25th September 2020

To the Editor:

We appreciate the revision of our manuscript entitled “Effect of non-alcoholic beer, diet and exercise on endothelial function, nutrition and quality of life in patients with cirrhosis” for publication in World Journal of Hepatology.

Below please find a point-by-point response to the comments from the revision.

Best regards,

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1 Peer-review report

Reviewer #1:

1. Major points: Figure 1, finding on MMAC - The authors performed unpaired tests for baseline and post-treatment, which is inappropriate. It seems that there was a numerical trend towards higher MMAC percentile in the intervention group already at baseline. Therefore, please perform an ANCOVA to confirm the impact of treatment assignment on MMAC. This statistical tests should be used for all comparisons of treatment effects throughout the study.

We would like to thank the reviewer for the timely suggestions to improve our manuscript.

We performed both paired and unpaired tests, for inter and intragroup differences, as stated page 14, statistical analysis section; we appreciate the suggestion of including ANCOVA analysis, which has now been performed and can be found below:

In figure 4 (MAMC), the results are presented as baseline and post-treatment percentile of MAMC in each group, using a paired test (Wilcoxon´s) to evaluate changes after the respective interventions. We provide the results of the output from SPSS, and added the following in the footnote: Wilcoxon´s paired test. The numeric results of the MAMC percentile are the following (as depicted in Figure 4), showing that the baseline value of MAMC was higher in the control group than in the intervention one:

	Control			**Intervention**		
	Baseline	Post-intervention	p	Baseline	Post-intervention	p
MAMC Percentile	38.1 ± 29.9	40.2 ± 32.3	0.561	31.8 ±31.5	40.2 ± 33.1	0.045

As requested by the reviewer, we performed ANCOVA, finding that independently of the baseline value of MAMC, there was a significant increase in MAMC in the Intervention group than in the control group (adjusted mean 42.9 [95% IC 35.3-50.5] vs 37.3 [95% IC 29.5-45.1], respectively, p=0.000).

	Unadjusted and adjusted values for **MAMC (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	38.1	6.5	40.2	7	37.3	3.8
Intervention	22	31.8	6.7	40.2	7	42.9	3.7

	Unadjusted and adjusted values for **PhA (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	6.05	0.15	5.97	0.14	5.86	0.08

Intervention	22	5.77	0.15	5.85	0.16	5.96	0.08

	Unadjusted and adjusted values for **HGS (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	19.95	2.45	20.88	2.39	20.00	0.71
Intervention	22	17.69	2.06	19.67	2.30	20.59	0.73

	Unadjusted and adjusted values for **sit-to-stand test (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	24.19	1.30	20.92	0.96	20.73	0.67
Intervention	22	23.42	1.33	20.91	0.85	21.09	0.67

	Unadjusted and adjusted values for **number of steps/day (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	8717	654	11391	937	11305	581
Intervention	22	8533	868	11141	864	11223	568

	Unadjusted and adjusted values for **CLDQ (global) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	5.20	0.19	5.44	0.19	5.28	0.16
Intervention	22	4.55	0.22	5.28	0.17	5.43	0.16

	Unadjusted and adjusted values for **endothelial function (AUC) (p<0.001)**		
	Baseline	**Final (unadjusted)**	**Final (adjusted)**

Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	101.10	2.70	94.19	2.46	92.64	2.05
Intervention	22	96.63	2.09	91.79	2.38	93.34	2.05

	Unadjusted and adjusted values for **PHES (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	-1.00	0.47	-0.33	0.49	-0.54	0.40
Intervention	22	-0.14	0.45	0.45	0.48	0.18	0.39

	Unadjusted and adjusted values for **CFF (p=0.004)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	43.9	1.64	45.1	1.28	46.1	1.29
Intervention	22	47.18	1.76	44.5	1.33	43.9	1.23

	Unadjusted and adjusted values for **thigh circumference (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	53.4	1.52	52.5	1.51	52.1	0.99
Intervention	22	52.5	1.1	51.5	1.3	51.8	0.96

	Unadjusted and adjusted values for **SF-36 (physical function) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	78.5	3.14	87.6	2.70	85.4	2.08
Intervention	22	72.4	5.16	79.3	4.2	81.3	2.03

	Unadjusted and adjusted values for **SF-36 (general health) (p=0.007)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	39.8	2.03	44.2	2.37	44.6	2.74
Intervention	22	41.4	3.82	44.3	3.36	44.0	2.68

	Unadjusted and adjusted values for **SF-36 (vitality) (p=0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	60.2	3.83	63.3	4.02	63.4	3.53
Intervention	22	60.6	3.91	66.8	3.84	66.7	3.45

	Unadjusted and adjusted values for **SF-36 (social function) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	85.1	4.08	84.1	3.65	80.8	3.16
Intervention	22	74.5	5.34	80.8	4.62	83.9	3.08

	Unadjusted and adjusted values for **CLDQ (fatigue) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	4.77	0.25	5.27	0.19	5.11	0.18
Intervention	22	4.17	0.26	5.06	0.25	5.21	0.18

	Unadjusted and adjusted values for **CLDQ (systemic symptoms) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	5.62	0.22	5.61	0.20	5.22	0.51
Intervention	22	4.33	0.27	5.06	0.19	5.43	0.14

