Peer Review File

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Response to Reviewer A

<1> *BDI-II is a subjective self-administered questionnaire. My interpretation of the authors stratification for "progression of depressive state" (p.6 line 9) is that a ≥1 increase is considered as progression of depression. I am not sure whether this is clinically meaningful (i.e. what about going from 1 to 2, 5, or even 9, whereas a <13 BDI-II score is considered normal?). It would probably be more clinically relevant to assess the changes from one category to another (ex: minimal depressive state to mild or moderate depression) and eventually including an ordinal value to rank these changes (i.e. going from minimal to mild would be less "impactful" than going from minimal depression to moderate or severe depression). Alternatively, authors could use a Z-score normalization to estimate the impact of a one standard deviation increase in the BDI-II score.*

Our response:

Thank you for your valuable comments. We think you are right. However, in the current analysis, we primarily aimed to analyze factors linked to a ≥1 increase of BDI-II score during follow-up period, and we concentrated on the association between sarcopenia-related factors and ≥1 increase in BDI-II score. Thank you for your warm understanding.

<2> *What is the rationale for the BDI-II cut-off of 11 to define depression? Authors cites REF 26-30 (p.6 line 3-9), yet in the original study by Beck et.al (REF 27), the mean±SD of "no depression" is 10.9 +- 8.1. In the REF (29), I found no signs of BDI-II utilization and in REF (26) cutoffs used are the most commonly applied, i.e. 0–13 = normal to minimal depression; 14–19 = mild depression; 20–28 = moderate depression; and 29–63 = severe depression. In the latest cited study (ref 30), patients with <20 BDI-II score are even considered as "controls". Altogether, I am not sure whether 11 is a meaningful cutoff.*

Our response:

Thank you for your comments. In the methods section, we revised to "A Japanese researcher categorized patients into normal (BDI-II score, 0-10), minimal depressive state (BDI-II score, 11-16), mild depressive state (BDI-II score, 17-20), moderate depressive

state (BDI-II score, 21-30), and severe depressive state (BDI-II score ≥31), and defined depression as BDI-II score ≥11. In the current analysis, this classification system was applied." Unnecessary references were deleted. Thank you for your understanding.

<3> *Methods p6. Line 20: this is not clear. A loss of muscle mass or strength cannot be categorized as the mere presence of a low muscle mass or strength at baseline. I do not see any longitudinal data for muscle mass/strength, hence the manuscript should be reworded to avoid confusion. For instance, it is not clear what the GS/SMI "decline" category represents (fig. 3-5). Was the GS/SMI measurement repeated? From the data presented, I guess this was not the case hence these figures represent the relationship between low GS/SMI at baseline and depression progression after follow-up. This should be reworded.*

Our response:

Thank you for your valuable comments. We agree. In the revised methods section, we added the following statement:

"Impacts of baseline GS and SMI on the elevation of BDI-II score were examined."

In addition, to avoid confusing, the phrase "at baseline" was added as needed in the revised results section.

<4> *It is interesting that muscle mass dissociates from muscle strength, and we know that other factors such as muscle composition likely influence the muscle mass – strength relationship. Do authors have any BIA-derived muscle quality indicators available (ex: phase angle) that could influence this relationship?*

Our response:

Thank you for your valuable comments. In the present study, other BIA-derived indicators such as phase angle were not included. Thank you for your warm understanding.

<5> *The manuscript needs thorough revision for gramma r and syntax: ex: "falling into sarcopenia" p.20, although it is a nice pun)*

Our response:

We carefully revised throughout the paper.

Response to Reviewer B

<1> *Skeletal muscle index (SMI) was calculated as sum of muscle mass in upper and*

lower extremities divided by height squared (kg/m2)? Is this muscle same as skeletal muscle?

Our response:

SMI calculated as sum of muscle mass in upper and lower extremities divided by height squared is a well-accepted marker for the assessment of muscle mass.

<2> *Cirrhosis itself is a risk factor for depression and also like L3 SMI or Psoas muscle area is better marker for sarcopenia in these patients. I assume authors did not calculate it this way which can lead to confounding results. Please clarify on this?*

Our response:

As shown in table 2, presence of LC and SMI were included into analysis.

<3> *Decreased Grip strength could be due to sarcopenia or loss of muscle mass in these patients and still does not support the conclusion.*

Our response:

As you indicated, decreased grip strength could be due to sarcopenia or loss of muscle mass, however, in our multivariate analysis, only lower GS at baseline (P=0.0022) was identified to be an **independent** factor associated with the elevation of BDI-II score. We thus concluded that reduced GS rather than loss of muscle mass is independently associated with an elevated risk for the progression of depression. Thank you for your understanding.

<4> *Did ascites in cirrhotic patients affect BIA?*

Our response:

We believe SMI can be overestimated in cirrhotic patients with massive ascites. Such patients were not included in our cohort.

<5> *Pt s with GS and non-GS decline what were there SMI?*

Our response:

In the revised results section, we added the following data:
In patients with GS decline (n=50) and non-decline (n=139), there were 26 patients (52%) and 39 patients (28.1%) with SMI decline.

