

# Association between fatigue and exercise capacity in patients with chronic liver disease awaiting liver transplantation

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**ABSTRACT** – **Background** – Fatigue is highly prevalent in end stage liver disease, the studies about its association with exercise capacity in cirrhotic patients before liver are scarce. **Objective** – In this study, we evaluated fatigue in 95 in end stage liver disease patients awaiting transplantation, compared to healthy volunteers, and tested the association between exercise capacity and fatigue. **Methods** – Cross-sectional study of patients with chronic liver disease treated at a referral center in Fortaleza, Brazil. Fatigue was quantified with the Fatigue Severity Scale. The patients were submitted to the 6-min walk test, the 6-min step test, the Hospital Anxiety and Depression Scale, C-reactive protein measurement and hematocrit count, measurement of dyspnea among other tests. Fatigue data were obtained from healthy individuals for comparison with patients. **Results** – The mean age of patients was  $45.9 \pm 12.3$  years, and 53.7% were male. Fatigue, anxiety and depression levels were higher among end stage liver disease patients than among controls. A negative correlation was observed between 6 min step test and Fatigue Severity Scale score ( $r = -0.2$ ;  $P = 0.02$ ) and between hematocrit count and Fatigue Severity Scale score ( $r = -0.24$ ;  $P = 0.002$ ). Dyspnea on the Borg scale and fatigue were positively correlated ( $r = 0.31$ ;  $P = 0.002$ ). In the multivariate analysis, low 6-min step test values and high levels of dyspnea were associated with fatigue. **Conclusion** – Fatigue was more prevalent and severe in end stage liver disease patients than in healthy controls. Low 6MST values and high levels of dyspnea were associated with fatigue in this scenario.

**HEADINGS** – Fatigue. Liver diseases. Liver transplantation. Walk test. Exercise test.

## INTRODUCTION

Many chronic illnesses are accompanied by fatigue, including end-stage liver disease (ESLD)<sup>(1,2)</sup>. Patients with ESLD often suffer from muscle wasting, malnutrition and weakness as well<sup>(1)</sup>.

Using a reliable fatigue scale and a validated questionnaire is an important issue for both clinicians and researchers. The Fatigue Severity Scale (FSS) has well-documented psychometric properties and may be used to evaluate fatigue in cirrhotic patients<sup>(3)</sup>.

The 6-minute walk test (6MWT) and 6-minute step test are simple and practical tests to measure exercise capacity. They evaluate the global and integrated responses of all the systems involved in exercise: cardiopulmonary systems, systemic and peripheral circulation, neuromuscular function, and muscle metabolism<sup>(4)</sup>. Patients with cirrhosis are reported to have significantly lower 6MWT values than individuals with stable chronic viral hepatitis, or healthy volunteers<sup>(5)</sup>. In a cohort study with 100 patients submitted to liver transplantation, Magalhães et al. found 6MST and 6MWT to be associated with postoperative respiratory complications<sup>(6)</sup>.

The association between exercise capacity and fatigue has been observed for other chronic diseases<sup>(7,8)</sup>. However, to our knowledge, no previous study has specifically addressed this association in patients with end stage liver disease (ESLD). A better understanding of fatigue in end stage liver disease (ESLD)

patients and its correlation with physical function is useful when tailoring physical training interventions for patients awaiting liver transplantation.

The primary objective of this study was to evaluate fatigue in end stage liver disease (ESLD) patients undergoing pretransplantation assessment, compared to a control group of healthy volunteers. We also tested the potential association between exercise capacity and fatigue in our patients.

## METHODS

This was a cross-sectional study of 100 adult ESLD patients undergoing pretransplantation assessment at a teaching hospital in Brazil between July 2015 and July 2017. Previous studies found correlations between exercise capacity and fatigue in chronic diseases<sup>(6,7)</sup>. This sample size calculation was based on the hypothesis that functional exercise capacity was at least well correlated with fatigue. We enrolled 100 patients, at  $\alpha$ (two-side) = 0.05,  $\beta$  = 0.20 and  $r = 0.30$ . Five patients were excluded due to musculoskeletal conditions limiting their ability to walk, leaving a final sample of 95. All subjects attending the outpatient liver transplantation clinic performed the functional tests (6MWT and 6MST). Demographic and clinical data were collected, including sex, age, history of chronic live disease, Child-Pugh classification and MELD score.

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In addition, all patients had their serum level of C-reactive protein measured and were evaluated with the Hospital Anxiety and Depression Scale (HADS), the Borg scale for dyspnea, and the FSS. The control group consisted of healthy volunteers from a local senior community center. They were evaluated for liver diseases and others comorbidities by a questionnaire. The study was approved by the local research ethics committee and filed under entry #1.421.378. All subjects gave their written informed consent prior to study entry.

