**ORIGINAL ARTICLE** 



# **Evaluating Frailty and Exercise Capacity in Liver Cirrhosis: Comparative Insights** from Field Tests

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# ABSTRACT

**Purpose:** Liver cirrhosis, a chronic disease marked by progressive liver dysfunction, leads to increased frailty and diminished physical performance. We aimed to assess frailty and exercise capacity in individuals with cirrhosis using field tests and evaluate their correlation with frailty.

**Method:** Participants' demographic data and Model for End-stage Liver Disease (MELD) scores were recorded. Field tests included the Incremental Shuttle Walk Test (ISWT), 6-Minute Walk Test (6MWT), and 1-Minute Sit-to-Stand Test (1MSTST). Frailty was evaluated using the Liver Frailty Index (LFI), comprising chair stands, grip strength, and balance.

**Results:** Twenty-four patients were included in the study, with 85% identified as frail or pre-frail according to the LFI. A strong correlation was found between the 6MWT and ISWT (r=0.783; p<0.001), and a moderate correlation between the 6MWT and 1MSTST (r=0.604; p=0.004). The ISWT had a strong positive relationship with 1MSTST (r=0.713; p=0.001). Physical frailty scores were negatively correlated with the 6MWT (r=-0.474; p=0.035), ISWT (r=-0.582; p=0.009), and 1MSTST (r=-0.654; p=0.002). Principal component analysis (PCA) revealed component loadings in descending order: ISWT (0.956), 6MWT (0.859), and 1MSTST (0.818).

**Discussion:** This study identified a significant association between various field tests and frailty status in patients with liver cirrhosis. All field tests demonstrated a negative correlation with frailty. The strong correlation between the exercise tests and PCA results highlights ISWT as a key indicator of overall physical performance. These findings suggest that ISWT, along with the 6MWT and 1MSTST, can reliably assess physical frailty and exercise capacity in patients with liver cirrhosis.

Key Words: Liver cirrhosis, exercise test, frailty, physical fitness

## **INTRODUCTION**

Liver cirrhosis is a chronic liver disease associated with significant morbidity and mortality worldwide (1). It is characterized by the formation of fibrotic tissue and nodules in the liver parenchyma, resulting in several complications including portal hypertension, ascites, hepatic encephalopathy, and hepatocellular carcinoma (2). In recent years, along with the complications commonly seen in liver cirrhosis, the impact of sarcopenia and frailty has been frequently investigated, revealing a significant effect on mortality and morbidity (3). While the prevalence of sarcopenia in cirrhosis ranges from 40% to 70%, the prevalence of frailty ranges between 18% and 43% (4).

Frailty in cirrhosis is a clinical syndrome characterized by decreased physiological reserves and resistance to stressors resulting from chronic liver disease and associated metabolic and muscular dysfunctions (5). The relationship between liver cirrhosis and skeletal muscles leads to decreased exercise capacity, reduced muscle strength and endurance, and increased complaints of dyspnea and fatigue. Physical inactivity, endocrine disorders, and issues related to calorie and protein intake and utilization create a vicious cycle, further contributing to the onset of sarcopenia and frailty (3). Patients may also experience fatigue and dyspnea, further limiting their ability to perform physical activities (6-8).

The relationship between frailty and exercise capacity in liver cirrhosis is closely interlinked, influencing each other bidirectionally. Frailty exacerbates the decline in exercise capacity; conversely, reduced exercise capacity can accelerate the progression of frailty. This cycle significantly affects morbidity and mortality rates in patients with cirrhosis, influencing outcomes such as hospitalization rates and overall survival (9). Exercise capacity, often assessed through field tests such as the 6-Minute Walking Test (6MWT), is increasingly recognized as a vital indicator of frailty in liver cirrhosis. Additional measures like grip strength and gait speed provide complementary insights into frailty. Reduced exercise capacity not only correlates strongly with frailty but also serves as an independent predictor of adverse outcomes. including waitlist mortality. hospitalizations, and post-transplant complications (10).

