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Functional Decline in Patients with Cirrhosis Awaiting Liver Transplantation: Results from the Functional Assessment in Liver Transplantation (FrAILT) Study

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Abstract

Background & Aims—Cirrhosis is characterized by sarcopenia and malnutrition, leading to progressive functional decline. We aimed to objectively measure functional decline in cirrhotics awaiting liver transplantation (LT) and its association with wait-list mortality.

Methods—Consecutive adults listed for LT with laboratory MELD 12 at a single center underwent functional status assessments *at every outpatient visit* using the Short Physical Performance Battery (SPPB; 0=impaired to 12=robust) consisting of gait, chair stands, and balance tests. Joint linear time-to-event analyses modeled the simultaneous impact of longitudinal trajectory of physical function on wait-list mortality (=death/delisted for being too sick for LT).

Results—Included were 309 LT candidates. Median laboratory MELD was 15, serum albumin was 3.0 g/dL, 28% had ascites, 18% hepatic encephalopathy, and 83% were Child class B/C. At a median follow-up of 14 months, 15% died/were delisted and 28% underwent LT. Average physical function worsened per 3 months on the wait-list: −0.38 kg in grip strength, −0.05 meters/

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second in gait, 0.03 seconds in chair stands, and −0.16 SPPB points. In joint models of longitudinal trajectories of physical function and wait-list mortality adjusted for MELD-Na, albumin, hepatocellular carcinoma, and baseline physical function, the longitudinal trajectories of each physical function measure were significantly associated with wait-list mortality: grip [hazard ratio (HR)=0.89, 95%CI=0.83–0.95], gait (HR 0.72, 95%CI=0.62–0.84), chair stands (HR=1.17, 95%CI=1.09–1.25), and SPPB<10 (HR=1.45, 95%CI=1.15–2.20).

Conclusions—LT candidates experience significant functional decline on the wait-list, despite modest wait-time and low baseline MELD. Decline in physical function is associated with an increased risk of death/delisting, independent of liver disease severity.

Keywords

surgery; functional status; sarcopenia; age; disability

INTRODUCTION

For patients with end-stage liver disease, liver transplantation offers the hope for cure. However, the majority of liver transplant candidates wait over one year for a liver, and nearly a quarter of candidates wait over four years (1). During this time on the wait-list, they are vulnerable not only to the easily diagnosed complications of cirrhosis such as spontaneous bacterial peritonitis and acute variceal bleed, but also to the more subtle – but equally lethal (2) – effects of muscle wasting, under-nutrition, and functional decline.

According to several conceptual models in the field of geriatrics (3,4), the accumulation of deficits that result from both aging processes (i.e., muscle loss, physical inactivity, and malnutrition) and chronic disease can manifest as frailty and functional impairment. Geriatrics tools to measure physical function have construct validity in cirrhotics, and liver transplant candidates display high rates of frailty and functional impairment at baseline (2). However, little is known of how the *cumulative* effect of cirrhotic complications impacts physical function over time in patients awaiting liver transplantation.

We hypothesized that liver transplant candidates experience accelerated functional decline, and that the trajectory of change in physical function is associated with wait-list mortality, independent of baseline physical function. Using data from the Functional Assessment in Liver Transplantation (FrAILT) Study, we tested this hypothesis.

METHODS

Study population

The FrAILT Study, initiated in 2012, is an ongoing prospective cohort study of adults (18 years) with cirrhosis who are actively listed for liver transplantation at the University of California, San Francisco (UCSF) and are seen in the outpatient UCSF Transplant Hepatology clinics. To ensure an adequate number of events during follow-up, only patients with a laboratory Model for End-Stage Liver Disease (MELD) score   12 are enrolled in the cohort. Patients were excluded if they had severe hepatic encephalopathy, as defined by the time to complete a Numbers Connection Test (5) of >120 seconds, as this may impair the

patient's ability to provide signed informed consent and completion of tests of physical function. The FrAILT Study cohort has a 97% recruitment rate (6). For this specific study evaluating changes in physical function on the wait-list, we analyzed data only from subjects with at least two assessments of physical function and six months of follow-up (322 excluded in total).

Study procedures and data collection

Physical function was assessed using the following four performance-based measures:

1. <u>Grip strength in kilogram (kg), average of three trials</u>. This was measured in each subjects' dominant hand using a hand dynamometer (Jamar Hydraulic hand dynamometer).