Response to Reviewer C

Introduction

<1> *Page 4 Line 2- The authors refer to 'depressive condition', the wording doesn't flow within the sentence and should be modified.*

Our response:

We did.

<2> *Page 4 Line 2-3- Depression is a leading mental illness, which is frequently linked to adverse clinical outcomes and decreased compliance Perhaps the authors may choose to mention the significance of the condition, as justification for its investigation in relation to CLD.*

Our response:

In the revised introduction, we added the following statement:
"depression is a leading mental illness in CLD patients".

<3> *Page 4 Line 2- The authors mention that depression is a common condition within CLD, however the authors may choose to include reference the prevalence of sarcopenia within CLD (17-57%).*

1. Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. Aliment Pharmacol Ther. 2014;40:880-892.
2. Nardelli S, Pentassuglio I, Pasquale C, et al. Depression, anxiety, and alexithymia symptoms are major determinants of health related qual- ity of life (HRQoL) in cirrhotic patients. Metab Brain Dis. 2013;28:239-243.

Our response:

Thank you for your comments. Your recommended papers were additionally quoted.

<4> *Page 4 Line 7- The authors mention a decrease in QoL and health costs in relation to depression, however sarcopenia also contributes to an increase in health care costs and hospitalization which could be included at a later point within the introduction. Therefore, both conditions should be emphasized in relation to their importance within CLD and as a consequence why it is important for the association to be investigated.*

Our response:

Thank you for your comments. In the revised 2nd paragraph on the introduction, we added the following sentence:
"Thus, the relationship between sarcopenia and depression in CLD patients appears to be essential."

<5> *Page 4 Line 9- Please could the authors briefly mention what adverse clinical outcomes is related to depression within CLD. For example, depression is thought to be a contributor to fatigue, sleep disturbances and poor health-related quality of life. Additionally, depression, pre transplant has been associated with increased length of hospital stay and mortality.*

1. Nardelli S, Pentassuglio I, Pasquale C, et al. Depression, anxiety, and alexithymia symptoms are major determinants of health related quality of life (HRQoL) in cirrhotic patients. Metab Brain Dis. 2013;28:239-243.

2. Rogal SS, Mankaney G, Udawatta V, Chinman M, Good CB, Zickmund S, et al. Pre-transplant depression is associated with length of hospitalisation, discharge disposition,and survival after liver transplantation. PLoS ONE. 2016;11: e0165517.

3. Bianchi G, Marchesini G, Nicolino F, et al. Psychological status and depression in patients with liver cirrhosis. Dig Liver Dis. 2005;37:593-600.

Our response:

Thank you for your comments. In the revised introduction section, we added the following sentence:

"Pre-transplant depression can cause length of hospitalization and poorer survival after liver transplantation"

We quoted one article you recommended below:

- Rogal SS, Mankaney G, Udawatta V, Chinman M, Good CB, Zickmund S, et al. Pre-transplant depression is associated with length of hospitalisation, discharge disposition,and survival after liver transplantation. PLoS ONE. 2016;11: e0165517.

<6> *Page 4 Line 14- The authors first refer to depression within their introduction before mentioning sarcopenia within their second paragraph. However, there is no link between the inclusion of both depression and sarcopenia, they appear as stand-alone topics within the text.*

Our response:

Thank you for your valuable comments. In the final paragraph, we surely stated, "In our previous cross-sectional study, we demonstrated the close relationship between sarcopenia and depression in CLD patients. Chang, et al. reported in their meta-analysis that sarcopenia was independently associated with depression in elderly people, while the causal relationship between sarcopenia and depression needs further studies. The causal relationship between sarcopenia and depression in CLD patients is also unclear. To elucidate these issues, we aimed to investigate the impacts of sarcopenia-related factors

(i.e., muscle strength and muscle mass) on the progression of depression in CLD patients." Thus, we believe further revision will not be necessary. Thank you.

<7> *Page 4 Line 20- The authors list mechanisms which are thought to contribute to sarcopenia within CLD, however they neglect to include key contributors such as hyperammonemia and inflammation.*

1 Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65(6):1232-1244.

Our response:

We adequately revised.

<8> *Page 4 Line 24- The authors make reference to sarcopenia being linked to adverse clinical outcomes, however they may wish to provide more specific information such as an increase in mortality, increased length of hospital stay and infections.*

1 Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS One. 2017;12(10):e0186990.

2 van Vugt JLA, Buettner S, Alferink LJM, Bossche N, de Bruin RWF, Darwish Murad S, Polak WG, Metselaar HJ, IJzermans JNM. Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation-a retrospective study. Transpl Int. 2018 Feb;31(2):165-174

Our response:

In the revised introduction section, we revised to "Sarcopenia can be associated with decreased QOL and adverse clinical outcomes such as mortality, increased length of hospital stay and severe infections in CLD patients."

Your recommended above two articles were quoted.

Methods

<9> *Page 5 Line 13- The authors state the number of times the BDI-II questionnaire was completed twice or more. Please may the authors justify why the number of questionnaires completed varied between participants?*

Our response:

In the revised methods section, we added the following sentence:

"The follow-up intervals were determined by the attending physician, and the patient's free will was used to make decisions regarding entries on the BDI-II questionnaire."