A variety of methods have been used to evaluate frailty in individuals with liver cirrhosis, including the Liver Frailty Index (LFI), Clinical Frailty Scale, Fried Frailty Index, and performance-based assessments such as the 6MWT, grip strength, and gait speed (11). Among these, the 6MWT has been extensively used in clinical settings to evaluate submaximal exercise capacity, which provides valuable insights into the functional reserve of cirrhotic patients (10). However, the performance of different field tests in this patient population and their relationship with frailty remains largely unexplored. In clinical practice for other disease groups, maximal exercise capacity is often assessed using field tests such as the Incremental Shuttle Walk Test (ISWT), which offers a graded assessment of functional capacity (12, 13). Additionally, simpler and time-efficient tools, such as the 1-Minute Sit-to-Stand Test (1MSTST), can provide valuable insights into physical fitness but both of the tests have not been studied in liver cirrhosis (14).

Despite the assessment of frailty as a critical determinant of health outcomes in patients with liver cirrhosis, there is a lack of studies evaluating exercise capacity using field tests. Furthermore, the relationship between these field tests and frailty has not been comprehensively investigated. This study aims to assess frailty and exercise capacity in individuals with liver cirrhosis using field tests and to evaluate their correlation with frailty. We hypothesize that physical frailty will demonstrate significant correlations with exercise capacity across all field tests used in the study, providing further insights into these tests' role in frailty assessment in liver cirrhosis.

# **METHODS**

# **Study Design**

This cross-sectional study was conducted at the Department of Internal Medicine, Division of Gastroenterology, Hacettepe University, focusing on patients with liver cirrhosis. The study received ethical approval from the Hacettepe University Health Sciences Research Ethics Committee on 09/10/2019 (GO-19/786). All participants provided informed consent.

## Patients

Volunteer participants aged 35-75 years, who had been followed up for liver cirrhosis for at least one year and/or were on the liver transplantation waiting list, were included in the study. Participants receiving primary prophylactic treatment for gastroesophageal varices were also included. The exclusion criteria were undergoing liver and/or other organ transplantation, large gastrointestinal varices without beta-blocker use, persistent hepatic encephalopathy, an ejection fraction <50%, a positive stress test (>1 mm ST segment depression), hepatocellular carcinoma, uncontrolled pulmonary hypertension, and orthopedic or neurological conditions that could interfere with study procedures.

#### Assessments

Demographic data, including participants' age, height, weight, and body mass index (BMI), were obtained from medical records. The Model for End-Stage Liver Disease (MELD) and MELD-Na scores, which provide an estimate of the severity of liver disease based on sodium level, serum bilirubin, serum creatinine, and the international normalized ratio (INR), were also calculated for each participant (15).

The following assessments were conducted to evaluate physical performance and frailty levels:

*Incremental Shuttle Walk Test:* The ISWT is a widely used tool for assessing cardiorespiratory fitness and exercise capacity. The test involved walking along a 10-meter distance at a predetermined pace regulated by an audio signal. Participants walked down a corridor and back in time with audio signals that increased in frequency until they were unable to keep pace or until the test ended. The distance covered and time taken to complete the test were recorded to evaluate an individual's exercise capacity and cardiorespiratory fitness levels (16).

**6-Minute Walking Test:** The 6MWT has been used in both research and clinical settings to evaluate exercise tolerance, monitor disease progression, and assess treatment efficacy in various chronic conditions that affect functional capacity. The test was conducted in a marked 30-meter corridor, and participants were instructed to walk as far as possible at their own pace for six minutes. Verbal encouragement was given during the test, and participants were allowed to rest for short periods if needed. The distance covered by the participants was recorded in meters (17).

*1-Minute Sit-to-Stand Test:* The 1MSTST was used to evaluate exercise capacity (18). The participants were asked to sit on a 43 cm-high chair without using their arms folded in front of their chest. After the word "go," participants were instructed to stand up completely and then return to the seated position as many times as possible in one minute. Standardized verbal encouragement was provided during the test, and the number of successful stand-ups completed was recorded (19).

