Comments

<u>**Reviewer comments**</u>

Reviewer 1: This is an awesome work; so enlightening. The efforts put into this is highly appreciated, and commendable. Thank you. I just wanted to take your attention to the 6th line in the conclusion section, which reads: "If these interventions completely reverse sarcopenia remain to be studied." I just wanted to be sure it conveyed what you intended

Response: We thank reviewer for their comments and their effort in reviewing the manuscript. We have edited the conclusion (6th line) to avoid confusion.

"However, it is unclear about the degree of improvement of the sarcopenia with all of these measurement combined."

<u>**Editor comments.**</u>

1 Scientific quality: The manuscript entitled "Sarcopenia in Hepatocellular Carcinoma: Current Knowledge and Future Directions" is a systematic review of the literature that focuses on the problem of sarcopenia in liver cancer. The topic is within the scope of the WJG. (1) Classification: Grade A;

Response: We thank editor for their comments on this manuscript.

2 Language quality: Classification: Grade A

Response: We thank editor for their comments on this manuscript.

3 Academic norms and rules: (A), (B) (D) This is a literature review. (C) No COI disclosure form has been provided yet.

Response: We have included a signed conflict of interest disclosure form.

5 Issues raised: The paper is not written according to the guidelines for manuscript preparation. Please, follow the guidelines described at https://www.wjgnet.com/bpg/GerInfo/203. All articles must be prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins. Please, ensure main sections of the manuscript are present in the abstract, as well as in the body of the manuscript (including aims, methods, results and conclusions).

Response: Thank you for the comment. We edited the manuscript per the WJG guidelines with change of font and spacing. All references has been changed per journal style. Spacing and margins were changed per journal guidelines. The body of the manuscript has main sections including introduction, methods, description and conclusions. Furthermore, the abstract has been changed as suggested with subheading of aims, methods, results and conclusions.

6. Please, add PRISMA Checklist to the supported documents. In the methods section of the manuscript, please, disclose more details on the search strategy: types of papers selected; time frame for selection; whether papers' quality assessment was performed and whether guidelines for quality assessment were followed.

Response: We thank editor comments on this. We included PRISMA checklist for the article. We elaborated the methods section. We reviewed basic science and clinical

An electronic search was performed using databases PubMed/Medline, EMBASE, Cochrane, Web of Science, and CINAHL on April 1, 2021, to identify published reports on sarcopenia in HCC. We used the following search terms- "carcinoma, hepatocellular" or "cancer, hepatocellular" and "sarcopenia" or "sarcopenias." A total of 4,762 articles were published on sarcopenia and 167,571 on hepatocellular cancers. Both basic science and clinical studies were included. A combined search revealed 2,289 articles over the last 12 months. The authors AP and HG reviewed the articles independently. Clinical reviewers, case reports, case series were excluded. A manual search was performed by evaluating the references from included studies and related articles in multiple databases. If any discrepancies, these articles were re-reviewed by the author RT. After removing non-relevant/duplicates/non-English language articles, including a manual search, 80 full length published articles were finally reviewed.

7. Is there any information on the potential use of selective androgen receptor modulators for the treatment of sarcopenia in HCC?

The role of non-steroidal Selective Androgen Receptor Modulators (SARMs) is increasingly being recognized in the treatment of sarcopenia[105-107]. As SARMs increase the synthesis of the

muscle with inhibition of protein degradation, they could decrease the rate of sarcopenia. Multiple animal models were utilized to evaluate mechanisms of SARMs to reverse muscle atrophy in degonadized mice. For instance, SARM treatment in ovariectomized rat model can increase muscle mass by enhanced mitochondrial biogenesis, actin and myosin[106]. SARMs can target androgen receptors and decrease sarcopenia via paracrine growth factor signaling on vimentin positive muscle fibroblasts[105]. Further, upregulation of mTOR, glycogen synthase kinase[107]. These SARMs by exhibiting anabolic effects can increase the bone and muscle mass which are affected in patients with HCC.

7. Recommendation: Conditional acceptance. Revision of format and style are required.

Response: We thank editor for their comments. We thoroughly revised the manuscript per the WJG style and format.

We hope that these changes will satisfactorily answer all the comments raised.

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