Dear editors,

Please find below all answers to reviewers' comments and main text modifications indicated.

Sincerely

Study authors

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The topic is very important and the manuscript highlights a good research activity. Comments: a. the authors specify that „Cirrhosis was defined by clinical history, physical examination, laboratory analysis and at least one radiology data" – would be better imaging data??? b. the exclusion criteria need to be reviewed: it is not clear whether or not patients with previous/current cardiovascular disease were included; why patients with hemochromatosis were excluded?. More, "Whether patients who have previously received a liver transplant have been excluded？" should be included in the exclusion criteria.

Responses:

Thank you for your time and contribution to our manuscript. We are pleased to have the opportunity to answer all your questions and suggestions.

1- We modified the term "radiology" for "imaging"

2- We double-checked all exclusion criteria and performed all corrections based on your suggestions.

Bellow, you can find how the "exclusion section" was revised:

"Exclusion criteria were any previous or current cardiovascular or pulmonary disease, heart failure or diagnosis of hemochromatosis (when cardiac involvement was documented). Patients who had a history of alcohol abuse (more than 20g and 60g of ethanol per day for women and men, respectively)[21] were included if they had

abstained from alcohol use for at least 6 months prior to enrollment. Patients with non-sinus rhythm, decompensated arterial hypertension, low peripheral oxygen saturation (SpO2<90%), recent history (less than 3 months) of new liver related decompensation or hospitalizations were also excluded (patients with previous ascites or encephalopathy were included, those characterized with chronic decompensated patients). Patients with neuromuscular diseases, myopathy, balance deficits or orthopedic disorders were also excluded. Patients who have previously received a liver transplant were not included. No paracentesis was performed within at least one week prior to exercise, avoiding volume depletion or electrolyte imbalances."

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: Physical fitness and functional status in cirrhotic patients are two main features related to survival in this cohort of patients. It is very interesting the attention payed on a simple way (eg. 6MWT) to estimate the functional impairment. Previous studies focused on more complex methods, such as the psoas muscle volume on CT scan, but this approach is not widely applied in clinical practice. I have few suggestions: ENGLISH (it should generally be implemented): Line 10: "RECENT studies" Line 22: "Chronic obstructive PULMONARY disease" Line 26: "There ARE also evidenceS...." Line 31-32: "The aim of this study was to analyze the association between 6MWT and long-term mortality IN A COHORT OF CIRRHOTIC PATIENTS" Line 35-36: A total of 106 outpatients with liver cirrhosis (57 male .....) WAS included in the present study" Line 61: Patients were stratified according TO their ability...." Line 213: "follow-up" Line 213-214: "Poor performance during 6MWT may warrant that the at-risk patients SHOULD be followed more closely..." ERRORS IN FIGURES AND TABLES: Table 1: Hepatocellular carcinoma (with two L) Table 1: electolytes should all be written with or without apex (Na, K, Mg, Ca or Na+, K+, Mg2+, Ca2+) Table 1: I suppose that all continuous variable are shown as mean +/- DS... this must be specified Table 2: This table should be implemented with %6MWD according to Child-Pugh classes and according to ascites, encephalopathy, previous decompensation, hospital admission and survival Table 3: there are layout problems (i don't kown if it is a file download problem). If not, layout must be improved Table 3: Confidential intervals must be added Figure 4: there are lines in portuguese, they should be traduced STATISTICAL AND TEXT ISSUES: 1) In the methods chapter you say that the main outcomes are death and liver transplantation (line 64), but then in results chapter you do not consider patient underwent transplantation in survival analysis. In my opinion "liver transplantation" should be deleted among outcomes 2) As you said, the progressively reduction of 6MWD among Child classes in not unexpected. But quantifying the difference of 6MWD among Child classes remain interesting. In the result chapter and in Figure 2 you show the statistical difference between CP-A vs CP-C and CP-A vs CP-B/C, while no statistical difference came out between CP-A vs CP-B and CP-B and CP-C. Are the correlation between the three classes corrected by a multiplicity test? If yes, it should be clarified in the text; if not, it should be made. Another option is presenting the results as differences in 6MWD between compensated (CP-A) and decompensated (CP-B/C) patients. 3) I have some doubts between 6MWD and %6MWD. If you consider the data "6MWD", in all further analysis (first of all univariate and multivariate) you have to correlate this parameter with others (sex, age, weight, height). So all data presented in Table 3, Figure 3a and Figure 4a are not statistically correct. Otherwise, the data "%6MWD" is already adjusted by age/sex/weight/height so is a more correct parameter for all further evaluations. In my opinion you should focus all your attention

and discussion on the correlation of %6MWD and outcome 4) Based on ROC analysis, you found a cut-off of 0.82 as the most accurate in predicting mortality. You should produce a table with all the main characteristics (sex, age, BMI, MELD, Child-Pugh, previous decompensation, ascites, encephalopaty, HCC) of the two cohort of patients (%6MWD <0.82 vs >0.82) and the respective p values. If there are differences between the two groups, they should be added in univariate and multivariate analysis.