*Liver Frailty Index:* The LFI score was calculated using the standardized measurements obtained from hand grip strength, time to chair stands, and balance tests. The LFI score was derived using the equation provided on the LFI website (https://liverfrailtyindex.ucsf.edu), which integrates these physical performance measures into a composite frailty score. The following standardized tests were conducted on the patients (20):

*Hand Grip Strength:* The patients were instructed to grip the dynamometer (Jamar Hydraulic Hand Dynamometer, The Baseline, USA) with their dominant hand in the standard position and squeeze it as hard as possible. This was repeated thrice, and the values were recorded in kilograms for each attempt. The device was zeroed after each trial and the patient was not allowed to rest on any surface while gripping it.

*Time to Chair Stands:* The patient was timed for the duration it took to stand up and sit down in a chair five times without using their arms, while keeping their arms folded across their chest. The timer was started when the patient first rose out of the chair, and stopped when they were standing after the fifth chair rise.

*Balance:* The patient was tested in three positions: side-byside, semi-tandem, and tandem, and was asked to maintain each position for 10 seconds. The timer was started when the patient's feet were in the correct position and they had let go of any support. If the patient was unable to complete the whole ten seconds, the time in seconds was recorded to one decimal place. If the patient was able to hold the position for ten seconds, ten was recorded as the time, and they were then asked to move to the next pose.

Based on the LFI score, participants were classified into three categories; robust (LFI score <3.2), pre-frail (LFI score between 3.2 and 4.4), and frail (LFI score  $\geq 4.5$ ).

LFI and 1MSTST were initially administered to patients with liver cirrhosis. Subsequently, the 6MWT was conducted, followed by the ISWT after one hour of rest. All measurements were performed on the same day. Categorical variables were reported as frequency and percentage (%), and continuous variables were reported as mean ± SD, median, minimum, and maximum. Pearson and/or Spearman correlation coefficients were calculated to determine associational significance. We also interpreted them as weak (<0.40), moderate (0.40-0.70), and strong (>0.70). For normality, the Shapiro-Wilk test was used. The Kruskal-Wallis H test and One-Way ANOVA were used to differentiate the frailty group, and Bonferroni adjustment was applied. In addition, we evaluated the exercise tests (6MWT, ISWT, and 1MSTST) using principal component analysis (PCA) to identify the shared variance among the tests and determine their contributions to a unidimensional construct of exercise capacity. PCA allowed us to assess the relative importance of each test in explaining the total variance in exercise performance. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 26.0) for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was set at 0.05. The sample size computed as 23 for the correlation coefficient provided a large effect size (0.50), type I error (0.05), and power (0.80)using GPower 3.1.9.6.

#### RESULTS

A total of 24 patients with liver cirrhosis (16 female and 8 male) who met the inclusion criteria were included in the study. The patients included in the study comprised of 62.5% with compensated cirrhosis and 37.5% with decompensated cirrhosis. Their MELD and MELD-Na scores were 10.32 (*SD* = 3.85), and the MELD-Na was 11.09 (*SD* = 3.89), respectively. The descriptive statistics and measurement results for the patients with cirrhosis are presented in Table 1.

**Table 2.** The relationship among the frailty groups

Exercise Tests	Frail (n=8)	Pre-frail (n=9)	Robust (n=3)	F/H	р
	Mean <i>(SD)</i>	Mean <i>(SD)</i>	Mean <i>(SD)</i>		
6MWT Distance (m)	405.44 <sup>a</sup> (49.86)	529.33 <sup>b</sup> (81.45)	427.53 (72.66)	7.32	0.005*
ISWT Distance (m)	261.71 <sup>a</sup> (50.91)	451.89 <sup>b</sup> (99.63)	377.33 (127.60)	8.94	0.002*
1MSTST (reps)	17.87 <sup>a</sup> (6.20)	29.00 <sup>b</sup> (7.76)	31.33 (11.01)	5.73	0.024*

 $^{\delta}$ 6M WT: 6-Minute Walking Test, ISWT: Incremental Shuttle Walk Test; 1MSTST: 1-Minute Sit-to-Stand Test, <sup>a,b</sup> There is a difference among different letters; \* Kruskal Wallis test p<0.05

The mean distance of patients according to exercise tests was 427.48 m (SD=132.41) for 6MWT, 370.05 m (SD=122.50) for ISWT, and mean repeats of 1MSTST were 24.29 (SD=9.55). Twenty patients with liver cirrhosis had LFI scores, and the mean LFI score was 4.16 (SD=0.83). Forty% (n=8) of the patients in the study were frail, 45% (n=9) were pre-frail, and 15% (n=3) were robust according to the LFI.

