of frailty for patients with ESLD. The simplicity and time efficiency (<3-5 minutes) of CFS and LFI means that they can be incorporated into most clinical environments and conducted by any member of the multidisciplinary team (MDT), alongside well-established basic, clinical observations (i.e., blood pressure, oxygen saturations). This enables early identification of those at highest risk of physical frailty, physical decline, and most in need of MDT-delivered prehabilitation (e.g., liver-specialist dieticians/physiotherapists). Once triaged, a more thorough assessment of muscle mass, strength, functional capacity, and physical ability (Fig. 1) can be conducted, to guide individualized prehabilitation programs (i.e., high-protein diet, exercise, psychotherapy) and provide longitudinal assessment.

Summary

The development of physical frailty in ESLD is associated with poor outcomes. It is therefore of paramount importance that all patients with ESLD undergo an assessment of physical frailty, to support life-and-death decision making and aid with prioritization of evolving prehabilitation services. Over the last decade, numerous nonspecific and specific tools have emerged for assessing the frail patient with ESLD, yet there is still uncertainty among clinicians as to the appropriate use of these tools. A combination of simple, user-friendly, objective, performance-based measures should be used first to identify frailty in ESLD (i.e., LFI or CFS), followed by a combination of serial tools to assess sarcopenia (i.e., muscle ultrasound), physical function (i.e., HGS and/or chair

stands), functional capacity (i.e., 6MWT), and physical disability (i.e., ADLs).

Appendix 1

LITERATURE SEARCH

A MEDLINE and PubMed search was undertaken using the following research terms: "physical activity," "functional capacity," "aerobic capacity," "muscle mass," "muscle strength," "muscle function," "sarcopenia," "disability," "frailty," "liver cirrhosis," "liver failure," "liver transplantation," "chronic liver disease," and "end-stage liver disease" from January 1, 1990, to March 31, 2020.

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;19:1896-1906.
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 2001;56:M146-M157.
3) Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transplant 2017;23:625-633.
4) Lai JC, Dodge JL, McCulloch CE, Covinsky KE, Singer JP. Frailty and the burden of concurrent and incident disability in patients with cirrhosis: a prospective cohort study. Hepatol Commun 2020;4:126-133.
5) Tapper EB, Konerman M, Murphy S, Sonnenday CJ. Hepatic encephalopathy impacts the predictive value of the Fried Frailty Index. Am J Transplant 2018;18:2566-2570.
6) Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14:1870-1879.
7) Lai JC, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: results from the functional assessment in liver transplantation (FrAILT) study. Hepatology 2016;63:574-580.
8) Kremer WM, Nagel M, Reuter M, Hilscher M, Michel M, Kaps L, et al. Validation of the clinical frailty scale for the prediction of mortality in patients with liver cirrhosis. Clin Transl Gastroenterol 2020;11:e00211.
9) Tandon P, Tangri N, Thomas L, Zenith L, Shaikh T, Carbonneau M, et al. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the clinical frailty scale. Am J Gastroenterol 2016;111:1759-1767.
10) 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;66:564-574.
11) 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 Jun 3. https://doi.org/10.1002/hep.31406. [Epub ahead of print]
12) Lai JC, Rahimi RS, Verna EC, Kappus MR, Dunn MA, McAdams-DeMarco M, et al. Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. Gastroenterology 2019;156:1675-1682.
13) Wang CW, Lebsack A, Chau S, Lai JC. The range and reproducibility of the Liver Frailty Index. Liver Transpl 2019;25:841-847.
14) 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;113:235-242.
15) Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70:172-193.
16) Ebadi M, Tandon P, Moctezuma-Velazquez C, Ghosh S, Baracos VE, Mazurak VC, et al. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. J Hepatol 2018;69:608-616.
17) van Vugt JLA, Levolger S, de Bruin RWF, van Rosmalen J, Metselaar HJ, IJzermans JNM. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. Am J Transplant 2016;16:2277-2292.
18) Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23:625-633.
19) Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JXQ, et al. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. Clin Transl Gastroenterol 2015;6:e102.
20) Kuo SZ, Ahmad M, Dunn MA, Montano-Loza AJ, Carey EJ, Lin S, et al. Sarcopenia predicts post-transplant mortality in acutely ill men undergoing urgent evaluation and liver transplantation. Transplantation 2019;103:2312-2317.
21) Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastro Hepatol 2015;27:328-334.
22) Belarmino G, Gonzalez MC, Sala P, Torrinhas RS, Andraus W, D'Albuquerque LAC, et al. Diagnosing sarcopenia in male patients with cirrhosis by dual-energy X-ray absorptiometry estimates of appendicular skeletal muscle mass. JPEN J Parenter Enteral Nutr 2018;42:24-36.
23) Sinclair M, Hoermann R, Peterson A, Testro A, Angus PW, Hey P, et al. Use of dual X-ray absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk. Liver Int 2019;39:1089-1097.
24) Hari A, Berzigotti A, Štabuc B, Caglevič N. Muscle psoas indices measured by ultrasound in cirrhosis—preliminary evaluation of sarcopenia assessment and prediction of liver decompensation and mortality. Dig Liver Dis 2019;51:1502-1507.
25) Kobayashi K, Maruyama H, Kiyono S, Ogasawara S, Suzuki E, Ooka Y, et al. Application of transcutaneous ultrasonography for the diagnosis of muscle mass loss in patients with liver cirrhosis. J Gastroenterol 2018;53:652-659.
26) Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, et al. A model to identify sarcopenia in patients with cirrhosis. Clin Gastroenterol Hepatol 2016;14:1473-1480.e3.
27) Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445-450.
28) Plauth M, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019;38:485-521.