<10> *Page 5 Line 18- Please may the authors state the length of the follow up period in which participants were followed?*

Our response:

In the revised results section, we added the following data:

The mean (± SD) follow-up period was 1.3 ± 1.1 years.

<11> *Page 5 Line 20- The authors state that the most suitable intervention was performed throughout the duration of this study. Does this include transplants? Whether this questionnaire was completed pre- or post-transplant may influence the results and reliability of the results.*

Our response:

In the revised methods section, we added the following data:

In this study, there was no patient receiving liver transplantation during the follow-up period.

In our country, liver transplantation is not so common due to lacking in donors.

<12> *Page 6 Line 15- Please could the authors briefly include more details about the measurement of muscle mass utilizing the BIA.*

Our response:

In the original version, we surely stated:

"For the evaluation of muscle mass, bioelectrical impedance analysis (BIA) was performed using InBody 720 to calculate appendicular muscle mass. Skeletal muscle index (SMI) was calculated as sum of muscle mass in upper and lower extremities divided by height squared (kg/m^2)."

We believe these are enough.

<13> *Page 6 Line 18- Please could the authors briefly include more detail in the measurement of strength using HGS. For example, were 3 trials completed with both the dominant and non-dominant hands, and was the highest score recorded for analysis?*

Our response:

In the revised methods section, we added the following sentence:

"GS of the left hand and the right hand were measured twice each, and the mean value of the better of the two was adopted."

<14> *Page 5 Line 23- The authors present the data as median values; please may the*

authors present the data as mean and standard deviations?

Our response:

We did according to your suggestions.

Results

<15> *Page 7 Line 15- Please could the authors present their data as the mean and standard deviations.*

Our response:

We did according to your suggestions.

<16> *Page 8 Line 7- What was the follow up period?*

Our response:

The observation period at the outpatient clinic.

<17> *Page 8 Line 12- The authors consistently refer to increases in BDI-II scores during the follow up, however they do not include p-values to show statistical significance in the paragraphs entitled 'Cumulative elevation rates of BDI-II score according to cirrhosis status' and Cumulative elevation rates of BDI-II score for all cases.*

Our response:

In the revised results section, we added the following data:

The difference of cumulative elevation rates of BDI-II score between cirrhotic and non-cirrhotic cases was noted with significance (P=0.0112).

<18> *Page 8 and 9- Please could the authors include effect size within their results section.*

Our response:

We believe effect size will not be necessary in the results section.

Discussion

<19> *Page 12 Line 1- Please could the authors include a more specific reference of chronic illnesses and depression, are these illnesses linked to poor functional outcomes?*

Our response:

In the revised discussion section, we revised to "It is well accepted that particular cohorts of patients with chronic illnesses such as malignancies, musculoskeletal diseases,

cardiovascular diseases and respiratory disease involve a much higher prevalence of affective disorders than the general population, which may be linked to poorer functional outcomes."

<20> *Page 12 Line 3- The authors state the importance of the skeletal muscle functioning in relation to regulation of protein synthesis, however they do not mention protein breakdown, perhaps the regulation of muscle protein turnover is more appropriate to account for both synthesis and breakdown.*

1. Breen L, and Phillips SM. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. Nutr Metab 8: 2011.

Our response:

Thank you for your comments. "Protein synthesis" was revised to "protein synthesis and breakdown (i.e., protein turnover)". Your recommended article was additionally quoted.

<21> *Page 12 Line 17- It is possible that depression is linked to sarcopenia due to its association with reduced mobility and ability to complete daily tasks. A reduction in ability to complete these daily tasks has been found to reduce QoL, in particular the mental components of QoL, which infer a potential increase in susceptibility to depression.*

1 Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. Am J Gastroenterol. 2001 Jul;96(7):2199-205.

2 Younossi Z, Henry L. Overall health-related quality of life in patients with end-stage liver disease. Clin Liver Dis (Hoboken). 2015;6(1):9-14.

Our response:

Thank you for your valuable comments. In the revised discussion section, we added the following sentences:

"Depression is possibly linked to sarcopenia due to its association with reduced mobility and ability to complete daily activities. A reduction in ability to complete these daily activities has been found to reduce QOL, in particular the mental components of QOL, which infer a potential increase in susceptibility to depression."

Your recommended two articles were also quoted.

<22> *Page 13 Line 1- The authors should also acknowledge that in addition to muscle strength, it is possible that decreases in QoL, which may include, or contribute to depression it is possible that the disease progression alone may also contribute.*

1 Younossi Z, Henry L. Overall health-related quality of life in patients with end-stage liver disease. Clin Liver Dis (Hoboken). 2015;6(1):9-14.

Our response:

In the revised discussion section, we added the following sentence:

“Disease progression and QOL decline can also affect prognosis.”

<23> *Page 13 Line 11- The authors mention unfavourable clinical outcomes were in line with the data they identified. Please may the authors elaborate and state what outcomes this statement refers to?*

Our response:

We did as you suggested.