Table 1. De	scriptive	statistics	of the	participants

		Patient with Cirrhosis (n=24)	
Characteristics	Median (IQR)		
Age (years)		59 (17.25)	
Height (cm)		160 (15.25)	
Weight (kg)	73.25 (15.50)		
BMI (kg/m <sup>2</sup> )		27.26 (7.24)	
		n (%)	
Gender	Female	16 (66.7)	
	Male	8 (33.3)	
		Mean (SD)	
MELD (score)	10.32 (3.85)		
MELD-Na (score)	11.09 (3.89)		
Exe	ercise Capa	acity Tests	
6MWT Distance (n	427.48 (132.41)		
ISWT Distance (m	370.05 (122.50)		
1MSTST (reps)	24.29 (9.55)		
Liver Frailty Index	(n=20)		
Hand Grip (kg)	28.00 (13.09)		
Time to Chair Star	12.33 (3.57)		
Balance (seconds)	12.19 (2.41)		
Frailty Score	4.16 (0.83)		

BMI: Body Mass Index, MELD: Model for End-Stage Liver Disease (MELD) score; 6 MWT: 6-Minute Walking Test, ISWT: Incremental Shuttle Walk Test; ISST: 1-Minute Sit-to-Stand Test; sec: second

As for the exercise capacity tests, the 6MWT had a strong relationship with the ISWT (r=0.783; p<0.001), and a moderate positive relationship with the 1MSTST (r=0.604; p=0.004).

As for the exercise capacity tests, the 6MWT had a strong relationship with the ISWT (r=0.783; p<0.001), and a moderate positive relationship with the 1MSTST (r=0.604; p=0.004). ISWT had a strong positive relationship with 1MSTST (r=0.713; p=0.001). In addition, we evaluated the interrelational structure using PCA. In the unidimensional performance structure, the total variance was 77.36%. The component loadings of the three measures according to magnitude were obtained ISWT (0.956), 1MSTST (0.818), and 6MWT (0.859).





The physical frailty score was negatively correlated with the 6MWT (r=-0.474; p=0.035), ISWT (r=-0.582; p=0.009), and 1MSTST (r=-0.654; p=0.002). There was a statistically significant difference in 6MWT, ISWT, and 1MSTST in LFI categories labeled frail and pre-frail (p<0.05) (Table 2, Fig 1).

#### DISCUSSION

This study highlights the important connection between performance measures and frailty in patients with liver cirrhosis. The majority of patients with cirrhosis in the study were frail, and frailty was related to reduced exercise capacity. Although the 6MWT, ISWT, and 1MSTST can all be used to assess exercise capacity, our findings suggest that the ISWT is the most reflective measure for patients with liver cirrhosis.

Physical frailty, often measured using performance-based tools like the LFI, has garnered significant attention due to its strong association with exercise capacity and adverse clinical outcomes in patients with liver cirrhosis. Notably, frailty and reduced exercise capacity are associated with poorer clinical outcomes and higher mortality rates in this population (21,

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22). Reduced exercise capacity and muscle strength are independently related to lower survival rates after liver transplantation, highlighting the importance of exercise capacity as a prognostic tool for liver cirrhosis (21). In our study, frailty was assessed using an index of hand grip strength, balance, and lower-extremity muscle strength. A significant proportion of patients with cirrhosis had frailty, with a notable correlation between the degree of frailty and exercise capacity. Specifically, patients categorized within the frail group demonstrated substantially reduced exercise capacity compared with those in the pre-frail group. Previous studies utilizing the LFI have demonstrated similar relationships, where higher LFI scores are significantly associated with reduced exercise capacity, as measured by tests such as the 6MWT (23). A systematic review emphasized that frail patients with liver cirrhosis on the transplant waiting list often show diminished exercise capacity (24). These findings are consistent with our results, where frail patients exhibited substantially reduced exercise capacity compared to their pre-frail counterparts.