29) 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;23:899-905.
30) Alvares-da-Silva MR, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition 2005;21:113-117.
31) Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition 2015;31:193-199.
32) Sinclair M, Chapman B, Hoermann R, Angus PW, Testro A, Scodellaro T, et al. Handgrip strength adds more prognostic value to the Model for End-Stage Liver Disease score than imaging-based measures of muscle mass in men with cirrhosis. Liver Transpl 2019;25:1480-1487.
33) Tapper EB, Baki J, Parikh ND, Lok AS. Frailty, psychoactive medications, and cognitive dysfunction are associated with poor patient-reported outcomes in cirrhosis. Hepatology 2019;69:1676-1685.
34) Treacy D, Hassett L. The Short Physical Performance Battery. J Physiother 2018;64:61.
35) Wang CW, Covinsky KE, Feng S, Hayssen H, Segev DL, Lai JC. Functional impairment in older liver transplantation candidates: from the functional assessment in liver transplantation study. Liver Transpl 2015;21:1465-1470.
36) 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;25:995-1006.
37) Dunn MA, Josbeno DA, Tevar AD, Rachakonda V, Ganesh SR, Schmotzer AR, et al. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. Am J Gastroenterol 2016;111:1768-1775.
38) Hamilton DM, Haennel RG. Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardpulm Rehabil 2000;20:156-164.
39) Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
40) Alameri HF, Sanai FM, Al Dukhayil M, Azzam NA, Al-Swat KA, Hersi AS, et al. Six Minute Walk Test to assess functional capacity in chronic liver disease patients. World J Gastroenterol 2007;13:3996-4001.
41) 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;16:1373-1378.
42) Yadav A, Chang Y-H, Carpenter S, Silva AC, Rakela J, Aqel BA, et al. Relationship between sarcopenia, six-minute walk distance and health-related quality of life in liver transplant candidates. Clin Transplant 2015;29:134-141.
43) Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, et al. Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. Am J Respir Crit Care Med 2003;167:1522-1527.
44) Criner G. 6-minute walk testing in COPD: is it reproducible? Eur Respir J 2011;38:244-245.
45) Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". J Geriatr Phys Ther 2009;32:46-49.
46) Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci 2013;68:39-46.
47) Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ 2011;183:E487-E494.
48) 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;20:54-62.
49) Prentis JM, Manas DM, Trenell MI, Hudson M, Jones DJ, Snowden CP. Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation. Liver Transpl 2012;18:152-159.
50) 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;44:796-806.
51) 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;391:2631-2640.
52) 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;64:651-654.
53) 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 Cardpulm Rehabil 2002;22:298-308.
54) Tang WHW, 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:e000960.
55) 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;31:236-244.
56) Dohrn IM, Sjostrom M, Kwak L, Oja P, Hagstromer M. Accelerometer-measured sedentary time and physical activity–a 15 year follow-up of mortality in a Swedish population-based cohort. J Sci Med Sport 2018;21:702-707.
57) Lee IM, Shiroma EJ, Evenson KR, Kamada M, LaCroix AZ, Buring JE. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the women's health study. Circulation 2018;137:203-205.
58) Matthews CE, Keadle SK, Troiano RP, Kahle L, Koster A, Brychta R, et al. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. Am J Clin Nutr 2016;104:1424-1432.
59) Sasaki S, Ukawa S, Okada E, Wenjing Z, Kishi T, Sakamoto AI, et al. Comparison of a new wrist-worn accelerometer with a commonly used triaxial accelerometer under free-living conditions. BMC Res Notes 2018;11:746.
60) Tudor-Locke C, Burkett L, Reis JP, Ainsworth BE, Macera CA, Wilson DK. How many days of pedometer monitoring predict weekly physical activity in adults? Prev Med 2005;40:293-298.
61) Loprinzi PD, VanWagner LB. Survival effects of physical activity on mortality among persons with liver disease. Prev Med Rep 2016;3:132-134.
62) Dunn MA, Josbeno DA, Schmotzer AR, Tevar AD, DiMartini AF, Landsittel DP, et al. The gap between clinically assessed physical performance and objective physical activity in liver transplant candidates. Liver Transpl 2016;22:1324-1332.
63) Webb GJ, Hodson J, Chauhan A, O'Grady J, Neuberger JM, Hirschfield GM, et al. Proximity to transplant center and outcome among liver transplant patients. Am J Transpl 2019;19:208-220.
64) Case MA, Burwick HA, Volpp KG, Patel MS. Accuracy of smartphone applications and wearable devices for tracking physical activity data. JAMA 2015;313:625-626.

