Replies to the Reviewers

Dear editor:

Thank you very much for the comments and suggestions.

These comments were all valuable and very helpful in the revision and improvement of the manuscript. The corrections were made, accordingly. We hope that the revised manuscript may reach the standard of your journal.

The revised sections were marked in the manuscript, and the point-to-point responses to the reviewer's comments are listed below.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The study of Yin et al. analyzed the contribution of Sarcopenia and Myosteatosis in Development HE after TIPS. It is a well written article, but its contribution as novelty is limited. In addition, there are some aspects that require attention.

Specific comments In the title it is not mentioned the effect on survival.

Response: The title was modified, accordingly.

Response: The entire sentence was rephrased, accordingly.

Response: The text "muscle mass attenuation" was replaced with "muscle fatty infiltration".

Response: The term sarcopenia was introduced for the first time by Rosenberg *et al*.[1]., and this is presently defined as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass with consequent loss of strength and function. Although sarcopenia is usually associated with aging, it can also present as the result of chronic diseases and malignancy. Several studies have revealed that sarcopenia is a negative prognostic index in liver cirrhosis, in terms of mortality and morbidity[2-4].

[1]Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr. 1997 May;127(5 Suppl):990S-991S. doi: 10.1093/jn/127.5.990S. PMID: 9164280.

[2]Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World J Gastroenterol. 2014 Jul 7;20(25):8061-71. doi: 10.3748/wjg.v20.i25.8061. PMID: 25009378; PMCID: PMC4081677.

[3] Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, Esfandiari N, Lieffers JR, Sawyer MB. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clin Gastroenterol. 2013 Nov-Dec;47(10):861-70. doi: 10.1097/MCG.0b013e318293a825. PMID: 23751844.

[4]Liu J, Ma J, Yang C, Chen M, Shi Q, Zhou C, Huang S, Chen Y, Wang Y, Li T, Xiong B. Sarcopenia in Patients with Cirrhosis after Transjugular Intrahepatic Portosystemic Shunt Placement. Radiology. 2022 Jun;303(3):711-719. doi: 10.1148/radiol.211172. Epub 2022 Mar 15. PMID: 35289658.

Line 53: here it is reported that for the study "records of cirrhotic patients who underwent the TIPS procedure" were used. However, in the material and methods section, the data are presented as prospective.

Response: The sentence was rephrased accordingly in the Materials and Methods section.

Line 57: change "are" with "were"

Response: This was modified, accordingly.

Line 58: "The area under curve (AUC) represented the test discriminative power…" should be changed with "The area under curve (AUC) represented the test to evaluate the discriminative power.."

Response: The sentence was rephrased, accordingly.

Line 62: it is mentioned mortality, but it is not reported in the results.

Response: The post-TIPS mortality was presented in the results part of the Abstract.

Response: Covert HE (<grade 2) cannot be definitively diagnosed due to the lack of symptoms and non-specificity of diagnostic measurements. The present study aimed to investigate the association and predictive value of sarcopenia and myosteatosis for overt HE (grade ≥2) after TIPS. Thus, patients with a history of covert HE were excluded from the study.

Response: The authors used the Skeletal Muscle Index (SMI) from a study (Ref. 35) to evaluate the sarcopenia in cirrhotic patients. The results were normalized to height squared, and presented in cm²/m².

$$\text{Skeletal Muscle Index (SMI)} = \frac{\text{Total Muscle Area (cm2)}}{\text{Height(m)} \times \text{Height(m)}}$$

However, the present study used transverse psoas muscle thickness (TPMT) to diagnose the low muscle mass (sarcopenia). TPMT was defined as the transversal diameter of the right psoas muscle perpendicular to the largest axial psoas muscle diameter at the level of L3. Therefore, the results were normalized using the following equation[5].

$$\text{TPMT} = \frac{\text{Largest axial psoas muscle diameter } (mm)}{\text{Height (m)}}$$

[5] Paternostro R, Lampichler K, Bardach C, Asenbaum U, Landler C, Bauer D, Mandorfer M, Schwarzer R, Trauner M, Reiberger T, Ferlitsch A. The value of different CT-based methods for diagnosing low muscle mass and predicting mortality in patients with cirrhosis. Liver Int 2019; 39(12): 2374-2385 [PMID: 31421002. doi:10.1111/liv.14217]

Results Line 261: for the calculation of survival, you should have used different TPMT values since your cut-off, which are reported by Paternostro et al. (ref. 11), were adopted for low muscle mass and not for survival.

Response: We thank the reviewer for the valuable comment. Paternostro *et al.* (Ref. 11) reported that TPMT (the cut-off values were adopted for low muscle mass) is independently associated with increased risk for mortality (aSHR: 2.82, 95% CI: 1.20-6.67, P=0.018). The cut-off value and diagnostic efficiency for sarcopenia and myosteatosis were heterogeneous across studies in the literature. Thus, more studies and external validation of data are needed to standardize the CT-derived diagnostic criteria for sarcopenia and myosteatosis.

Discussion Line 310: change "contribute to" with "reduce" (see 10.3389/fnut.2022.1051157)

Response: This has been changed, accordingly.

Contribution to the field statement Line 383: put space "to detoxify".

Response: A space was added for the text "to detoxify".

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Dear authors, I congratulate you on a very well researched and excellently written paper. I have next to no comments, disagreements or modification suggestions. This paper was a joy to reivew!