

## **RESPONSE LETTER**

Dr. Fang-Fang Ji

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Manuscript Title: Nutritional Support in Chronic Liver Disease and Cirrhotics

July 29<sup>th</sup>, 2018

Dear Dr. Fang-Fang Ji,

We thank you and the reviewers for their interest in our work and for helpful comments that will greatly improve the manuscript and we have tried to do our best to respond to the points raised. The reviewers have brought forward some good points and we appreciate the opportunity to address their concerns.

As indicated below, we have checked all the general and specific comments and provided either a revision or explanation. We have broken down the reviewer's comments by each reviewer.

### **Reviewer #1: 02663375**

#### **Comment:**

This is an interesting and well written review. It is addressed to an international audience, thus the prevalence of CLD and the number of deaths worldwide, and not only in the United States, must be given.

#### **Reply:**

Thank you for the suggestion. You are absolutely correct that it is much more relevant to cite epidemiological statistics on a global scale rather than just focus on the United States. I have addressed this and made the necessary changes below.

#### **Change made:**

“Although it is difficult to assess, experts believe that over 5.5 million people in the United States presently live with CLD. In the US alone, over 35 000 people die each year from this condition.”

Was changed to:

“Although it is difficult to assess, experts estimate that over 844 million people worldwide have chronic liver disease, and this associated with a mortality rate of approximately 2 million deaths per year.”

**Reviewer #2: 01588404**

**Comment:**

This mini review deals with the nutritional assessment and support of patients with cirrhosis and chronic liver diseases. There have been multiple publications dealing with the same issue in the recent past. 1)The authors should consider adding tables with technique and fallacies of various anthropometric measurements. 2)A significant number of patients are being found to have coexisting celiac disease; the dietary advice for these Chronic liver disease patients should be added. 3) A standard dietary plan for a 70 KG adult would be a good addition along with changes for cholestatic disease and specific situations such as HRS, HE etc. 4) Radiological techniques for assessing sarcopenia (tabular form) and evidence related to outcomes both in non transplant candidates and transplant recipients may be added. 5) Nutritional strategies for overweight NASH cirrhosis patients

**Reply:**

Thank you kindly for your suggestions. We will address your comments corresponding to your numbered scheme:

- 1) We initially considered this when writing the manuscript, so thank you for addressing this as well so that we may explain our rationale. A table with technique and fallacies of various anthropometric measurements would simply be a regurgitation of what is already currently typed and we feel that currently the paragraph format highlighting this information is sufficient. If you feel that the information would be better represented in table format, then we are happy to get rid of the text and create a table instead but having both would not provide any additional value.
- 2) Thank you for raising this point, we unfortunately neglected that population entirely. I have included a paragraph discussing dietary advice for patients with CLD and celiacs, and the change made can be seen below.
- 3) This is a very good suggestion to add. Unfortunately, the benefit of providing an entire dietary plan would likely not prove significantly useful as research as shown that the dietary plan for CLD is largely based on a normal diet, just with added supplements (particularly with protein) as needed. Highlighting the general guidelines with regards to caloric intake, protein intake, frequency of meals, and importance of maintaining standard diet is essential. I have added a paragraph to highlight just that, and you may read it below.
- 4) This would be a very informative addition, however we currently feel that it would be out of the scope for this paper to discuss the various radiological techniques and evidence related to outcomes in transplant vs non-transplant patients. We do however agree that mentioning the value of assessing sarcopenia, particularly with a DEXA scan, is of benefit and so a sentence was added to address this. Please see below.
- 5) Thank you for this suggestion, we have added a paragraph on this. Please see below.

### Changes made:

- 1) No changes made.
- 2) Following paragraph was added:

“Increasing numbers of patients with CLD are being found to have coexisting celiac disease and this introduces an additional barrier with regards to tailoring feeds to achieve appropriate nutrition<sup>33–35</sup>. Given that general recommendations for diet include meals that are rich in complex carbohydrates, it is essential that patients with concomitant celiac disease ensure the carbohydrates that they intake are gluten-free. Many BCAA supplements do not contain gluten, and further supplementation with protein mixtures can be achieved by ensuring the protein mixture acquired is gluten-free<sup>36</sup>. Although celiac disease does in fact introduce an additional barrier, much of it can be overcome with a fastidious approach to which foods are consumed. These principles apply to other methods of nutritional intake explored below as well.”
- 3) Following paragraph was added:

“Generally speaking, guidelines suggest that the required energy intake for cirrhotic patients is 35–40 kcal/kg-BW/d and a protein intake of 1.2–1.5 g/kg-BW/d<sup>30,31</sup>. The dietary plan for an average 70 kg adult does not significantly differ from a practically “normal” diet, as long as the above caloric and protein intake guidelines are met (usually through protein supplementation). In fact, the diet of CLD patients is largely based on a standard diet with added supplements as needed<sup>32</sup>. It is however important to discuss variations in a patient’s condition, as they may concomitantly have hepatic encephalopathy or hepatic-renal syndrome, and these must be addressed as well. With regards to hepatic encephalopathy, the general recommendation currently is to simply continue usual diet, while maximizing appropriate treatment with lactulose rifaximin, and so on<sup>31</sup>. In hepato-renal syndrome, there do not appear to be any recommendations as per the current literature to adjust nutrition, and the current approach remains to address the underlying mechanism causing HRS (e.g. correcting hypovolemia with albumin infusions)<sup>33</sup>.”
- 4) The following sentence was added:

“Sarcopenia is the most common complication of cirrhosis and DEXA scans can also be used to assess skeletal muscle mass<sup>30</sup>”
- 5) The following paragraph was added:

“Note that CLD can arise through different pathologies, including non-alcoholic fatty liver disease (NAFLD). This is of particular importance because the pathophysiology through which NAFLD arises is metabolic syndrome and diet/lifestyle is largely implicated<sup>34</sup>. Given this, addressing diet in patients with chronic liver disease from NAFLD is of utmost importance. General recommendations are to reduce total fat, saturated fats, trans fats, and fracture, while simultaneously increasing intake of polyunsaturated fats, and monosaturated fats<sup>34</sup>. These changes will likely benefit any patient with CLD but are especially important in those with NAFLD.”

**Reviewer #3: 03646639**

**Comment:**

The authors focused on pathophysiology and management of nutrition of chronic liver disease. This paper represents a contribution to the field. I found only minor comment. On page 3, third paragraph, I recommend that low hepatic glycogen stores found in patients with cirrhosis.

**Reply:**

Thank you for this suggestion, we have made the change asked for. Please see below.

Change made:

This sentence:

“This may be a reflection of the low hepatic glycogen stores found in patients with chronic liver disease.”

Was changed to:

“This may be a reflection of the low hepatic glycogen stores found in patients with cirrhosis”

**Reviewer #4: 02904354**

**Comment:**

The review paper is eligible for publication in this journal. Some minor comments were listed. The authors should clarify the titles and subtitles for each paragraph. The authors should add the figures to show the Anthropometry. The authors should add the tables to show the evidence regarding management.

**Reply:**

Thank you for the feedback. We will clarify the titles and subtitles by reformatting them. With regards to figures to show anthropometry, and tables to show evidence regarding management, we are unsure exactly what you mean. Are you suggesting we include figures to show what BMI is, and what mid-arm muscle circumference is? And with regards to a table to show evidence regarding management, do you simply want a table consisting of the type of management (oral, enteral, parenteral etc.) and a list of journal articles and references that pertain to that specific type of management? Sorry, we would appreciate some clarification, and we are happy to make the changes asked!

Changes made:

1. Changed titles and subtitles to follow more consistent and logical pattern.

**Reviewer #5: 02526287**

**Comment:**

We read with interest the paper entitled: “Nutritional Support in Chronic Liver Disease and Cirrhotics” by Shergill et al. This is a minireview dealing with malnutrition which is the most common, reversible complication of cirrhosis that adversely affects survival, response to other complications, and quality of life and, therefore, a prominent problem in cirrhosis. The manuscript is well organized and every section is meaningful and all the most important topics are exhaustively addressed. The language is fairly good and style appropriate. Major concern: The author did not mention in their minireview sarcopenia. Sarcopenia, or loss of skeletal muscle mass, and loss of adipose tissue is thought to be one of the major components of malnutrition in cirrhosis. The authors should include a paragraph on sarcopenia including the role of Computed Tomography to assess its extent. Minor comment: In the introduction the reference numbers in brackets should be modified: 1-30 and not 1,30.

**Reply:**

Thank you for the feedback. We agree with you completely with regards to including information on sarcopenia. We had mistakenly neglected it, but have now made the changes you have suggested.

Changes made:

1. Have added the following paragraphs:

“Of particular importance is being able to recognize and assess sarcopenia, which is the generative loss of skeletal muscle mass. Sarcopenia is the most common complication of cirrhosis and so will often be the initial or only presentation of someone with malnutrition secondary to chronic liver disease<sup>17</sup>”

“Sarcopenia is the most common complication of cirrhosis and DEXA scans can also be used to assess skeletal muscle mass<sup>31</sup>. Additionally, CT and MRI scans can be used to measure the extent of sarcopenia as they both can determine muscle cross-sectional area. These two tests are not used as commonly as DXA scans would be in assessment of sarcopenia however because CT scans are expensive and expose the patient to significant radiation, while MRI scans are also expensive and less available<sup>17</sup>.”

2. Have changed the reference numbers as asked.

We hope to have addressed all of the concerns of the reviewers. Should there be further revisions needed, we are open to making changes.

**Regards,**

**Syed Ali Rizvi, Wajahat Syed, Ravi Shergill**