2. <u>Gait speed in meters/second</u>. Subjects were asked to walk eight feet as quickly as they could. Patients unable to walk at all (i.e., wheelchair bound) were assigned a gait speed of 0.01 meters/second.

3. <u>Timed repeated chair stands</u>. Starting from a seated position, subjects were asked to stand up and sit down without using their arms for assistance for a total of five times without assistance. Patients unable to perform this test at all were assigned a chair stands score of 32 seconds, the 99%ile value among patients who were able to perform this test.

4. <u>Short Physical Performance Battery</u> (7). This is an instrument of physical function that was developed and validated in a population of community-dwelling older adults (Supplementary Table). It comprises a summary of three separate measures (maximum of 4 points for each component): gait speed, balance, and timed repeated chair stands. Given that we evaluated gait speed and chair stands individually in their own models as continuous variables, we elected to dichotomize this variable (9 or >9), as evaluating the Short Physical Performance Battery as a continuous variable would simply reflect the sum of gait and chair stands. Conceptually speaking, a score of 9 or lower requires a patient to be deficient to a mild degree in *each* of the 3 components (1 point deducted for each measure) or at least 2 points deducted for one component (representing significant functional impairment) plus 1 point deducted for another component. This score of 9 has also been used as a cut-point in one of the original papers reporting the prognostic value of the Short Physical Performance Battery.(8) The Short Physical Performance Battery takes approximately 2–3 minutes to complete in the outpatient clinic setting.

All subjects underwent testing at enrollment and at every subsequent clinic visit. Demographics, medical co-morbidities, degree of ascites, and laboratory tests were collected from the patients' electronic health records at the time of their clinic visit. Degree of ascites was graded as severe/refractory if the patient was noted to have "severe" or "tense" ascites on physical exam during the clinic visit or required regular large volume paracenteses.

Statistical analysis

We compared differences in baseline characteristics between groups using chi-square, Wilcoxon rank sum, or Kruskal-Wallis tests for categorical and continuous variables, as appropriate. The primary outcome was time from first study assessment to wait-list mortality, defined as death prior to liver transplantation or delisting for being too sick for transplant. Patients who underwent live donor liver transplant were censored at the time of transplant as the timing of live donor surgery interrupts the natural trajectory of liver disease on the wait-list. Patients delisted for reasons other than being too sick (e.g., substance abuse, non-adherence) were censored from the FrAILT Study at the time of wait-list removal.

The primary predictor of interest was the longitudinal effect of physical function, as assessed by each of the four measures of physical function. We analyzed the data using a three-part approach.

a. To account for the inter-dependence of repeated measures of physical function from the same subject, linear mixed-effects models were first employed to evaluate both the fixed and random effects of physical function over time, adjusted for MELD-Na as a marker of liver disease severity. Time was included as a linear term, as both fixed and random effects. Random intercepts were included for each individual.

b. Cox proportional hazards models estimated survival on the wait-list. The clinically relevant variables that were evaluated in univariable analysis were: age, MELD-Na at enrollment, albumin, chronic HCV, hepatocellular carcinoma (HCC), moderate or severe hepatic encephalopathy (defined as a Numbers Connection Test (5) time of >60 seconds, and moderate or severe/refractory ascites). Co-variates associated with the primary outcome with a p<0.05 were included in the final multivariable models (MELD-Na at enrollment, albumin, and HCC).

c. Four separate joint models – one for each measure of physical function (grip strength, gait speed, chair stands, and the Short Physical Performance Battery) were created to model the simultaneous impact of the longitudinal trajectory of physical function on the time to death/delisting (R package "JM" (9)). The model posits that the hazard function at any given instant has the familiar proportional hazard from for baseline covariates, but is also allowed to vary proportionally with the longitudinal trajectory of physical function. More specifically, the hazard at time t is:

$$h(t) = h0(t) \exp(b*x+a*f(t))$$

where h(t) is the hazard at time t, h0(t) is a baseline hazard function, x is a baseline covariate, b is the log hazard ratio for covariate x, and a is the log hazard ratio for the functional status time t, f(t). We approached the analysis using a joint model rather than the more "traditional" Cox proportional hazards model because the Cox model assumes the value of the time-varying covariate remains constant between measurements (i.e., physical function remains the same or constant until physical function is actually measured again). The joint model, on the other hand, allows the covariate to vary between measurements by modeling the trajectory of the covariate

between data points. Above, we expressed the model for a single baseline covariate, but it is easily extended for multiple covariates.