	Unadjusted and adjusted values for **CLDQ (activity) (p=0.008)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	5.34	0.26	5.34	0.27	5.23	0.28
Intervention	22	4.80	0.31	5.52	0.31	5.62	0.27

	Unadjusted and adjusted values for **CLDQ (emotional) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	4.93	0.20	5.31	0.23	5.12	0.18
Intervention	22	4.27	0.27	5.33	0.21	5.51	0.18

	Unadjusted and adjusted values for **CLDQ (worry) (p<0.001)**						
	Baseline			**Final (unadjusted)**		**Final (adjusted)**	
Group	n	mean	SE mean	Mean	SE mean	Mean	SE mean
Control	21	5.09	0.24	5.25	0.24	4.98	0.23
Intervention	22	4.31	0.39	5.20	0.38	5.47	0.22

All the outcomes remained significant after adjustment through ANCOVA test. We added PhA, that surprisingly, resulted significant after this analysis in the intervention group. We performed the analysis of this variable, because we have studied this outcome extensively, and in our recent paper it has been proposed as a surrogate of CT assessment for muscle mass, correlating with the presence of sarcopenia. **[Ruiz-Margáin A, … Macias-Rodríguez RU, Duarte-Rojo A. et al. Clin Gastroenterol Hepatol. 2020 Sep 2:S1542-3565(20)31225-8]**

All tables were added to supplementary Appendix 2 and with those results, the following information was added to the statistical analysis and results sections:

- Statistical analysis: Finally, to control for baseline differences ANCOVA analysis was performed.
- Results: In order to adjust for baseline differences among groups, ANCOVA analysis was also performed, controlling for baseline MAMC, number of steps, AUC for endothelial function, PhA, HGS, sit-to-stand test, CLDQ (global score). The main results, including PhA, remained significant after adjustment for those baseline variables (Appendix 2/Supplementary material).

2. Another measure of endothelial dysfunction that also has strong prognostic implications in patients with cirrhosis is VWF (see Mandorfer et al Aliment Pharmacol Ther 2018) - was this performed or are stored plasma samples available?

We agree with the reviewer on the usefulness of vWF, however we did not measure it so far, however we appreciate the suggestion and hopefully we can eventually measure it. Our results of endothelial function are based in plethysmography, showing the behavior of the AUC throughout time (baseline, 30, 60, 90 and 120 min).

3. It is a pity that only hand-grip strength, and not a more detailed functional assessment (e.g., 6MWT, isometric knee extension, and maximal step length) was performed.

We appreciate the observation regarding functional assessment for muscle. Due to the complexity of the study we were not able to evaluate the measures of functional assessment mentioned by the reviewer, however we did include, sit-to-stand test and handgrip strength which are regarded as functional measurements, furthermore several nutritional parameters were evaluated to complement the assessment.

4. Minor points: Of note, this research was sponsored by the Mexican Beer Council (MBC), however, the authors disclose that the funding source had no role in research design, study conduct, or analysis/interpretation. Abstract, methods - a race is missing. Page 9, inclusion criteria - 'and portal hypertension' is redundant.

Thank you for the observation. We deleted -portal hypertension- from page 9.

In addition, as suggested for the reviewer

2 Editorial Office's comments

1) Science Editor: 1 Scientific quality: The manuscript describes a clinical trials study of the non-alcoholic beer in patients with cirrhosis. The topic is within the scope of the WJG. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: Overall the study seems well-conducted and the manuscript is well-written, however, the authors tend to over-interpret these findings, in particular when considering the shortcomings of the statistical analysis. The study should be re-analyzed using ANCOVA - if its findings are robust, it may be further considered for publication. Figure 1, finding on MMAC - The authors performed unpaired tests for baseline and post-treatment, which is inappropriate. The questions raised by the reviewers should be answered; and (3) Format: There are 5 tables and 4 figures. A total of 43 references are cited, including 9 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, Clinical Trial Registration Statement, CONSORT 2010 Statement, the Institutional Review Board Approval Form, and informed consent. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by a research grant awarded in 2014 to Ricardo U. Macías-Rodríguez. The topic has not previously been published in the WJG. The corresponding author has published 1 article in the BPG. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) I found

the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (4) please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

2) Editorial Office Director: I have checked the comments written by the science editor.

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Hepatology.

Best regards,

Lian-Sheng Ma, Company Editor-in-Chief, Editorial Office

Baishideng Publishing Group Inc

Thank you for the comments:

- We provide the documents asked by the Science Editor.
- We would like to kindly ask for the re-consideration of this paper in World Journal of Gastroenterology, based in the following facts: a) The intervention is novel. There is not any other paper addressing the use of non-alcoholic beer in patients with cirrhosis, therefore it can be easily cited; b) We propose a new and easy to implement exercise program, that can be used as a model for training patients with cirrhosis in an outpatient setting; c) Our group has vast experience regarding nutritional assessment and treatment, as well as in exercise prescription in patients with cirrhosis; d) The results remained solid after adjusting for the baseline variables in the ANCOVA analysis as recommended by the reviewer.

  We have previously published several studies both in WJG and WJH, therefore if the above mentioned information is not sufficient for the publication in WJG, we are happy to publish it in WJH.