Dear professors,

We sincerely appreciate the time you took to review our manuscript and provide us with your valuable comments. Your insightful feedback has been instrumental in improving the current version. The authors have taken great care to consider each of your comments and have made every effort to address them. We hope that the revised manuscript meets your high standards and expectations. We welcome any further constructive feedback you may have. For your convenience, we have provided point-by-point responses to your comments, and all modifications have been highlighted in yellow within the manuscript.

Number	Comment	Location	Amendment/ Response
1	The influence of frailty should be discussed in depth.	Pages 15-17	We have incorporated a comprehensive chapter that delves into the profound implications of frailty in liver cirrhosis. This addition encompasses the latest research findings, shedding light on the far-reaching effects of frailty on various aspects of patients' lives, such as quality of life, depression, hospitalization rates, morbidity, and mortality.
2	In the chapter of "2. the pathophysiology of frailty in end-stage liver disease", several factors contributing to frailty have been discussed, including hyperammonemia, hormonal disturbances, and proinflammation. Additionally, the significance of gut microbiota and amino acid metabolism in frailty is also suggested. To provide a more comprehensive understanding, it would be beneficial to include additional detailed information regarding these aspects.	Pages 6,7	We have included two additional paragraphs that delve into the crucial role of gut dysbiosis and impaired amino acid metabolism in the pathogenesis of frailty in liver cirrhosis. These paragraphs are based on the latest research findings and provide a comprehensive understanding of the molecular pathophysiology of these two topics.
3	Portal hypertension in the end stage of liver disease results in the dilation of splanchnic arteries and triggers neurohumoral responses. These responses, in turn, impair the excretion of sodium by the kidneys, leading to a positive sodium balance. As a result, salt restriction plays a vital role in the management of ascites. It is considered the mainstay of treatment for this condition. In the chapter of "3. the predisposing factors for frailty in cirrhosis", the author cites evidence from two randomized controlled trials suggesting that unrestricted salt intake may help decrease the risk of sarcopenia and frailty in patients. However, it is important to note that the benefits of salt restriction are still a subject of debate. While there is evidence supporting the effectiveness of an unrestricted salt diet, evidence of strict salt restriction in the application of improve live ascites and risk for induce sarcopenia and frailty should also be provided. There is a significant association between the development of ascites and the risk of protein malnutrition and sarcopenia. Therefore, when managing liver cirrhosis	Pages 8,9	We have revised the paragraph to provide a clearer understanding of the key role of salt restriction in ascites treatment. While salt restriction is essential in all stages of ascites treatment, we have emphasized the importance of avoiding strict salt intake (< 5gm NaCl daily) due to its potential impact on food palatability, patient malnutrition, and worsening of ascites. Our manuscript cites previous studies that suggest the benefits of strict salt intake for ascites removal in ascites patients. However, our research demonstrates that this approach does not provide long-term benefits in ascites treatment. In contrast, leading hepatology scientific societies (AASLD, EASL, APASL, BSG, and JSGE)[i] [ii] [iii] [iv] [v] now recommend a daily salt intake of no less than 5 gm NaCl/day for cirrhotic patients with ascites to avoid frailty and worsening of patient's condition

	patients, the role of salt intake requires further evidence from evidence-based medicine to provide individualized management approaches. It is essential to consider both the evidence supporting unrestricted salt intake and the potential benefits of strict salt restriction in improving ascites and addressing issues related to protein malnutrition and sarcopenia in this patient population. This approach ensures that patient management is based on comprehensive evidence and tailored to their specific needs.		
4	In the chapter of "3.3 Hepatic encephalopathy", the author made a statement that protein intake should not be restricted in patients with encephalopathy. The original literature referred to the recommended protein intake in adults with cirrhosis, which is 1.2-1.5 g/kg/day. This protein intake range is considered safe, does not worsen HE, and minimizes protein loss compared to lower protein doses. It also noted that the protein intake standard may vary for children with liver cirrhosis. The description of protein intake for liver cirrhosis patients' needs to be more accurate.	Page 10	We have included the safe recommendation for protein intake to prevent frailty and improve anthropometric measurements in patients with liver cirrhosis, including critically ill cirrhotic patients and children with cirrhosis.
5	In chapter of "3.5 MASLD and sarcopenic obesity", it mentioned that to manage sarcopenia and MASLD, increasing physical activity and following a healthy diet can be helpful. The author supports this claim by citing evidence that suggests elderly men who engage in moderate-to-vigorous exercise for at least thirty minutes a day have a reduced risk of developing sarcopenic obesity. However, considering the impact of physical performance in individuals with and without end-stage liver disease, it would be more appropriate to reference studies to focus on evaluating the response to exercise specifically in liver cirrhosis patients. This would provide valuable insights into the effectiveness of exercise interventions in improving physical performance and combating sarcopenia in this particular population.	Pages 12,13	We agree with the reviewer's perspective and have incorporated a comprehensive range of recent, updated studies, specifically randomized controlled trials that examine the impact and potential advantages of exercise on cirrhosis patients. The findings consistently demonstrate that exercise can effectively contribute to weight and fat mass reduction, while also enhancing skeletal muscle mass and physical capacity. This is particularly advantageous for patients with cirrhosis who are also experiencing sarcopenic obesity.
6	The gut microbiota has been proposed as a significant player in the development and progression of liver frailty via intestinal barrier dysfunction, bile acid metabolism, production of toxic metabolites, absorption of nutrients and etc. In addition to the interventions mentioned in the chapter of "5. Management of Frailty in Liver Diseases", understanding the role of the gut microbiota in liver frailty has opened up new possibilities for therapeutic interventions.	Page 25,26	We have included a new paragraph that delves into the potential benefits of rifaximin as a treatment for gut dysbiosis and frailty in liver cirrhosis patients. This addition provides an explanation of the target action of rifaximin and how it can potentially improve the health outcomes of patients suffering from these conditions. Additionally, we have highlighted the potential role of probiotics and fecal microbial transplantation in this context.