We used MELD-Na as the marker of liver disease severity in our models; we selected this composite measure over the individual MELD-Na components in order to reduce the likelihood of model overfitting. However, a sensitivity analysis using the *individual* MELD-Na components (rather than the composite MELD-Na) in our analyses did not substantially change the hazard of death/delisting associated with each measure of physical function.

The UCSF Institutional Review Board approved this study. Statistical analyses were performed using SAS version 9.4 (Cary, NC) and R version 3.1.2 (10).

RESULTS

Baseline characteristics of the cohort

Included in this study were 309 liver transplant wait-list candidates with MELD 12 at enrollment, at least 2 assessments of functional status, and a minimum of 6 months of follow up in the FrAILT Study. Patients in this study had a median of 3 [interquartile range (IQR) 2–4, maximum 9] assessments during the study period with a median of 9.6 months (4.7–17.7) between the first and last assessments. Baseline characteristics of the cohort are shown in Table 1. Median (IQR) follow up time was 13.7 (8.0–22.8) months for the entire cohort. Median age was 59 years, 57% were non-Hispanic White, 51% had chronic hepatitis C (HCV). Only 20% of the cohort was listed with hepatocellular carcinoma, reflecting the study eligibility criterion of a laboratory MELD score 12. Median body mass index was 29 kg/m^2. Median laboratory MELD and MELD-Na were 15 and 18, respectively, and median serum albumin was 3.0 g/dL. The majority (72%) did not have ascites at enrollment while only 18% had moderate hepatic encephalopathy (patients with severe hepatic encephalopathy, defined as Numbers Connection Test score >120 seconds were excluded from the study). Rates of Child Pugh class A, B, and C were 17%, 65%, and 18% respectively.

Changes in physical function on the wait-list

The median (IQR) time between clinic visits was 116 days (91–182). In general, physical function worsened on the wait-list. Every 3 months, grip strength decreased by 0.38 kg [standard error (SE) −0.08, p<0.01], gait speed decreased by 0.05 meters/second (SE −0.05, p<0.01), and chair stands time increased by 0.03 seconds (SE −0.01, p<0.01). Short Physical Performance Battery score decreased by 0.16 points (SE −0.03, p<0.01) per 3 months.

By the end of follow up, 46 (15%) died or were delisted for being too sick for transplant, 85 (28%) underwent deceased donor liver transplant, and 23 (7%) were removed for reasons other than being too sick (e.g., inadequate social support, violation of substance abuse policies); 155 (50%) were still waiting on the list (including 18 patients who underwent live donor liver transplant, who were censored at the time of their transplant).

Patients who were still waiting on the list had more assessments compared with those who died/were delisted or underwent DDLT (3 vs. 2 vs. 3, p=0.02), but the number of

assessments did not differ between patients who died/were delisted compared with those who underwent DDLT (p=0.23). The median (IQR) change in MELD-Na every 3 months was 1.04 (0.00–2.96) for those who died/were delisted, 0.25 (−0.55–1.61) for those who underwent DDLT, and −0.03 (−0.68–0.42) for those who were still waiting (p<0.001 for the comparison of all 3 groups; p=0.07 for the comparison between died/delisted versus DDLT groups).

Table 2 shows physical function scores at baseline and last assessment among those who died/were delisted for being too sick (column A), those who underwent DDLT (column B), and those who were censored at the end of the study follow-up (either because they were still waiting, were removed for reasons other than being too sick, or underwent live donor liver transplant; column C).

Associations between changes in physical function and outcomes

We then employed joint models to analyze the association of longitudinal trajectories of physical function with wait-list mortality, adjusting our analyses for MELD-Na at enrollment, albumin, HCC, and baseline physical function (Table 3). We observed significant associations between the trajectories of physical function and wait-list mortality (Table 3). Specifically, for every 1 kg increase in grip strength (i.e., improvement in physical function), the risk of wait-list mortality decreased by 11% (p<0.01). Similarly, an increase in gait speed by 0.1 meters/second (i.e., improvement in physical function) was associated with a 28% decrease risk of wait-list mortality (p<0.01). A 1 second increase in chair stands (i.e., impairment of physical function) was associated with a 17% increase in wait-list mortality (p<0.01). Finally, compared to those who were robust by the Short Physical Performance Battery (score 10), those with a Short Physical Performance Battery score <10 had a 45% increased risk of wait-list mortality (p<0.01).

