

## **RESPONSE TO THE REVIEWERS (Manuscript ID: 86887)**

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled "Dietary salt in liver cirrhosis: with a pinch of salt!" (manuscript no 86887, Opinion review). These are very helpful for revising and improving our manuscript. The revised manuscript has been edited for proper English language by a professional body (certificate included). All the changes have been highlighted in yellow.

Our point-by-point responses to the issues raised in the peer review report are as follows:

### **Reviewer #1:**

**Specific Comments to Authors:** Hepatic cirrhosis is a chronic disease defined with hepatocytes necrosis and fibrosis in which nutrition and salt intakes play a crucial role. The main aim of this paper is to critically analyse the existing literature (conflicting data) with regards to salt intake and recommendations for patients with liver cirrhosis. Overall, this review is very interesting and well written. I have just the following minor comments:

1: In some passages, the authors talk about salt (Salt intake or consumption, high-salt intake, salt restriction), while in others, they focus more on "sodium" (Sodium intake, Sodium balance, Na excretion, Na retention, Na balance etc...), this may seem obvious to some, but confusing for others (non-experts in the field). Therefore, it would be important to add a few sentences in order to clearly explain to the "novice" reader the importance of sodium, per se, in the salt recommendations for patients. Also, given that (as indicated by the authors, page 6) the serum chloride concentration is also very important, what would be the role of "chloride", per se, in all this?

**Authors' response:** We concur with the reviewer's concern. The guidelines have focused on dietary salt restriction in order to accomplish sodium restriction because salt is the most common source of sodium consumed by humans. Therefore, salt and sodium have been used interchangeably in this paper. We have added a sentence to the introduction section to clear up any confusion between the 'salt' and 'sodium'. (change highlighted as yellow).

Regarding role of chloride, the text has been modified as followings:

“Serum chloride, the most important anion in the blood, has received less attention in cirrhosis patients, even though hypochloraemia has been recognised as an important prognostic marker in patients with advanced cirrhosis. According to the findings of two recent studies, hypochloraemia may be an even better predictor of mortality in patients with decompensated cirrhosis than serum sodium.<sup>[29,30]</sup> The chloride reabsorption in renal tubule constitutes a crucial process for the auto-regulation of the acid-base balance as well as the electrochemical equilibrium. Moreover, hypochloraemia causes activation of the RAAS and the upregulation of NaCl channel in the distal convoluted tubules, which can aggravate sodium retention and contribute to diuretic resistance.<sup>[31]</sup>”

2: Several errors and/or typos need to be corrected...For example, in the abstract: "Mainatance" , "recomenedations" , Etc. The whole manuscript needs to be revised in a more careful manner.

**Authors' response:** We regret these typos. A through editing has been done in the revised manuscript

**Reviewer #2:**

**Specific Comments to Authors:** This was a review on pros and cons of a low-salt diet in patients with cirrhosis. The paper describes the current evidence about this issue, highlighting how a restricted salt diet could be detrimental rather than beneficial in such

patients, especially during decompensated disease. The paper summarizes already known concepts, although in an interesting way. The title is nice.

1. I suggest to modify the abstract, which has many typos and does not send the actual message of the paper.

**Authors' response:** The abstract thoroughly modified and re-written as per the suggestion (highlighted as yellow)

2. I agree with most of consideration and hypothesis made by the Authors on the role of salt restricted diet in cirrhosis. I think, however, that several points may be added/discussed. - first, there is an interplay between low-salt diet, daily water intake, diuretics. Salt restricted diet is not the only therapy to be used in patients with cirrhosis and portal hypertension. This point should be discussed, in my opinion –

**Authors' response:** We concur with the reviewer's point of view. Although, a detailed discussion on aforementioned subject would be outside the scope of this manuscript, we have provided a brief contextual view on the diuretic and fluid restriction in relation to the salt restriction. It reads as follows:

“For patients with grade 2 or higher ascites, salt restriction alone would be insufficient and diuretic therapy would need to be implemented. The first-line diuretics are often aldosterone antagonists, such as spironolactone, which can be administered alone or in conjunction with a loop diuretic such as furosemide. Restriction of fluid intake is required only in patients with dilutional hyponatraemia.”

3. second, there are different disease stages, as described in the section on patients with compensated cirrhosis. In the first part of the manuscript, it seems that a salt restricted diet should be useful to treat ascites and should be considered only in such patients (with ascites

of any degree? With refractory ascites?). I suggest, therefore, to specify when patients should be counselled against high salt diet or a low salt diet.

**Authors' response:**

As per current recommendations, salt restriction should be considered for all cirrhotic patients with ascites, including those with refractory ascites. When it comes to the grade of ascites at which salt restriction should start, the International Ascites Club suggests grade 1, and the European Association for the Study of the Liver (EASL) suggests grade 2; however, the American Association for the Study of Liver Diseases (AASLD) does not provide any specific grade of ascites to this purpose. For compensated cirrhosis patients, salt restriction is currently not recommended. (However, evidence to support the view is insufficient, and we have discussed this issue in a separate section). It is not clear whether salt should be restricted in refractory ascites patients with concomitant hyponatremia. As amply described in the text regarding detrimental effects of both too high salt or too low salt, thus all patients should generally be advised against these. All these points have been discussed in the relevant sections of revised manuscript, highlighted as yellow)

4. Third, I agree with the Authors when they said that it is very difficult for a patient to measure his/her daily salt intake. Natriuresis may be useful, but it can be influenced also by loop diuretics. I suggest to add a table which can provide useful information that the Reader can deliver to his/her patients (what type(s) of food can be avoided? What measures can be applied in order to make food palatable even without high amount of salt?) –

**Authors' response:** Foods with high sodium content have been provided in a table (Table 2), which can help physicians advise patients against their consumption.

