Peer Review File

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Review comments

Reviewer A

Authors showed a narrative review about HCC and sarcopenia. As authors mentioned, sarcopenia is frequently found in patients with HCC. It is a serious issue in the management of HCC. But, in this review, the presentation was unclear and the significance was also unclear.

1. A schema showing review process is required.
   Response; The schema has been added in the revised submission (figure.1)
2. Abbreviation should be with full spelling a the first appearance.
   Response: This errors have been corrected
3. In the introduction, NAFLD should be described as the etiology of CLD.
   Response: NAFLD described as the etiology of CLD is added to the introduction
4. The data in the manuscript should be shown with appropriate references.
   Response: The data and the manuscript has undergone major revisions, also with revised references
5. The significance of diagnosis or treatment in HCC was unclear. Authors should focus on those with HCC.
   Response: The focus is now on HCC regarding diagnosis and treatment, with major revisions.

Reviewer B

Sarcopenia is a prognostic factor in patients with hepatocellular carcinoma therefore a review of sarcopenia and hepatocellular carcinoma is important. Despite the title of this review being sarcopenia and hepatocellular carcinoma, it contains much content other than sarcopenia and hepatocellular carcinoma. There is also little content on sarcopenia. The content is insufficient for a review.
Response: The revised manuscript has undergone major revisions, as describe below

Definition:
The diagnostic methods for sarcopenia need to be described in more detail. The methods of measuring muscle mass need to be described, including the diagnostic criteria for sarcopenia, advantages and disadvantages of each method, and points to be noted in their interpretation. In addition, many reports only measure skeletal muscle mass, although skeletal muscle functions such as grip strength are considered more important than skeletal muscle mass. These also need to be described in detail.
Cancer cachexia and malnutrition are different from sarcopenia and should be omitted

here.
Response:
The diagnostic methods and criteria for sarcopenia are now discussed in more detail. These include criteria for identifying patients, their assessment, confirmation and severity. The importance of hand grip strength is emphasized both for assessment and prognostication. The different methods for imaging muscle are described in more detail. All references to malnutrition are removed. Cancer Cachexia is only used when sarcopenia is an outcome measure in a particular trial.

Mechanisms contributing to Sarcopenia:
Chronic liver disease itself is not the cause of sarcopenia, but chronic inflammation, anti-ammonaemia and decreased appetite associated with chronic liver disease cause sarcopenia. Therefore, chronic liver disease itself should not be mentioned as a cause. With regard to anti-neoplastic therapy, not only TKIs but also TACE and surgery can cause it. They should be described in detail and the mechanism by which they cause sarcopenia should also be mentioned.
LI-1, IL-6 and TNFα are also listed as causes of sarcopenia in the Figure, but are not mentioned in the text. These should also be reviewed.

Response:
We have removed chronic liver disease per se as the cause of sarcopenia and revised the mechanisms section to include chronic inflammation, anti-ammonaemia. We have added and expanded on LI-1, IL-6 and TNFα as causes of sarcopenia in the text. We have added other anti-neoplastic therapies including TACE and surgery and their associations with sarcopenia

4 Screening and assessment of sarcopenia and malnutrition
This review is about sarcopenia; malnutrition is not required; a description of SARC-F and SPPB and the diagnostic criteria should also be mentioned.
Response: All references to malnutrition have been removed and SARC-F and SPPB are described as diagnostic criteria for sarcopenia severity. Additional studies using SPPB as an outcome measure are now also in the revised manuscript

5 Sarcopenia and prognosis in HCC
There is little content on prognosis. There are numerous reports on this and they should be thoroughly reviewed. The content of reference 45 is not relevant to this review; it is not clear what you want to say about Treatment modality for HCC. Please clarify what you want to say.
For the section on Sarcopenia combined with markers of inflammation, please check all reports and present them in a table for easier reading.

