INSTITUTO NACIONAL DE
CIENCIAS MÉDICAS
Y NUTRICIÓN
SALVADOR ZUBIRÁN

Lian-Sheng Ma,
President and Company Editor-in-Chief
Baishideng Publishing Group Inc

Yuan Qi
Science Editor, Editorial Office

We appreciate the revision of our work, enclosed please find the revised version of the manuscript entitled, LOW PHASE ANGLE IS ASSOCIATED WITH THE DEVELOPMENT OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS, for its publication in WORLD JOURNAL OF GASTROENTEROLOGY.

The revised version of the manuscript was approved by all Authors. Below please find a point-by-point response to the reviewer's comments. The changes made can be found highlighted in yellow in the updated manuscript.

We really appreciate the consideration of our work in your journal.

Sincerely,

Aldo Torre, MD, MSc

INSTITUTO NACIONAL DE
CIENCIAS MÉDICAS
Y NUTRICIÓN
SALVADOR ZUBIRÁN

Yuan Qi, Science Editor:

We appreciate the revision of our manuscript
-The postal codes were added to each institution
-The required statements were added
-The reference numbers were formatted
-The comments section is now provided
-The references were edited

REVIEWER 1

The authors presented data from 220 patients with cirrhosis, and they concluded that the patients with lower phase angle had higher incidence of hepatic encephalopathy in a 48-month of follow-up compared to the group with normal phase angle. The contents of this manuscript meet the mission of World Journal of Gastroenterology, their method of measuring bioelectrical impedance is easy and can be repeated in the clinical practice by others, the analysis and statistical methods are reasonable, the writing is fluent, and the conclusion was gotten from their results. Their study was approved by the local Institutional Ethics Committee, and they also got informed consent from each participant. According to the data and writing, I would like to recommend this manuscript to you for publishing.

Response:

We appreciate the revision of our manuscript and the comments from the reviewer.

REVIEWER 2

This MS addresses a clearly defined and relevant issue in the field of gastroenterology, namely the association between hepatic encephalopathy in cirrhosis patients and the process of malnutrition in general, and with cachexia (defined as depletion of both muscle and fat mass combined with release of inflammatory mediators) in particular. Nutritional status is assessed in this paper mainly through Biological Impedance Analysis (BIA), and supported by antropometric measurements. The focus is on the reliability of phase angle data directly generated through a noninvasive, cost-effective, reproducible BIA as a predictor of risk of development of HE over a period of two years, which is long enough considering the morbidity and mortality associated with cirrhosis. The assumptions underlying the study are that low phase angle (low PhA, i. e., PhA up to 4.9) can be considered synonymous with cachexia; that being able to predict successfully through this measeurement an increased risk of developing repeated episodes of HE is an improvement over the current situation in managing these patients, even though it is unlikely to identify all patients at risk; and that no such study has been previously reported. I have a few recommendations to improve the text, especially the methodological section, and a few comments on the interpretation of the study results. Methodological. The third-

level hospital in which the study was designed and conducted should be named. There is no rationale for keeping it unnamed, and naming it will facilitate the evaluation of the study results by independent researchers. Along the same lines, the approval data and license number issued by this institution's Ethics Committee should be included in the revised MS. These are part of the factual information associated with the study, and can be the target of independent verification. Scientific. The definition of cachexia is given as PhA < or =4.9o, based on the specific cut-off for the population. This definition, based on BIA, is restrictive in comparison with original definitions of cachexia, which were not based on BIA alone. It does not necessarily improve on previously used definitions which were based on clinical and biochemical criteria.

This choice of definitions should be discussed and justified in a revised version. In a sense, equating cachexia with low PhA means that people presenting PhA>4.9o cannot be considered cachectic by other investigations (if this criterion really supplants preexisting ones). In other words, anyone not fitting this new definition of cachexia would only be called cachectic by mistake, and other studies not based on BIA would for the same reasons be considered flawed. In my opinion, the present study did not make a consistent case for replacing preexisting definitions of cachexia with its own, novel definition. As a result, instead of promoting an objective measurement on which everyone can rely, it would promote subjective versions of "cachexia" as defined by different investigators. I think this risk can be eliminated if the authors refrain from advancing a novel definition of cachexia, but emphasize what they really did, which is to define a very good, objective BIA measurement which seems to make a difference in predicting the risk of HE. It is possibly very well correlated with cachexia as understood by others, but this is not shown in the paper, and does not really matter, since the positive achievement is to show that it has a cutoff that c

Response:

We appreciate the revision of our manuscript and the very helpful comments from the reviewer.

*As requested by the reviewer the name of the third level hospital was added to the methods section.

*The reference number from the local ethics committee was also added to the methods section

*Concerning the definition of cachexia, the reviewer makes a really good point in regard to the definition of cachexia only by PhA, which is not the traditional definition for it. As reflected by several studies cachexia can be defined as loss of muscle and fat mass, accompanied by an inflammatory component given mainly by the presence of chronic disease, and decreased biochemical markers. Liver disease is very challenging in terms of nutritional assessment given that most markers and methods are biased either by fluid retention or decreased liver synthesis. Therefore we defined the loss of muscle mass and fat mass with PhA and the vector analysis with RXc graph to establish the alteration of body composition, and based on studies that showed that PhA angle is related to inflammatory markers such as PCR or proinflammatory cytokines, we measured IL6, in order to establish inflammation and correlate it to low PhA, and finally obtain the diagnosis of cachexia. We agree with the reviewer that this could be mistaken if not clarified; therefore we added the definition of cachexia used in this study to the methods section.