The primary test used to evaluate exercise capacity in liver cirrhosis is cardiopulmonary exercise testing (CPET), which measures maximal oxygen consumption (VO<sub>2max</sub>) during peak exercise (25). This test is particularly valuable in the context of liver cirrhosis because it can reveal the impact of extrahepatic complications, such as deconditioning, muscle weakness, anemia, and cirrhotic cardiomyopathy on exercise capacity (20). However, there are disadvantages and challenges associated with these tests. CPET is a complex and resource-intensive procedure that requires specialized equipment and trained personnel. However, it may not be readily available in all clinical settings. Research has demonstrated that the 6MWT is a useful tool for assessing physical function in cirrhosis patients, with the distance of the 6MWT serving as a potential prognostic indicator in patients with liver cirrhosis (26). In addition to its prognostic value, the 6MWT has been found to predict mortality in patients with cirrhosis awaiting liver transplantation (10). This underscores the importance of including the 6MWT in the Cirrhosis frailty toolkit, as recommended by the American Society of Transplantation (10).

Although the 6MWT is a well-established test, the ISWT has also been used to evaluate exercise capacity, particularly in chronic respiratory diseases (27). The other functional exercise capacity test, 1MSTST, correlates with clinical outcomes such as exercise capacity and physical activity in daily life in patients with chronic obstructive pulmonary disease, suggesting its utility in assessing functional capacity in chronic diseases (28).

Our findings suggest that the 6MWT and ISWT are significantly correlated with each other, indicating that both tests could be interchangeably used to assess physical endurance and capacity in cirrhotic patients. Moreover, the 1MSTST also showed a substantial relationship with the other two tests, albeit slightly weaker, suggesting that it can serve as a viable alternative when more comprehensive assessments are not feasible owing to time constraints or patient conditions.

Our study revealed a moderate negative correlation between physical frailty score and all three exercise capacity tests (6MWT, ISWT, and 1MSTST). This underscores the impact of frailty on diminishing physical capabilities, thus highlighting the importance of regular physical assessments in the clinical management of liver cirrhosis. The association between physical frailty and diminished physical capabilities is supported by the findings of a study, where frail patients with cirrhosis had poorer performance in the 6MWT, 30second chair stands, and other exercise capacity tests (29). This study also emphasized that frailty in cirrhosis is a multidimensional construct that incorporates endurance, strength, and balance, which are critical factors in physical performance.

The ISWT is a significant determinant of physical fitness and the likelihood of meeting physical activity recommendations in patients undergoing cardiac rehabilitation (30). The strong correlation between the ISWT and VO<sub>2</sub>max in patients undergoing cardiac transplantation further supports the validity of the ISWT as a surrogate measure of exercise capacity (31). In COPD, the ISWT has been shown to correlate significantly with peak exercise capacity, suggesting that it could estimate peak exercise capacity with an accuracy similar to that of laboratory cycle tests (32). The outcomes of our PCA underscore the pivotal role of ISWT as the primary determinant of overall physical performance within the context of this study. The ISWT's established role in assessing physical performance across various diseases, its correlation with VO<sub>2peak</sub> (33, 34), and its prognostic value in predicting clinical outcomes make it an essential tool for evaluating physical performance in liver cirrhosis patients. Our study's results suggest that ISWT should be considered a key component of the clinical assessment of patients with liver cirrhosis.

### Limitations

While this study provides valuable insights into the relationship between frailty and exercise capacity in liver cirrhosis, several limitations should be acknowledged. Larger, multi-center studies are needed to validate these results. Future longitudinal studies could explore how changes in exercise capacity over time correlate with clinical outcomes in cirrhosis patients.

# CONCLUSION

This study highlights the critical role of frailty and its significant prevalence among patients with liver cirrhosis, as a large proportion of the participants were categorized as frail. Additionally, the findings establish important relationships between frailty and exercise capacity assessed through field tests, underscoring the utility of these tests in evaluating frailty in this population. Among the tests used, the ISWT demonstrated particular promise as an effective and practical tool for assessing physical performance. Incorporating frailty assessments and exercise capacity tests like the ISWT into routine clinical practice could improve the understanding and management of frailty in liver cirrhosis, ultimately leading to better patient outcomes.

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Ünal; Formal Analysis, Validation, Software. Naciye Vardar Yağlı: Supervision, Project Administration, Methodology.

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