Peer Review File

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Reviewer A

The authors are to congratulated on a nicely designed and generally well written retrospective study. The findings are of potential great clinical interest but there a number of things that would be worth addressing, at the very least in discussion, if such data is unavailable.

1. Have sarcopenia measurements such as LSI been validated for different populations/ ethnicities? Are the same cutoffs appropriate for a Japanese cohort and a European cohort for example?

Reply1: Thank you for your comment.
Racial differences are known to affect body composition(1). However, there are reports of no differences, suggesting that L3SMI varies among populations(2). Carey EJ et al, the authors consider that the prognosis can be more accurately determined by obtaining race-specific cutoffs. Some Asian data also report a cutoff value of 40 cm2/m2 for L3SMI in men(3). Therefore, we think that racial cutoff values are necessary. In addition, gender differences need to be considered.

(1) Silva AM, Shen W, Heo M, et.al.Ethnicity-related skeletal muscle differences across the lifespan. Am J Hum Biol. 2010;22:76-82. PMID: 19533617
(2) Carey EJ, Lai JC, Wang CW,et al.Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl. 2017;23:625-633. PMID: 28240805
(3) Zhang Y, Wei L, Chang C, et al.Sarcopenia defined with L3-SMI is an independent predictor of survival in male patients with ARLD in mainland China. Front Nutr. 2023 ;10:1238433. PMID: 37781108

2. How was cirrhosis defined/ diagnosed? The study describes the cohort as patients with chronic liver disease. There were less cirrhotic in the high zinc group and lower zinc levels were associated with pre-sarcopenia but apparently no association was seen between cirrhosis and pre-sarcopenia status which might have been expected. Further was there any correlation with severity of liver disease? I think some clarity around definitions of cirrhosis and analysis by cirrhosis status would be helpful.

Reply2: Thank you for your important comment. We added in methods part some texts that Liver cirrhosis was diagnosed based on physical findings, serum biomarkers, and clinical imaging characteristics. Irregularity and deformity of the shape of the liver was detected imaging modalities (abdominal echography, CT and MRI) .

We have added data pertaining to cirrhosis as supplementary Table 1.

In supplementary data1 on cirrhosis, Age, Fib4index, ALBI score and the rate of HCC were significantly higher in the cirrhosis group. No significant differences were found between patients with and without cirrhosis.
When the 278 cases compared by ALBI grade as severity of liver disease, there was no significant difference in the rate of presarcopenia in each grade(supplementary Figure 1). In addition, 67 cases of cirrhosis were examined, with no significant differences.

3. Were any other nutritional markers or vitamin levels measured? Could this just be a surrogate of malnutrition? It was noted that dietary intake was not available but apart from albumin, no other serum markers seem to be mentioned.

Reply3: Thank you for your comment. We did not consider other nutritional markers in our initial study design. Thus, we did not obtain data on other items.

4. The median age of the cohort was 68 overall and the sarcopenia patients were older than the non-sarcopenia patients (70.5 vs 66). Although age was not borne out as a factor for sarcopenia on multivariate analysis, given overall age of cohort is it clear that sarcopenia was liver disease and not age related? Is there any healthy control data for comparison or could analysis be adjusted for confounding factors such as age and be discussed appropriately?

Reply4: Thank you for your very important comment.
There is no any healthy control data for comparison. Revised text.
The cutoff value for the elderly was considered as 65 years of age. (Supplementary Table 2)
In supplementary data 2, the rate of presarcopenia was significantly higher in the group over 65 years of age(<65:34.9%(37/106),≧65:54.1%(93/172) in univariate analysis.
Thus, it cannot be said that it is not related to age.
Generally sarcopenia is said to be an age-related loss of muscle mass.
However, age was not a significant factor in the multivariate analysis in this study.
On the other hand, patients with chronic liver disease is a disease-specific associated sarcopenia (secondary sarcopenia)
Therefore, Another factor may be that in patients with chronic liver disease, various events also increase with age.

5. Sarcopenia is associated with poor prognosis in liver disease. Were any clinical outcomes examined? May be possible given the long timeframe of the study.

Reply5: Thank you for your very valuable advice. However, we were not able to investigate the prognosis in this study. We would like to implement in the future.

6. The authors summarise other data and suggest that "interventions such as zinc supplementation for latent zinc deficiency may reduce the risk of presarcopenia development in patients with chronic liver disease" but there is no data presented to support this. Rather studies describe associations with or report zinc as predictor of various outcomes and JSCN guidelines may recommend zinc replacement but there did not seem to be evidence presented for zinc replacement and benefits for sarcopenia.

Reply6: Thank you for your comment. We have revised the text.

Reviewer B

Dr. Suzuki et al. investigated the predictive performance of low serum zinc level for the presence of presarcopenia in patients with chronic liver disease. The authors demonstrated that serum zinc concentration <60 μg/dl as well as male sex and BMI could be a factor associated with presarcopenia. In cirrhotic patients, zinc deficiency occurs due to decreased albumin synthesis, impaired intestinal absorption, increased urinary excretion of zinc associated with port-systemic shunt, and poor oral intake. It has been established that zinc deficiency is closely relevant to skeletal muscle atrophy in cirrhotic patients. Although the findings in this manuscript may be beneficial for clinical practice, I have some concerns in this manuscript as below.

1. This study is “a preliminary study”. So, the authors should describe future perspectives based on the results in this manuscript.

Reply1: Thank you for your comment. We have revised the text.

2. Increasing number of reports have demonstrated that zinc deficiency could be an independent predictor for the presence of sarcopenia. In comparison with these reports, what is the novelty in this manuscript?

Reply2: Thank you for your important comment.
The ability to consider gender differences in zinc deficiency (<60 μg/dL) as defined by JSCN guidelines and presarcopenia for the treatment of patients with chronic liver disease.

3. Muscle strength such as hand grip strength is critically important to evaluate the sarcopenia. The authors should include muscle strength in evaluation items for sarcopenia.

Reply3: Thank you for your comment.
We acknowledge the validity of your comment regarding
Hand Grip measurement as the gold standard for diagnosing sarcopenia. However, we experienced a limitation in regularly measuring Hand Grip in our clinical practice, resulting in the unavailability of Hand-Grip score.