Responses:

Thank you for your time and contribution to our manuscript. We are pleased to have the opportunity to answer all your questions and suggestions.

1- Thank you for your time pointed out these English language mistakes. We double-checked all documents to prevent it from happening again. Also, one of the study authors is a native English speaker and she had the opportunity to review the document properly once again.
2- We provided a clearer legend to Table 1 specifying Means and + SD.
3- In table 2 we included data and tests using the 6MWD(%) variable as suggested. Also, we corrected layout problems.
4- Technical and language issues in tables and figures were corrected.
5- In Table 3 we highlighted that “Confidential intervals for OR are not represented but consider adequate for all analysis except for ORa.”. We preferred to explain following the table as by showing IC it would turn it too large and probably not able to be published in its totality.
6- Figure 2 was adjusted.

Statistical Issues
7- All participants were from a liver transplantation center, although not all were on the liver transplantation list. In the results section, we highlighted “During the study period, 11 patients died and 3 underwent liver transplantation.” Also, in the method section, we reinforced that “We performed subgroup analysis according to the achievement of liver transplantation to evaluated 6MWT distance as a predictor of death.” Participants who underwent liver transplantation were excluded during mortality analysis.
8- Thank you for the comment on figure 2. Following your suggestion, we redid this figure, now comparing only two groups: compensated (Child-Pugh A) and decompensated patients (Child-Pugh B and C). Means were different, as expected (p=0.031)
9- Regarding 6MWD and %6MWD. All authors agreed with your point of view, so we presented %6MWD as our focus on important analysis as mortality prediction and multivariate regression. In some analysis, we adopt the 6MWD (m) as it is a known parameter used in cardiopulmonary studies and easy to understand and implement by physicians. It is also better to correlate in practice with normal parameters presented in literature and give us a practical way to compare and follow those patients. As 6MWD and %6MWD correlated with each other, it was just a way to present this variable in different forms and help its applicability.
10- We also presented here, as requested, a table comparing demographics parameters between groups according to their achievement or not of predicted 6MWD (cut of calculated in this cohort: >0.82 vs. <0.82). Please see below this additional table. All the baseline parameters (sex, age, BMI, MELD, Child-Pugh, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, encephalopathy, and HCC) did not differ between groups. Note that, we did not include in this analysis the “previous decompensation” as this is a collinear (linear combination) variable with all the previous

ones (computed as the summation of them). So, we prefer not to include this table in the main document as it will not interfere with our univariate and multivariate analysis.

	Number of patients (non-parametric variables) and Means (parametric variables) according to %6MWD cut-of		
Parameter	<0.82	>0.82	p
Previous Ascites	26	39	0.257
Previous Encephalopathy	15	14	0.070
Hepatorenal syndrome	1	2	1.0
Spontaneous Bacterial Peritonitis	6	5	0.208
Hepatocellular carcinoma	1	4	0.650
Actual ascites	10	11	1.0
Gender (male/female)	22/17	37/30	1.0
Age	48.3	52.3	0.257
BMI	25.39	25.81	0.661
MELD	11.90	10.84	0.126
Child	7.48	6.80	0.062

Reviewer 3 (05769843)

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: World Journal of Hepatology MANUSCRIT NO: 64130 Comments to the Author General's comments: The manuscript is an original work and the topic is important. This study retrospectively evaluated the six –minute walk test (6MWT) in 106 outpatients with liver cirrhosis with a short follow up of one year. They reported that a decreased 6MWT is associated with CHILD PUGH score and that 6MWT was an independent predictor of death. And tolerated in selected patient (pas trop grave) Comments: 1) Methods: a. Can the authors specify why patients should have stopped alcohol for 6 months before enrollment and why do they exclude recent decompensations. b. Do they exclude all patients with alcohol peripheral neuropathy, arterial obliterating disease, or cardiac dysfunction (TTechocardiography results)? c. Did some patients have pulmonary complication of cirrhosis? d. Do all patients were included for survival analysis (even the 3 who had liver transplantation?), censured or not at liver transplantation? e. How was cirrhosis diagnosed (histologically for all patients? Morphological criteria?) f. Proportion of others cause of cirrhosis high, could the author's precise causes, do some patients had several cause of cirrhosis? 2) Results: a. Did 6MWD differ according to cardiovascular features? Pulmonary arterial pressure? Existence of hepatopulmonary shunt? b. Does 6MWD predict survival independently of MELD score (multivariate logistic regression)? If yes, what about a survival analyses (log rank) according to low MELD and 6MWD > 387 vs high MELD and 6MWD < 387 c. Do the authors could specify specificity and specificity of two cut off they observed?