DISCUSSION

The life of a cirrhotic awaiting liver transplantation depends, quite literally, on three blood tests – total bilirubin, creatinine, and international normalized ratio of prothrombin time – that comprise the MELD score by which he or she is prioritized for organ offers. While the average MELD score at liver transplant is generally in the high 20s (and even in the mid-30s in areas of the U.S. with extreme organ shortages such as California and New York), the majority of candidates are listed with MELD scores around 15 (11). The "lucky" liver transplant candidate will experience an acute decompensating event that will propel his MELD score to a level *high* enough to land at the top of the list and *soon* enough to retain sufficient physiologic reserve to withstand this life-threatening stressor. But many patients wait for a protracted time during which they suffer from the treacherous effects of muscle wasting, under-nutrition, and fatigue – factors that are often not reflected by the MELD score. The cumulative effects of these "extra-hepatic" factors that are nearly ubiquitous in cirrhosis can leave patients highly vulnerable to adverse outcomes (e.g., sepsis, respiratory failure) with acute hepatic decompensation, rendering them too sick for transplant.

Clinicians know it when they see it: a cirrhotic who progresses from ambulating independently to sitting in a wheelchair over the course of several clinic visits is not likely to

survive to transplant. Our study provides clinicians who manage cirrhotics with objective tools to measure this decline and quantify its risk. Using a novel statistical approach of joint longitudinal-survival models to adjust for changes in MELD-Na score, we observed that the more rapid the decline in a liver transplant candidate's physical function – as measured by any one of four performance-based tests – the greater the risk of wait-list mortality.

We have previously demonstrated that patients with poor *baseline* physical function experience higher rates of wait-list mortality (2), independent of liver disease severity. In other words, a patient who shows up at her initial liver transplant evaluation with a weak grip, slow gait speed, or inability to stand up from a chair without assistance is unlikely to make it to transplant. What we set out to prove in this study was that physical decline out of proportion to changes in MELD-Na – and independent of baseline physical function – can further identify patients at risk for death on the wait-list. We offer an example of this (Figure). Imagine three male, non-HCC patients who are identical by their liver disease severity (both MELD-Na and serum albumin), non-HCC status, and baseline grip strength (in this example, we will chose 30 kg, the median grip strength for our cohort). Each of the three patients maintains a MELD-Na score of 17 for an entire year of observation (i.e., no change in liver disease severity), but Patient A maintains a steady grip strength of 30 kg, Patient B experiences a slow decline in grip strength to 26 kg (13% decline), and Patient C experiences a rapid and severe decline in his grip strength to 20 kg (33% decline) over the course of a year on the wait-list. Patient B will be predicted to have lower survival than Patient A, but the predicted risk of mortality for Patient C – the one with severe decline – will be even greater than both Patients A and B (Figure).

The selection of tools that we analyzed in this study was deliberate. While instruments to measure physical frailty and disability have construct validity in this cohort (2), they rely, at least in part, on self-reported components. In the context of transplantation, patients on the wait-list may feel that their candidacy depends upon their answers (which, in truth, may influence the perception of their providers, consciously or subconsciously). Tests based on actual performance are less susceptible to manipulation and therefore have strong advantages over self-reported instruments when thinking forward to the systematic application of physical function in selection and allocation decisions in transplantation.

We offer the following caveats to translating these data in clinical practice. First, these results are not generalizable to the inpatient setting; all study assessments, including the last assessment for each subject, were administered to outpatients. Second, to maximize recruitment and retention into the study, we assessed physical function at patients' clinic visits rather than at regular study intervals. The timing of clinic visits, and therefore study assessments, is informative, as sicker patients are seen more frequently than healthy patients. We therefore analyzed the change in physical function divided by the time that elapsed between visits, thereby accounting for differential time between visits.