Response: There is extensive revision and additional information regarding sarcopenia and prognosis in HCC. We have also revised the relevant references. For easier reading we have revised the section on combining markers of inflammation, so

that it is more concise and relevant

6 Treatment
Androgens and vitamin D should be separate items; for NIS, the content is related to malnutrition, not sarcopenia. Please provide content related to sarcopenia.
Nutrition and exercise therapy are the only evidence-based treatments for sarcopenia. Please describe each in detail. Exercise therapy should be described separately for aerobic and resistance exercise.
A number of drugs are in clinical trials and animal studies, such as therapeutics for myostatin and ghrelin agonists. These also need to be described.
Response: We have separated Androgens and Vitamin D into two sections. We have removed all references to malnutrition and minimized references to NIS. We have added detail to nutrition and exercise and included symptom burden only as it relates to impaired physical performance/function and nutritional intake. We have emphasized the differences between resistance and aerobic exercise in trials and noted when they are used in combination therapy.
We have expanded the section on drugs that are in early phase trials and also included pre-clinical studies. We have also provided references to other recent manuscripts describing these early clinical studies in detail, for those readers interested in material beyond the scope of our manuscript.

Reviewer C

Thank you for the opportunity to read and study your work. Even if in this paper we can shed light on many issues regarding sarcopenia and malnutrition in cancer and HCC, I think that manuscript can't be accepted because of many criticisms. Among the others, the most relevant:

1) the authors do not address the cruciai role that cirrhosis plays in the development of sarcopenia in patients with HCC, since it is not possible to consider HCC without underlying chronic liver disease;
   Response: We have expanded on the role of cirrhosis as a major contributor to sarcopenia in CLD, including hyperammonemia, amino acid deprivation, chronic inflammation, excessive alcohol intake, and physical inactivity. The revised manuscript also discusses the role of underlying liver disease, and its relationship with sarcopenia and HCC

2) there is no a crucial focus on sarcopenia, while there is a confused construction on the role and diagnosis of sarcopenia and malnutrition in these patients;
   from a pathophysiological point of view, the paper lacks some relevant aspects that are crucial in this context, first of all the dysregulation of liver-muscle-adipose tissue axis (myostatin, etc) with all subsequent therapeutical issues.

Response: All references to malnutrition have been removed and the dysregulation of the liver muscle adipose axis has been added to the revised manuscript

Reviewer D

I suggest, you add the following into the review:
Response;We thank the reviewer for providing the relevant references and have added them to the revised manuscript.

1. Prevalence of sarcopenia in HCC in curative and palliative setting.
Response: We added the data from the meta-analysis suggested below to illustrate the difference in sarcopenia prevalence between palliative and curative patients. We have also included factors found to influence prevalence (e.g., Method of sarcopenia measurement and geography) and the prevalence of sarcopenia in the curative and palliative setting.

2. Clinical importance of sarcopenia in curative setting: influence of sarcopenia on occurrence of postoperative complications; influence of sarcopenia on RFS and OS.
Response; we have added a multi-center study of more than 1172 patients undergoing hepatic resection for HCC, reporting the influence of sarcopenia on RFS and OS

3. Clinical importance of sarcopenia in palliative setting: influence of sarcopenia on PFS and OS.
Response: We have added a paragraph on patients with advanced HCC (80% had extra-hepatic metastasis) and the impact of sarcopenia and myosteatosis on OS and PFS
4. Influence of sarcopenia on treatment related toxicity.
Some large meta analyses may be helpful:
Response: We have added the references suggested below reporting on sarcopenia and the effect on prognosis for patients receiving Kinase Inhibitors. In addition, the reference and information regarding greater toxicity with kinase inhibitors than conventional chemotherapy of check point inhibitors

Prevalence of sarcopenia in patients with solid tumors: A meta-analysis based on 81,814 patients. doi: 10.1002/jpen.2415.
Low skeletal muscle mass predicts treatment response in oncology: a meta-analysis. doi: 10.1007/s00330-023-09524-0. Online ahead of print.

Prevalence and role of low skeletal muscle mass (LSMM) in hepatocellular carcinoma. A systematic review and meta-analysis.
doi: 10.1016/j.clnesp.2022.04.009.

Low skeletal muscle mass is a predictor of treatment related toxicity in oncologic patients. A meta-analysis. doi: 10.1016/j.clnu.2021.08.023.