	Supplementing research and manipulating the gut microbiota in the management of frailty in liver cirrhosis hold potential benefits.		
7	In the section of "5.1 Exercise", the author provides an example of liver transplant candidates who experienced some degree of improvement in frailty after participating in an exercise program, suggesting that exercise can be an intervention for managing frailty in liver cirrhosis. However, the summary and discussion regarding the improvement of frailty in liver cirrhosis patients through exercise in this section appear to be general. Firstly, it is important to assess the risks and benefits of exercise for these patients' physical functions using appropriate risk assessment tools. Secondly, it is necessary to determine if the degree of improvement in frailty differs among decompensated and compensated liver cirrhosis patients or those in different liver function grades after engaging in low, moderate, or high-intensity exercise. Decompensated liver cirrhosis and higher liver function grades (Child-Pugh score) imply the presence of more complications associated with liver cirrhosis, such as hepatic encephalopathy, ascites, and abnormal coagulation function. The risks associated with these complications during exercise interventions for liver cirrhosis patients should be taken into consideration. Therefore, while exercise might bring certain improvements in exercise capacity, muscle mass, and function for patients with liver cirrhosis, more standardized evaluation tools are needed to assist clinicians in selecting suitable patients for exercise interventions and developing safer exercise intervention plans.	Pages 20 - 22	We agree with the reviewer's point of view. In response to this feedback, we have thoroughly revised the exercise paragraph to emphasize the significance of conducting a comprehensive risk assessment and developing a personalized exercise strategy for patients with cirrhosis, depending on degree of frailty. Additionally, we have incorporated recommendations from relevant studies regarding exercise for both compensated and decompensated patients, while also drawing attention to the unique challenges that these patients may face.
8	The dash '-' at the beginning of each sentence in Figure 1 should maintain consistent spacing with the first word.	Figure 2	We believe that Figure 2 is the intended reference for this. Thank you for bringing this to our attention. We have made the necessary modifications.

Sincerely,

Mazen Elsheikh, MD, MSc, PhD.
Research Assistant
Section of Gastroenterology and Hepatology
1 Baylor Plaza, Houston, TX 77030, USA
Email: dr_mazenelsheikh@hotmail.com

References:

[i] **Biggins SW**, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, Wong F, Kim WR. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the american association for the study of liver diseases. *Hepatology* 2021;**74**:1014–48 [PMID: 33942342 DOI: 10.1002/hep.31884]

[ii] **European Association for the Study of the Liver**. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;**70**:172–93 [PMID: 30144956 DOI: 10.1016/j.jhep.2018.06.024]

[iii] **Singh V**, De A, Mehtani R, Angeli P, Maiwall R, Satapathy S, Singal AK, Saraya A, Sharma BC, Eapen CE, Rao PN, Shukla A, Shalimar, Choudhary NS, Alcantara-Payawal D, Arora V, Aithal G, Kulkarni A, Roy A, Shrestha A, Mamun Al Mahtab, Niriella MA, Siam TS, Zhang C-Q, Huei LG, Yu M-L, Roberts SK, Peng C-Y, Chen T, George J, Wong V, Yilmaz Y, Treeprasertsuk S, Kurniawan J, Kim SU, Younossi ZM, Sarin SK. Asia-Pacific association for study of liver guidelines on management of ascites in liver disease. *Hepatol Int* 2023;**17**:792–826 [PMID: 37237088 DOI: 10.1007/s12072-023-10536-7]

[iv] **Aithal GP**, Palaniyappan N, China L, Härmälä S, Macken L, Ryan JM, Wilkes EA, Moore K, Leithead JA, Hayes PC, O'Brien AJ, Verma S. Guidelines on the management of ascites in cirrhosis. *Gut* 2021;**70**:9–29 [PMID: 33067334 DOI: 10.1136/gutjnl-2020-321790]

[v] **Yoshiji H**, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, Kawaguchi T, Kurosaki M, Sakaida I, Shimizu M, Taniai M, Terai S, Nishikawa H, Hiasa Y, Hidaka H, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T, Koike K. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. *J Gastroenterol* 2021;**56**:593–619 [PMID: 34231046 DOI: 10.1007/s00535-021-01788-x]