### Outcome parameters

The primary outcome parameter was fatigue scored on the FSS, a 7-point Likert scale (1=strongly disagree; 7=strongly agree). The total score was obtained by adding all the items and dividing the sum by the number of statements in the instrument (n=9). Higher scores indicate greater severity<sup>(9)</sup>. In this study we used the Portuguese-language version of the FSS<sup>(10)</sup>.

### Exercise capacity

A 30 m corridor was used to perform the 6MWT: the patients were instructed to walk the greatest possible distance during 6 min<sup>(4)</sup>. For the 6MST, the patients were instructed to step up and down a 20 cm step with anti-slip surface as many times as possible during 6 min. The greater the number of steps, the greater the exercise capacity<sup>(11)</sup>.

### Anxiety and depression

Depression and anxiety levels were determined with the Portuguese version of the HADS<sup>(12)</sup> which features seven items related to anxiety and seven items related to depression<sup>(13)</sup>.

### Borg scale

The Borg scale is a categorical scale scored from 0 to 10 (0=no breathing difficulty; 10=maximal breathing difficulty)<sup>(14)</sup>.

### Statistical analysis

The normality of distribution was verified with determination of frequencies and the Shapiro-Wilk W test with distribution plots. Normally distributed data were analyzed with Student's *t* test. Pearson's chi-squared test or Fisher's exact test was used for the categorical variables, as appropriate. The results of the tests (FSS, HADS, 6MWT, 6MST, MELD, hematocrit count) were submitted to Spearman's correlation test. Variables with a *P*-value of <0.05 in the correlation analysis were used as independent variables in a linear regression analysis, with fatigue as dependent variable. A backward stepwise elimination algorithm (*P*=0.05) was used for the variables remaining in the final model. All analyses were performed with the software IBM SPSS Statistics v. 17.0.

## RESULTS

Slightly over half the patients were male (53.7%; 51/95) and the mean age was 45.9±12.3 years. The main factors involved with liver disease were the following: alcoholism, Virus and alcoholic liver, virus (29.4%, 21.1%, 13.7% respectively). Liver cancer plus alcohol or virus was also frequent among patients (24.2%). The mean results of the 6MWT and the 6MST were 353.2±148 m and 68.2±19.9 steps, respectively (TABLE 1).

The levels of fatigue, anxiety and depression were significantly higher in ESLD patients than in the control group (TABLE 2).

**TABLE 1.** Baseline characteristics of all patients with end stage liver disease at Pretransplantation Evaluation (n=95).

	Patients
Gender	
Female N (%)	44 (46.3%)
Male N (%)	51 (53.7%)
Age (years) – mean (±SD)	45.9±12.3
6MWT – mean (±SD)	353.2±148
6 MST – mean (± SD)	68.2±19.9
Ht – mean (±SD)	36.3±4.4
C-reactive protein (mg/L) – mean (±SD)	2.39±1.1
Etiology of liver disease N (%)	
Only virus	13 (13.7%)
Virus + alcoholic liver disease	10 (21.1%)
Only alcoholism	28 (29.4%)
Virus + liver cancer	6 (6.3%)
Alcohol + liver cancer	5 (5.3%)
Virus + alcohol + liver cancer	12 (12.6%)
Autoimmune hepatitis	2 (2.1%)
Cryptogenic cirrhosis	9 (9.4%)
MELD – mean (±SD)	20.2±2.74
Child Pugh class B and C – N (%)	67 (70%)
Ascites – n (%)	36 (34.2%)
Respiratory symptoms – N (%)	47 (49.4%)
Borg scale – mean (±SD)	3.76±1.7

SD: standard deviation; 6MWT: 6 minute walking test; 6MST: 6 minute step test; MELD: Model For End-Stage Liver Disease; Ht: hematocrit.

**TABLE 2.** Comparison of the two groups (patients with end stage liver disease and healthy volunteers).

	Patients ESLD (95)	Healthy volunteers (95)	<i>P</i>
Age – mean (±SD)	45.9±12.3	45.8±12.7	0.9
Gender			
Male, n (%)	51 (53.6%)	43 (45.2%)	0.3
Female, n (%)	44 (46.3%)	52 (54.7%)	
FSS – mean (±SD)	4.2±1.6	3.7±1.04	0.003
Anxiety according to HAD – mean (±SD)	11.6±1.8	6.4±2.6	0.001
Depression according to HAD – mean (±SD)	11.8±2.3	6.6±2.2	0.001

A negative correlation was observed between 6MST and FSS scores ( $r = -0.2$ ;  $P = 0.02$ ) and between hematocrit count and FSS ( $r = -0.24$ ;  $P = 0.002$ ). Borg scores were positively correlated with fatigue ( $r = 0.31$ ;  $P = 0.002$ ) (TABLE 3).