65) Rakoski MO, McCammon RJ, Piette JD, Iwashyna TJ, Marrero JA, Lok AS, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. Hepatology 2012;55:184-191.
66) Samoylova ML, Covinsky KE, Haftek M, Kuo S, Roberts JP, Lai JC. Disability in patients with end-stage liver disease: results from the functional assessment in liver transplantation study. Liver Transpl 2017;23:292-298.
67) Beyer N, Aadahl M, Strange B, Kirkegaard P, Hansen BA, Mohr T, et al. Improved physical performance after orthotopic liver transplantation. Liver Transpl 1999;5:301-309.
68) Brezinski D, Stone PH, Muller JE, Tofler GH, Davis V, Parker C, et al. Prognostic significance of the Karnofsky Performance Status score in patients with acute myocardial infarction: comparison with the left ventricular ejection fraction and the exercise treadmill test performance. The MILIS Study Group. Am Heart J 1991;121:1374-1381.
69) Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol 1991;46:M139-M144.
70) Schmidt RJ, Landry DL, Cohen L, Moss AH, Dalton C, Nathanson BH, et al. Derivation and validation of a prognostic model to predict mortality in patients with advanced chronic kidney disease. Nephrol Dial Transpl 2019;34:1517-1525.
71) Orman ES, Ghabril M, Chalasani N. Poor performance status is associated with increased mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2016;14:1189-1195.e1.
72) Thuluvath PJ, Thuluvath AJ, Savva Y. Karnofsky performance status before and after liver transplantation predicts graft and patient survival. J Hepatol 2018;69:818-825.
73) Tandon P, Reddy KR, O'Leary JG, Garcia-Tsao G, Abraldes JG, Wong F, et al. A Karnofsky performance status-based score predicts death after hospital discharge in patients with cirrhosis. Hepatology 2017;65:217-224.