Regarding salt alternative to make food palatable, following statements have been incorporated in the revised manuscript:

“Because moderate salt restriction might make the foods unappealing and affect overall nutrition, some strategies need to be adopted in order to ensure adequate nutrients intake.

“One of the strategies is to partially substitute sodium with potassium or other minerals, such as calcium or magnesium.[47] However, there are concerns about possible negative

effects of such a replacement, such as hyperkalaemia with potassium-based salt, especially in cirrhotic patients with renal impairment or those taking potassium sparing diuretics. Additionally, flavours and sensory experiences can be imparted using herbs, spices and yeast extract. When used as salt alternatives, they have demonstrated good customer acceptance.[48]”

5. Fourth, I agree with the Authors when they say that hypoNa is often associated with hypervolemia. However, there are also other causes of hypoNa, as high dose of diuretics, that should be kept in mind. –

**Authors’ response:** We have mentioned that diuretic play important role in hyponatremia of cirrhosis (highlighted as yellow in section dealing with adverse impact of salt restriction)

6. The Authors said that salt restriction should be advised in patients with compensated cirrhosis and CSPH. This point should be better explained.

**Authors’ response:** Thank you for your suggestion. In the revised manuscript, We have re-written this section to make this point further clear. (highlighted in yellow)

7. Indeed, is there a role about salt restriction for other features of decompensated cirrhosis as HE or variceal bleeding?

**Authors’ response:** Thank you for comments. As of now, currently there is no literature available that describe the role of salt restriction for HE or variceal bleeding. However, GI bleeding can lead to volume depletion and hyponatremia in cirrhosis patients. Furthermore, hyponatremia can precipitate HE in cirrhosis patients.

Reviewer #3:

**Specific Comments to Authors:** Review comments World Journal of Hepatology review of Manuscript NO86887\_reviewer. It is my great honour and pleasure to review such an interesting manuscript. The authors tried to disclose that the measurement of salt consumption and compliance with salt guidelines are both problematic. There is insufficient evidence to say whether salt intake should be restricted in patients with compensated cirrhosis and liberalised in those with severe hyponatremia. Moreover, salt restriction guidelines do not take into account the salt sensitivity, nutritional state, volume status, condition of third compartment storage sites of patients, and the risk of hypochloremia. This is a narrative review. Could you show the turning point of salt management for liver cirrhosis? Innovation, or new drug emergence? The readers want to know. This topic is interesting and important. The present manuscript will be recommended for the publication of "World Journal of Hepatology".

**Authors' response:** Thank for your comments. As of today, the data with regard to salt recommendation for cirrhosis patients is quite confusing. Therefore, the turning point for salt management in cirrhosis patients would be the accumulation of more data through high quality randomized controlled trials. It is necessary to assess the efficacy of varied salt intake levels at various stages of cirrhosis, including those who also have concurrent hyponatremia. Studies on salt restriction must consider the patients' salt sensitivity, nutritional status, volume status, sodium storage sites, and hypochloremia risk. The innovative ideas in this area would be to evaluate the efficacy and safety of low-sodium salt substitutes (such as potassium-based salt) and ways to make low-sodium foods more palatable (by utilizing herbs, spices, and yeast extract, etc.) in order to assure appropriate nutrition. Until further data emerge, it seems appropriate for cirrhosis patients with ascites to consume 5–6 g of salt per day, which would mean avoiding foods with added salt. We have discussed these relevant issues in the conclusion section of revised manuscript (highlighted as yellow).

#### **4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH**

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

**Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further.**

**When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.**

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

**Authors' response:** The revised manuscript has been edited for proper English language by a profession body and a high quality has been achieved (certificate included).

#### **5 ABBREVIATIONS**

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

**Authors' response:** Thank you for your valuable comment. The revised manuscript has been thoroughly been edited keeping in mind the aforementioned suggestions.

## 6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **(1) Science editor:**

The manuscript has been peer-reviewed, and it is ready for the first decision.

**Authors' response:** Thank you so much for your opinion.

### **(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wignet.com/bpg/gerinfo/240>. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological

changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

**Authors' response:** Thank you for considering potential acceptance of our paper for the esteemed journal – World Journal of Hepatology. We have revised the manuscript thoroughly as per the revisers' suggestions and the journal's guidelines. The figures, tables and references have been provided as per the requirement of journal. The revised manuscript has been edited for proper English language by a profession body and a high quality has been achieved (certificate included).

Best regards,

**Ramesh Kumar,**

**MD, DM, Additional Professor, Head,**

Department of Gastroenterology, 4t floor, IPD Block-C,

All India Institute of Medical Sciences, Patna-801507, India.,

Email: [docrameshkr@gmail.com](mailto:docrameshkr@gmail.com)