The scores of FSS did not allow to differentiate between female and male (3.5±0.9 vs 3.8±1.09;  $P = 0.8$ ), Child Pugh class B/C and class A (3.7±1.07 vs 3.6±1;  $P = 0.9$ ) nor between alcoholic group and non-alcoholic group (4.3±1.5 vs 3.8±1.7;  $P = 0.17$ ).

To determine which factors were independent predictors of fatigue in ESLD patients, we performed a multivariate analysis. All factors with a *P*-value of <0.05 in the univariate analysis were submitted to regression model. In the multivariate analysis, low 6 MST and high scores borg dyspnea scale were identified in the linear regression analysis as good predictors of fatigue (TABLE 4).

**TABLE 3.** Factors correlated with Fatigue levels of Patients with end stage liver disease at Pretransplant Evaluation (n=95).

	FSS	
	r	P
Age (years)	-0.04	0.69
6MWTmeters	0.02	0.84
6 MST (steps)	-0.23	0.02
Borg dyspnea scale	0.25	0.01
Hematocrit	-0.24	0.01
C-reactive protein	0.03	0.77
MELD	0,06	0,53
Anxiety according to HAD	0.05	0.62
Depression according to HAD	0.07	0.47

FSS: fatigue severity scale; HAD: hospital anxiety and depression; 6MWT: 6 minute walking test, 6MST: 6 minute step test, MELD: Model For End-Stage Liver Disease.

**TABLE 4.** Independent Predictors of Fatigue Severity at Pretransplant Evaluation in Multiple Linear Regression Analyses.

Predictors	Coefficients	Standard error	Student' t test	P	95% CI
Constant	3.63	1.70	2.13	0.03	0.24–7.01
Borg dyspnea scale	0.20	0.09	2.07	0.04	0.08–0.39
6MST	-0.01	0.008	-2.001	0.04	-0.03–0.00
HT	0.01	0.039	0.433	0.66	-0.06–0.09

CI: confidence interval; 6MST: 6 minute step test; HT: hematocrit.

## DISCUSSION

In the current study, ESLD patients undergoing pretransplant assessment displayed high levels of fatigue. As shown by the univariate analysis, fatigue was associated with anemia and dyspnea. Our findings match those of earlier studies showing an association between anemia and fatigue in cirrhotic patients<sup>(15)</sup>. A common complaint in patients with chronic liver disease, dyspnea is strongly associated with fatigue and severely compromises daily activities and quality of life<sup>(16)</sup>.

The observed mean 6MST value (68.2±19.9 steps) is significantly inferior to the normal range of healthy Brazilian adults ( $P<0.0001$ )<sup>(11,17)</sup>. ESLD patients may display disorganized muscular, pulmonary and cardiovascular components of exercise capacity<sup>(18,19)</sup>. Previous studies have shown that exercise capacity is impaired in ESLD patients as well<sup>(5,20,21)</sup>. We used the six minute step test to evaluate the exercise capacity, this test provides an objective measure of global physical function with advantages of safety, simplicity and low cost.

Fatigue is a common complaint in end-stage liver patients in a transplant list<sup>(22)</sup>. According to van den Berg-Emons et al.<sup>(23)</sup>, this complaint remain for up to one year after liver transplantation. It is important to emphasize that fatigue can be difficult to measure and several questionnaires have been developed and tested in ESLD patients<sup>(3,15)</sup>. In this study we adopted the FSS, a validated fatigue scale known to provide reliable results in this setting<sup>(3)</sup>.

The present study confirmed an inverse correlation of 6MST and FSS in this patient population, indicating that the higher the degree of fatigue, the lower the exercise test. This reinforce the role of this test to quantify fatigue before liver transplantation and suggest that this is an important aid when tailoring physical training intervention for patients awaiting liver transplantation. Recently Duarte-Rojo et al.<sup>(24)</sup> in a review article, proposed that patients with ESLD on the transplant waiting list should perform 30 to 60 minute exercise sessions combining both aerobic and resistance training to achieve 150 minutes/week. There is a need for larger and better-designed clinical trials to investigate the role of exercise on clinical outcomes in LT candidates.

Significant correlations were found between dyspnea and fatigue. Previous study found significant correlations between chronic dyspnea and muscle fatigue<sup>(16,25)</sup>.

Anxiety and depression symptoms were not significantly correlated with fatigue, possibly because of the generally low anxiety and depression scores observed among our patients. Alcoholic abuse was not correlated with fatigue, a possible reason could be that patients were former alcoholic. This is because patients waiting for liver transplantation are commonly required to demonstrate six months of sobriety before they're allowed to register.