Despite these limitations, our study has important implications for the care that we provide to patients with end-stage liver disease. For all cirrhotics, our data provide objective metrics to assess the efficacy of interventions to halt functional decline. For those awaiting liver transplantation, these data can compel patients with rapid physical decline – out of

proportion to a rise in their MELD score – to seek live donor liver transplant or accept higher risk donor livers. Whether measures of longitudinal physical function have a role in liver allocation requires confirmation of these results in other large cohorts and analyses using additional outcomes, including post-transplant. However, our study provides provocative evidence to justify more research this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

List of abbreviations

DDLT	deceased donor liver transplant
HCC	hepatocellular carcinoma
HCV	chronic hepatitis C
IQR	interquartile range
MELD	Model for End-Stage Liver Disease
SE	standard error

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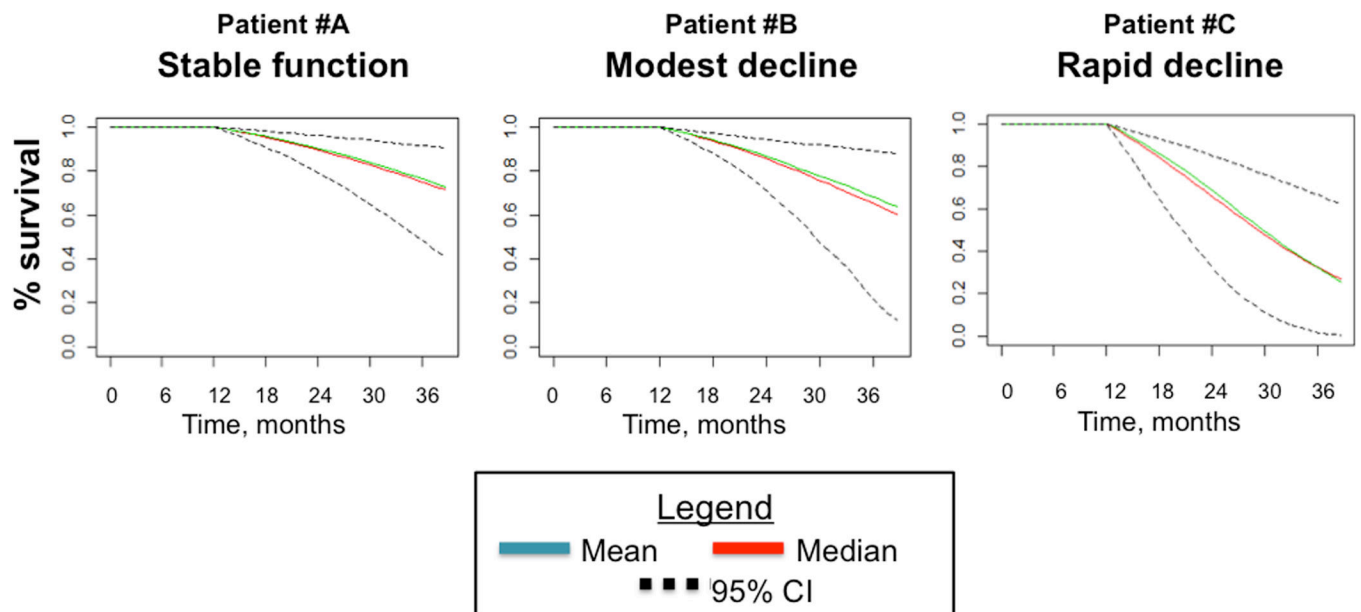
FIGURE 1.

Predicted probabilities of survival for three male non-HCC patients with a baseline grip strength of 30 kg and a baseline MELD-Na score of 17 with no change in MELD-Na over 12 months of observation (during which time they have 100% survival). Patient A experiences no change in grip strength, Patient B experiences a slow decline in grip strength to 26 kg, and Patient C experiences a rapid and severe decline in grip strength to 20 kg over 12 months.

Table 1

Baseline characteristics of 309 liver transplant candidates with MELD 12 who were included in this study.

Characteristic[*]		n=309
Follow up time, mos		13.7 (8.0–22.8)
Age, yrs		59 (53–63)
Female		110 (36%)
Race/ethnicity	White	176 (57%)
	Black	6 (2%)
	Hispanic	96 (31%)
	Asian	15 (5%)
	Other	16 (5%)
Etiology of liver disease	HCV	157 (51%)
	Alcohol	56 (18%)
	NASH	37 (12%)
	Cholestatic	34 (11%)
	Other	25 (8%)
HCC		62 (20%)
Weight, kg		85 (70–98)
BMI, kg/m^2		29 (25–33)
Laboratory tests		
Laboratory MELD		15 (13–18)
Laboratory MELD-Na		18 (1–21)
Total bilirubin, mg/dL		2.5 (1.7–3.6)
INR		1.4 (1.3–1.6)
Creatinine, mg/dL		0.9 (0.8–1.3)
Sodium, mEq/L		137 (134–139)
Albumin, g/dL		3.0 (2.6–3.4)
Ascites	Absent	222 (72%)
	Mild-moderate	77 (25%)
	Severe/refractory	10 (3%)
% hepatic encephalopathy[†]		56 (18%)
Child Pugh Score	A	53 (17%)
	B	200 (65%)
	C	56 (18%)

[*] Median (interquartile range) or n (%)

[†] Defined as Numbers Connection Test score >60 seconds at the time of enrollment.

