



Frailty in Children with Liver Disease: A Prospective Multicenter Study

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Objective To assess frailty, a measure of physiologic declines in multiple organ systems, in children with chronic liver disease using a novel pediatric frailty tool.

Study design We performed a prospective cross-sectional multicenter study at 17 liver transplantation (LT) centers. 71 children (5–17 years of age), 36 with compensated chronic liver disease (CCLD) and 35 with end-stage liver disease (ESLD) and listed for LT, were assessed for frailty using validated pediatric tools to assess the 5 classic Fried Frailty Criteria—slowness, weakness, exhaustion, diminished physical activity, and shrinkage. Test scores were translated to age- and sex-dependent z scores, generating a maximum frailty score of 10.

Results The median frailty score of the cohort was 4 (IQR 3, 5). Subjects with ESLD had significantly higher frailty scores (median 5; IQR 4, 7) than subjects with CCLD (median 3; IQR 2, 4); ($P < .0001$). Area under the curve receiver operating characteristic for frailty scores to discriminate between ESLD and CCLD was 0.83 (95% CI 0.73, 0.93). Forty-six percent of children with ESLD were frail and there was no correlation between pediatric frailty scores and physician's global assessments ($r = -0.24$, 95% CI -0.53, 0.10).

Conclusions A novel frailty tool assessed additional dimensions of health, not captured by standard laboratory measures and identified the sickest individuals among a cohort of children with chronic liver disease. This tool may have applicability to other children with chronic disease. (*J Pediatr* 2018;194:109-15).

A comprehensive health assessment of adults with chronic disease was subjective and unreliable, until the composite measure of frailty was conceived. Fried et al first described this frailty phenotype in 2001, which encompasses cumulative declines across multiple physiologic systems causing vulnerability to adverse outcomes.¹ Frailty is measured by 5 elements, namely weakness, slowness, shrinkage, exhaustion, and diminished physical activity.¹ Reliably and reproducibly measured in adults, frailty is a more powerful predictor of functional status deficits, falls, and mortality in the elderly, than age or comorbidities.² Although other frailty tools such as the Frailty Index now exist, the Fried Frailty Criteria remain the most widely used in clinical settings because of their robustness and practicality.^{3,4}

Recent data demonstrate that frailty is a validated marker and outcome predictor of morbidity and mortality in both geriatric and adult surgical patients.^{5,6} Of note, frailty has also been studied in patients listed for solid organ and liver transplantation (LT).⁷ Lai et al demonstrated that frailty is significantly associated with wait list mortality and delisting in adults listed for LT, even after adjustment for liver disease severity.^{8,9}

In children with end-stage liver disease (ESLD), reliable clinical and biochemical markers of disease severity are inadequate. The pediatric end-stage liver disease (PELD) and the model of end-stage liver disease (MELD) scores are used to allocate livers for transplantation (for patients under and over the age of 12 years,

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Funded by the Hospital for Sick Children Transplant and Regenerative Medicine Center Astellas Pilot Grant and the Lina Sweeney Foundation. The authors declare no conflicts of interest.

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<https://doi.org/10.1016/j.jpeds.2017.10.006>

6-MWT	6-minute walk test	LT	Liver transplantation
AUC	Area under the curve	MELD	Model of end-stage liver disease
BMI	Body mass index	PAQ	Physical Activity Questionnaire
CCLD	Chronic compensated liver disease	PELD	Pediatric end-stage liver disease
CDC	Centers for Disease Control	ROC	Receiver operating characteristic
ESLD	End-stage liver disease	TSF	Triceps skinfold thickness

respectively) and, hence, are thought to reflect an individual's disease severity. However, it is well accepted that the PELD and MELD scores neither capture the extent of morbidity associated with ESLD nor result in standardization of listing practices, as up to 50% of children listed for LT are allocated organs by an exception system, which bypasses the calculated numerical PELD score.¹⁰⁻¹² These data formed the basis of the rationale for assessing frailty in patients with liver disease who are listed for LT because additional tools are clearly needed to determine the comprehensive health status of children with ESLD.