There was an unexpected lack of association between child-Pugh class and FSS. Traditionally, instruments like FSS evaluate many aspects of fatigue such as motivation, exercise and physical functioning of the individual<sup>(10)</sup> and Child-Pugh score considers clinical and laboratory markers of disease. As previously demonstrated by Swain MG, the complaint of fatigue in the setting of chronic disease, including liver diseases, may not correlate with traditional markers of disease activity or severity<sup>(26)</sup>.

The study was limited by the cross-sectional design, making it impossible to evaluate the responsiveness of the FSS over time (liver transplantation). Moreover, our patients came from a single referral center; conceivably, the ESLD patient profile at other liver transplant centers may be somewhat different from ours. It was not possible to measure sarcopenia, but the patients performed exercise test, like six minute step test that provide an objective measure of global physical function. It is consider that low physical function is one of the factor associated with sarcopenia<sup>(24,27)</sup>.

Some relevant cofactors such as grade of ascites, encephalopathy and malnutrition were evaluated based on the child-Pugh score. The diagnosis of thyroid dysfunction, sleep disturbances, and subclinical cardiac disease, as well as hepatopulmonary syndromes, were not possible for the entire sample because these evaluations consist of costly and specific exams.

Future research focusing on validation of 6MST in predicting fatigue and evaluation of other variables (alcoholic neuropathy/myopathy, sarcopenia, cirrhotic cardiomyopathy, hormonal status, sleep disturbances and hepatopulmonary syndromes), independently or in combination with 6 MST is important in order to improve the diagnostic accuracy of fatigue in this patient population.

The strengths of this investigation include the following: (1) the use of validated instruments for quantifying fatigue, (2) confirmation of the role of exercise test as a determinant of fatigue before liver transplantation, and (3) description of the relationship between fatigue and dyspnea before liver transplantation.

In conclusion, the present study confirmed the high prevalence of severe fatigue in ESLD patients undergoing assessment prior to liver transplantation. Low 6MST values and high levels of dyspnea were associated with fatigue in this scenario.

## Authors' contribution

Pereira EDB, Lima YB, Prudente GFG and Magalhães CBA developed the research question and designed the study. Pereira EDB, Garcia JHP conducted the statistical analyses. Pereira EDB, Viana CFG, Lima YB contributed to the draft of the manuscript. All authors read and approved the final manuscript.

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Lima YB, Magalhães CBA, Garcia JHP, Viana CFG, Prudente GFG, Pereira EDB. Associação da fadiga com capacidade do exercício em pacientes hepatopatas crônicos candidatos a transplante hepático. *Arq Gastroenterol.* 2019;56(3):252-5.

**RESUMO – Contexto** – A fadiga é uma queixa comum em indivíduos com doença hepática crônica candidatos a transplante hepático. Estudos sobre sua associação com capacidade do exercício são escassos. **Objetivo** – Avaliar a fadiga de pacientes com hepatopatia crônica candidatos a transplante hepático comparando com um grupo de indivíduos saudáveis. Avaliar a associação da fadiga com capacidade de exercício. **Métodos** – Este é um estudo transversal com pacientes hepatopatas crônicos num centro de referência em Fortaleza, Brasil. Foi utilizado o questionário de gravidade da fadiga. Os pacientes realizaram o teste da caminhada dos 6 min, teste do degrau 6 min, foi aplicada a escala de ansiedade e depressão, foram dosados proteína C reativa e hematócrito. **Resultado** – A idade média dos pacientes foi de 45,9±12,3 anos, sendo que 53,7% eram homens. Os níveis de fadiga e ansiedade e depressão eram maiores entre os pacientes hepatopatas crônicos quando comparados ao grupo controle. Uma correlação inversa foi observada entre fadiga e o teste do degrau ( $r = -0,2$ ;  $P = 0,02$ ) também entre hematócrito e fadiga ( $r = -0,24$ ;  $P = 0,002$ ). Houve uma correlação positiva entre dispneia, através da escala de Borg, e fadiga ( $r = 0,31$ ;  $P = 0,002$ ). Na análise multivariada um baixo desempenho no teste do degrau e um nível maior de dispneia mostraram uma associação com fadiga. **Conclusão** – A fadiga é mais frequente entre os pacientes hepatopatas crônicos quando comparados ao grupo controle. O baixo desempenho na capacidade de exercício e uma queixa maior de dispneia apresentaram uma associação com fadiga nestes pacientes.

**DESCRIPTORES** – Fadiga. Hepatopatias. Transplante hepático. Teste de caminhada. Teste de esforço.

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