

Six-minute walk test predicts future decompensation in patients with compensated liver cirrhosis

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INTRODUCTION

Patients with chronic diseases tend to present a reduction in their exercise capacity and consequently to the impairment of several physiological functions of the body^{1,2}. This is also the case with cirrhotic patients whose exercise capacity is measurable through tests already validated, such as the 6-min walk test (6MWT)^{2,3}. Since it is known that clinical decompensation is a landmark for the reduction of survival in cirrhotic patients⁴, our research group aimed to examine the relationship between the exercise capacity, measured by means of the 6MWT, of clinically stable patients with liver cirrhosis and the development of clinical decompensation related to the disease⁵. However, the odds ratio showing the impact of the distance covered in the 6MWT on the risk of decompensation has not yet been determined.

The rationale for this study was to verify the plausibility of using a simple, easy-to-perform, low-cost, and reliable test that does not require advanced training or special equipment, such as the 6MWT⁶, to predict possible decompensation in clinically stable patients with liver cirrhosis. Once screening for the possibility of more severe outcomes can advance early clinical decision-making, the use of an accessible and reliable assessment (6MWT) can bring a safety advantage in the management of these patients. In this sense, one way to assess this possibility is to recruit compensated cirrhotic patients for the 6MWT and to follow them, prospectively, through a prospective longitudinal observational study. Therefore, the aim of this study was to assess the impact of the distance reached in the 6MWT on the risk of clinical decompensation of clinically stable patients with cirrhosis over 1 year.

METHODS

This is an observational, prospective, longitudinal study conducted at the Hepatology Outpatient Clinic of the Gastroenterology Service of the University Hospital of the Juiz de Fora Federal University, Brazil, involving male and female adult patients with an established diagnosis of liver cirrhosis. The inclusion of patients occurred from January to December 2018. A total of 55 volunteers with compensated liver cirrhosis completed an initial clinical evaluation, performed the 6MWT, and were followed up for 12 months. Patients with a history of hepatic decompensation in the past 12 months, such as those with jaundice, ascites, esophageal variceal bleeding, or hepatic encephalopathy, were excluded from the study.

After the initial approach, patients were followed up on an outpatient basis every 2–3 months or when not possible by telephone contact at 3rd, 6th, 9th, and 12th months. A questionnaire was used to inquire about the appearance of signs and symptoms of clinical decompensation of liver cirrhosis, or hospitalization on account of ascites, jaundice, esophageal variceal bleeding, or spontaneous bacterial peritonitis. The differences between the groups with and without clinical decompensation in the follow-up period were analyzed using the independent samples t-test. A parametric test (t-test) was performed after verifying that the data distribution was normal (Shapiro-Wilk test; $p > 0.05$) and that its variances were homogeneous (Levene's test; $p > 0.05$). To evaluate the effect of the distance walked on the 6MWT on the outcome variable (clinical decompensation), we used a binary logistic regression model (*stepwise*), in which clinical decompensation was the dependent variable. We included gender and age in the model as potential intervening variables to be controlled. We also included the variable Child-Pugh Score⁷ (which is known to be related to the

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risk of decompensation) to assess the clinical consistency of the model. The fit of the regression model was assessed by the area under the ROC curve of the regression and the Hosmer-Lemeshow test. All tests were two-tailed, and the significance level was set at 5%. Analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014).

RESULTS

Of the 55 patients followed for 12 months, 65% were male, with a mean age (\pm SD) of 56.3 (\pm 10.5) years. The main etiologies found for cirrhosis were alcohol, virus C, and non-alcoholic steatohepatitis. Also, 36 (65%) patients were of Child's class A and 19 (35%) were of Child's class B. Clinical and anthropometric characteristics are summarized in Table 1. There was a significant difference in the 6MWT walking distance between the group that did not present clinical decompensation of cirrhosis (33 patients) and the group that presented clinical decompensation (22 patients) during the 12-month follow-up (470 ± 76 m vs. 378 ± 19 m; $p<0.01$). There was no statistically significant difference in walking distance between Child-Pugh class A and B patients (451 ± 95 m vs. 401 ± 117 m; $p=0.90$).

The logistic regression analysis showed that, considering all the variables of the model, the increase of 1 m in the walking distance in the 6MWT reduced the risk of clinical decompensation at follow-up by approximately 2%. This result was adjusted by the regression model for sex, age, and Child-Pugh Score. The *goodness of fit* of the model was ensured by calculating the area under the curve (0.91 [95%CI 0.70–0.97]) and the Hosmer-Lemeshow test ($p=0.24$ [>0.05]). The result of logistic regression is shown in Table 2, which shows the *odds ratio* with the respective 95%CI for the predictor variable (6MWT) and the variable Child-Pugh Score in order to quantify how much this variable would increase the risk of decompensation.

DISCUSSION

Our research points to a strong association between a shorter walking distance on the 6MWT and a higher risk of clinical

Table 1. Clinical and anthropometric characteristics of the population.

Variables	Odds ratio	95%CI
Child-Pugh Score	6.9066	1.3411–35.5676
Distance 6MWT	0.9793	0.9679–0.9909

Data are presented as mean \pm standard deviation and frequency (%). NASH: nonalcoholic steatohepatitis.

decompensation in clinically stable patients with liver cirrhosis at 1-year follow-up, and an approximate 2% reduction in this risk for each meter increase in the walking distance at the end of the test. This corresponds to a 20% reduction in the risk of decompensation for a 10-m increase in the 6MWT result.