To date, frailty has not been assessed in children, and there is an unmet need for an objective comprehensive health assessment tool in chronic pediatric disease. We have designed the first prospective multicenter study of frailty in children with liver disease. We adapted the assessment of the 5 classic Fried Frailty Criteria for children, using validated pediatric tools and compared the results between children with ESLD listed for LT and children with chronic liver disease without evidence of hepatic decompensation (ie, compensated chronic liver disease). We hypothesized that frailty was prevalent among children with advanced liver disease and is a marker of morbidity that is not captured by conventional laboratory investigations.

Methods

Children aged 5-17 years with chronic liver disease awaiting LT (ESLD) or with compensated chronic liver disease (CCLD) without evidence of decompensation (as defined by progressive cholestasis, ascites, life-threatening gastrointestinal bleeding, hepatopulmonary syndrome, hepatorenal syndrome, life-threatening or recurrent sepsis) were identified from 17 academic pediatric North American LT centers between January 2013 and March 2016. Decisions regarding listing children for LT were based on standard clinical criteria and at the discretion of the individual center. At least the child or 1 caretaker had to speak English to participate in the study. Children had to be capable of performing the respective tests. Children taking corticosteroids at a dose higher than 0.1 mg/kg/day, with psychiatric disorders or physical disabilities (such as paraplegia or limb deformities), which may have impacted their ability to perform the frailty assessments, were not eligible to

participate. The lower cut-off of 5 years of age for eligibility was selected due to the availability of normative values for each test. Each participating site's institutional ethical research board approved the study.

Assessment of the 5 Fried Frailty Criteria was performed at a single time point in an ambulatory setting at one of the 17 participating centers. The Fried Frailty assessment was modified for children as described below and summarized in **Table I**. The assessments were typically performed by a combination of a research coordinator, dietician and/or physiotherapist. The lead site provided centralized training for each institution to ensure consistency in the assessments.

(1) Weakness—Grip strength was measured using a hand-held device, the Jamar Hand Dynamometer (Anatomy Supply Partners, Atlanta, GA).¹³ The device was squeezed 3 times by each hand, and the mean value of the recorded strength (in pounds) was taken as the final result and compared with standard values for age and sex.¹³ (2) Slowness—As in adults, slowness or endurance was assessed by the 6-minute walk test (6-MWT). Children used a standard hand wheel to capture the walked distance on a hard flat surface at their own pace. The covered distance expressed in meters (m) was compared with standard values for sex and age.¹⁴ (3) Shrinkage—The Fried Frailty Criteria capture unintentional weight loss (>10 pounds during the last year) as a measure of shrinkage. Because this is not feasible in growing children, shrinkage was assessed by triceps skin fold thickness (TSF) measurements. TSF was measured in triplicates by a dietician and the mean result was recorded in centimeters (cm) and compared with the Center for Disease Control age and sex normative values.¹⁵ (4) Exhaustion—In adult frailty studies, the presence of exhaustion is determined using 2 items drawn from the modified 10-item Center for Epidemiologic Studies-Depression scale.¹ For the adapted pediatric frailty assessment, the Pediatric Quality of Life Inventory 4.0 Multidimensional Fatigue Scale, a validated pediatric questionnaire, was used to assess fatigue.¹⁶ (5) Diminished Physical activity—The Minnesota Leisure Time Activities Questionnaire is used to ascertain physical activity in adults.¹ For children the age appropriate versions of the validated Modified Physical Activity Questionnaire (PAQ) (PAQ-A for children >13 years of age and PAQ-C for children <13 years of age) were used to assess physical activity.¹⁷

Table I. Tools used to assess frailty elements in adults compared with tools applied to assess frailty in children

Frailty elements	Concept used in adults	Concept used in children	Method used in our study
Weakness	Grip strength	Grip strength	Jamar hand dynamometer (kg/m ²)
Slowness	Gait speed	Walking distance	Hand wheel measured walking distance (m) after 6 min "normal" walking.
Shrinkage	Weight loss	Body constitution	Triceps skinfold thickness (cm)
Exhaustion	Self-report on scale	Validated pediatric questionnaires	PedsQL 4.0 Multidimensional Fatigue Scale 3 subscales (general fatigue, sleep/rest fatigue, cognitive fatigue) PedsQL Core 4.0 4 subscales (physical, emotion, social and school functioning)
Diminished physical activity	Estimated energy expenditure	Validated pediatric questionnaire	Modified PAQ PAQ-C (<13 y of age) and PAQ-A (>13y of age)

PedsQL, Pediatric Quality of Life Inventory.

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