Responses:

Thank you for your time and contribution to our manuscript. We are pleased to have the opportunity to answer all your questions and suggestions.

Method

a- We had to exclude patients with recent (less than 6 months) consumption of alcohol due to the potential cardiac compromise described in patients during alcohol intake, which could turn this variable into a vies during our cardiac evaluation. The literature reviewed describes this association in some reports, so we choose to not allow patients whit this potential statistical vies.
Also, patients with recent decompensation could still have been facing a worsening in hyperdynamic circulation, with a direct influence on cardiac performance.
b- Yes. We do exclude all patients with alcohol peripheral neuropathy, arterial obliterating disease, or cardiac dysfunction. We performed basal TTechocardiography before 6MWT evaluation, and patients diagnosed with cardiac dysfunction were excluded. TTechocardiography data were not presented as it was not the focus of this article.
c- No. In our cohort, we do not find any patients with pulmonary complications of cirrhosis.
d- No. Patients who had been submitted to liver transplant were excluded during survival analysis. We performed subgroup analysis during mortality evaluation.
e- Cirrhosis was defined by clinical history, physical examination, laboratory analysis, and at least one imaging data. These criteria were presented in the method section.
f- We chose to present data as “other cause” due to the variety of etiology and to focus on the most common etiology. Among the 30 patients with other etiologies, we diagnosed 8 patients with autoimmune hepatitis, 4 primary biliary cirrhosis, 1 primary sclerosing cholangitis, 1 Wilson disease, and 16 cryptogenic forms. Yes, one patient had hepatitis B and C etiology, and 4 patients hepatitis C and alcohol.

Results
a- We do not find any statistical significance regarding 6MWD among patients with or without hepatopulmonary shunts (in patients without vs. with hepatopulmonary shunts we identified: 6MWD 497 vs 524, p=0.40; %6MWD 640 vs. 692, p=0.08). We did not perform PAP measurement in this cohort.
b- No. 6MWD did not predict survival independently of the MELD score. Our interpretation of this fact is probably because our MELD cohort mean was low and with low SD (11 + 3.1). This fact probably prevented us to identify how 6MWD performed in a larger MELD spectrum. We are following a bigger cohort to answer this question in the future.
c- Thank you for your question. We included the information in the main manuscript. “Cutoff points associated with mortality was 387m for 6MWD (sensibility 90.9 and specificity 88.4) and 0.82 for %6MWD (sensibility 100 and specificity 83.2)”.

Reviewer 4 (05933767)
Reviewer #4:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Specific Comments To Authors: 6MWT is often used to evaluate the prognosis of patients with heart disease and chronic obstructive pulmonary disease. There are few studies on the correlation between 6MWT and cirrhosis. This study has certain clinical value. However, the manuscript needed to be revised. 1 The manuscript needs to be revised in the format required by the magazine. 2 The participants were all from a liver transplantation center; however, the manuscript does not indicate whether the patients had ever undergone a liver transplant. "Whether patients who have previously received a liver transplant have been excluded？" should be included in the exclusion criteria. 3 The manuscript mentions that "The study has been performed in accordance with The Declaration of Helsinki (2000) and approved by The Ethics Committee of our Institution".But no ethics statement was submitted.

Response:

Thank you for your time and contribution to our manuscript. We are pleased to have the opportunity to answer all your questions and suggestions.

1- All format required points were reviewed by our group and corrections were provided.

2- Yes, all participants were from a liver transplantation center, although not all were on the liver transplantation list. In the results section, we highlighted “During the study period, 11 patients died and 3 underwent liver transplantation.” Also, in the method section, we reinforced that “We performed subgroup analysis according to the achievement of liver transplantation to evaluated 6MWT distance as a predictor of death.” Participants who underwent liver transplantation were excluded during mortality analysis.

3- We are sorry for this point, and all documents related to approval from The Ethics Committee of our Institution will be submitted.

Reviewer #5:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This is a well designed and very useful manuscript. It just needs a little editing polishing.

Thank you for your time and contribution to our manuscript.