Regarding clinical decompensation, liver cirrhosis presents an initial phase, clinically silent, called “compensated cirrhosis,” followed by the phase of the appearance of signs and symptoms resulting from portal hypertension and/or hepatic dysfunction, called “decompensated cirrhosis.” It is well known that, as the pressure in the portal system increases, the disease evolves to the decompensated phase, when the clinical decompensation of hepatic cirrhosis appear⁴. Survival is related to the appearance of clinical decompensation, with liver-related mortality occurring almost exclusively after the progression of the patient's condition to “decompensated cirrhosis”⁸. In parallel, cirrhosis causes extrahepatic derangements that affect several organic systems and are related to the reduction of exercise capacity, an alteration that is directly related to the degree of hepatic function impairment⁹.

In our sample, there was a clear association between a lower exercise capacity, evaluated by the lower distance walked on the 6MWT, and a higher risk of clinical decompensation during the 12-month follow-up. In accordance with the studies that point out that low physical fitness is associated with higher morbidity and mortality by all causes in the presence of several chronic diseases, other studies with cirrhotic patients also point to a direct relationship between physical fitness and prognosis in these individuals^{5,10}.

Alameri and colleagues showed that the exercise capacity was an independent marker of survival in patients with liver cirrhosis³. Another study¹¹ identified the distance in the 6MWT

Table 2. Results of the logistic regression model evaluating the impact of the Child-Pugh score on the distance in the 6-min walk test.

Variables	n=55
Sex (M/F)	36/19
Age (years)	56.3 \pm 10.5
Etiology of cirrhosis	
Alcohol	20 (36.4%)
C virus	13 (23.6%)
NASH	11 (20%)
Others	8 (14.5%)
Indeterminate	3 (5.5%)
Child-Pugh score (A/B)	36 (65.4%)/19 (34.6%)

CI: confidence interval; 6MWT: 6-min walk test.

as an independent predictor of mortality in the candidates for liver transplantation; this physical test can identify candidates at higher risk of death on the waiting list. Our group has previously demonstrated that the 6MWT is a significant predictor of clinical decompensation in patients with cirrhosis and pointed to a cutoff point of 401.8 m as related to an increased risk of clinical decompensation in clinically stable cirrhotic patients⁵.

Although several studies with cirrhotic patients show an association between lower exercise capacity and higher mortality rate, to date, the approach that relates this impairment to the risk of the clinical decompensation of the disease is limited in the literature. In this study, the logistic regression adjusted for the model variables revealed a 2% reduction in the risk of clinical decompensation of cirrhosis for each gain of 1 m in walking distance on the 6MWT. One finding that corroborates the result found for the 6MWT in the logistic regression is the approximately seven times higher risk for the most severe patients (Child B) to present decompensation, as expected; this serves to demonstrate the consistency of the findings of the statistical model.

We believe that the strongest point of our study was that we showed the possibility of relating, and even predicting, a severe clinical outcome (cirrhotic decompensation) with an accessible and easy-to-perform test, such as the 6MWT. The impact of impaired exercise capacity in cirrhotic patients emerges as a promising area of study. Although a parallel between impaired hepatic function and exercise capacity is expected, there is a variation in clinical characteristics and measurements that makes the identification of accessible markers that help to indicate the evolution of the disease urgent. Another strength of our research includes the real-world data set that represents a cohort of ambulatory patients with compensated cirrhosis followed in the long term. In addition, all patients had detailed clinical data collected using a standardized questionnaire.

Notwithstanding, our study also has drawbacks that must be considered. Perhaps, the follow-up time used for the main outcome (i.e., hepatic decompensation) in this study is not long enough for meaningful analysis. Furthermore, if our study had been carried out with a larger sample, perhaps the results would have an even more robust clinical significance

for clinical practice. Despite we have found a measurable statistical significance in our analysis. In fact, observational studies can always be more informative as samples increase in size and observation time lengthens.

Future prospective longitudinal studies involving a broader population of patients with compensated cirrhosis are needed to determine the accuracy of 6MWT to predict clinical decompensation related to underlying liver disease. Additionally, it will be important to investigate whether a standardized physical activity protocol directed for patients with compensated cirrhosis aiming to gradually increase physical activity will result in better outcomes.

CONCLUSION

The results show a strong association between shorter distance walked in the 6MWT and higher risk of clinical decompensation in clinically stable patients with liver cirrhosis. Therefore, it allows us to assume that the 6MWT, a relatively simple and low-cost test, appears as a viable tool to predict decompensation in this population over a year. These findings add important information about cirrhosis decompensation and the measurement of exercise capacity in the routine evaluation of patients with the disease that should be considered.

AUTHORS' CONTRIBUTIONS

DMNH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Visualization, Supervision, Writing – original draft, Writing – review & editing. **CAMJ:** Data Curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **FHLP:** Investigation, Resources, Supervision, Validation, Visualization, Writing – original draft. **TMDO:** Data curation, Investigation, Validation, Visualization, Writing – original draft. **CM:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. **JMFC:** Conceptualization, Methodology, Project administration, Resources, Visualization, Writing – review & editing.

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