Table 2

Change in physical function over time, categorized by outcome.

Measure[*]	A Died/Delisted n=46 (15%)	B Transplanted n=85 (28%)	C Censored[†] n=178 (57%)	p-value[‡] (A vs. B vs. C)	p-value (A vs. B)
Assessments and follow up					
Total study follow up time, mos	11.3 (5.8–16.6)	10.2 (5.9–17.6)	16.9 (11.5–27.4)	<0.01	0.78
Time from first and last assessments	6.8 (3.5–10.9)	6.3 (3.5–14.0)	12.8 (6.5–21.7)	<0.01	0.70
Time from last assessment to outcome	2.9 (0.8–6.1)	2.2 (1.2–3.7)	3.4 (1.5–7.1)	0.01	0.52
# of assessments	2 (2–3)	3 (2–4)	3 (2–5)	0.02	0.23
Grip strength, kg					
First assessment	27 (22–33)	33 (25–39)	31 (24–38)	0.12	0.04
Last assessment	24 (18–33)	33 (23–40)	29 (21–37)	<0.01	<0.01
Rate of change, per 3 months	−0.72 (−2.73–0.63)	−0.58 (−1.92–1.00)	−0.31 (−1.47–0.66)	0.43	0.39
Gait speed, m/sec					
First assessment	1.17 (1.00–1.35)	1.31 (1.07–1.59)	1.31 (1.07–1.64)	0.04	0.06
Last assessment	1.02 (0.56–1.28)	1.14 (0.90–1.39)	1.17 (0.94–1.33)	0.04	0.03
Rate of change, per 3 months	−0.05 (−0.16–0.07)	−0.10 (−0.18–0.03)	−0.04 (−0.10–0.01)	0.34	0.62
Chair stands, seconds					
First assessment	12.6 (10.4–16.5)	12.3 (10.1–16.5)	11.4 (9.3–14.9)	0.10	0.77
Last assessment	18.1 (11.4–30.0)	11.9 (10.1–17.5)	11.3 (8.6–15.7)	<0.01	<0.01
Rate of change, per 3 months	0.72 (−0.72–3.57)	0.18 (−1.57–2.11)	−0.02 (−0.51–0.56)	0.07	0.11
Short Physical Performance Battery Summary Score[§]					
First assessment	11 (9–11)	11 (9–12)	11 (9–12)	0.15	0.44
Last assessment	9 (6–10)	11 (9–12)	11 (9–12)	<0.01	<0.01
Rate of change, per 3 months	−0.47 (−1.31–0.00)	−0.14 (−0.99–0.00)	0.00 (−0.25–0.13)	<0.01	0.20

[*] Median (IQR) or %

[†] Subjects were censored if they were still waiting on the list at the end of study follow-up, were removed from the list for reasons other than being too sick for liver transplant, or underwent live donor liver transplant.

[‡] By the Kruskal-Wallis test

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§Performance-based instrument that consists of three tests: repeated chair stands, balance testing, and gait speed. Range 0 (frail) to 12 (robust).

Table 3

Adjusted analyses evaluating the associations between longitudinal trajectories of physical function and wait-list mortality.

	Longitudinal Trajectory of Physical Function[†]			
	Grip Strength, per kg increase	Gait Speed, per 1 m/sec increase	Chair Stands, per 1 sec increase	Short Physical Performance Battery Score <10
Hazard Ratio (95% CI) p-value	0.89 (0.83–0.95) <0.01	0.72 (0.62–0.84) <0.01	1.17 (1.09–1.25) <0.01	1.45 (1.15–2.20) <0.01

[*] Adjusted for the baseline physical function, hepatocellular carcinoma, baseline albumin, baseline MELD-Na, and the longitudinal trajectory of MELD-Na.

[†] Decline in physical function is represented by a decrease in grip strength, decrease in gait speed, increase in chair stands time, and decrease in Short Physical Performance Battery score.