

Peer Review File

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Review comments

Reviewer A

Comment:

This review explores the potential benefits of prehabilitation, a multimodal pre-operative exercise and nutritional intervention, in enhancing outcomes among patients with hepatocellular carcinoma (HCC). First, in the background of the abstract, please explain the clinical needs for this narrative review and the clinical questions to be reviewed or addressed in this review. In the methods, please briefly describe the search strategies, data extraction, and how the findings from retrieved studies were analyzed and summarized. In the findings, please have comments on the development of the individualized prehab plan and the complexity of the HCC population. In the conclusion, please further clarify what further work is needed. Second, in the introduction of the main text, please have a brief comment on the challenges of the clinical management of HCC and explain why the narrative review on Prehabilitation for HCC is needed. A straightforward comment on the clinical questions to be examined or addressed in this review is needed. Third, in the main text, please provide more details on the inclusion of eligible studies, data extraction, and how the data were analyzed. In the conclusion, please have comments on the limitations and knowledge gaps of prior studies, and clearly suggest the unaddressed questions to facilitate the clinical implications of prehabilitation.

Reply:

This narrative review of prehabilitation in the context of hepatocellular carcinoma (HCC) is necessary due its growing prevalence in the world and the importance of augmenting oncologic treatments to improve clinical outcomes. Through our narrative review, we hoped to examine the impact of previously developed prehabilitation programs and determine the important components that can be further advanced upon in future studies. We queried major databases to establish the link between sarcopenia and outcomes in HCC. We focused on studies that used reproducible protocols and could be practically achieved in other U.S. healthcare settings.

As HCC is complex in etiology and affects a diverse patient population, we believe it essential to determine the key factors that have a measurable impact on clinical outcomes. We used sarcopenia as a variable that could be quantified and calculated over the course of a prehabilitation program.

We included studies examining prehabilitation in other GI solid organ malignancy due to the relative lack of studies in HCC. Using these models and data on prehabilitation's effect on sarcopenia, we were able to build a case for the importance of prehabilitation in HCC specific populations. Major limitations of current studies include a lack of a guideline for prehabilitation programs and differences in protocols within the major tenets of the program (specific exercise plan, nutrition models, etc..)

Changes in the text:

We added further clarification of our purpose (see Page 2, line 24-25), selection criteria (see Page

2, line 32-34), findings (see Page 3, lines 42-44), and call for future research (see Page 3, lines 49-51) within our abstract. Within our introduction, we have added a comment (see Page 5, lines 93-97) on the complexity of HCC and why this narrative review is warranted. In the methods section of the main text, we commented on the inclusion process (see page 6, lines 116-120). In the conclusion, we clarified specific limitations for prior studies and a direction for future research (see Page 18, lines 370-373)

Reviewer B

Comment:

Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths. Patients with HCC are often significantly affected by sarcopenia and cancer cachexia. In the manuscript “Potential and Value of Prehabilitation in Treating Hepatocellular Carcinoma and Enhancing Outcomes: A Narrative Review of Available Evidence”, authors offered guidance on how prehabilitation may be implemented for those with HCC based on available data published on other gastrointestinal malignancies and serve as a call for additional research specific to the value of prehabilitation in HCC.

Couple questions are required to be answered before it will be accepted.

- (1) Whether the prehabilitation was suitable for all patients with HCC?
- (2) In the text, it was better to add related reference (DOI: 10.21037/jtd.2018.08.18) about prehabilitation in thoracic surgery.
- (3) How to perform pain management for HCC patients? How about the effects of prehabilitation on HCC?
- (4) Whether there were differences between prehabilitation and ERAS?
- (5) What were your good suggestions for the prehabilitation for HCC patients? Please state in the text.

Reply:

- 1) Many of the prospective prehabilitation studies reviewed did not comment on how many patients were not able to tolerate the program, but, in theory, there is a high likelihood that older, more frail HCC patients or those with severe cardiopulmonary comorbidities may not be suitable for the exercise component of the prehab program. This would be addressed in the proposed risk stratification prior to enrollment to program (page 12, lines 247-250).
- 2) Not entirely sure what was meant here, further clarification from the reviewer would be greatly appreciated if there was a particular related issue here
- 3) Pain management in HCC is a unique challenge as many common analgesics including opioid medications require a healthy liver to either be activated or metabolized and excreted. This can lead to many of these medications to either be ineffective or lead to toxicity in this patient population. Morphine and buprenorphine is often preferred as they are metabolized by glucuronidation, a process that is unaffected by hepatic impairment. Procedure-based pain relief treatments are also available options depending on the cancer stage. Future studies into prehab models should examine whether having a physiatrist or other pain-management physician as a part of the model could lead to more positive clinical outcomes (37). There has been minimal research examining the effect of prehabilitation on

HCC at a cellular level. A study of breast cancer patients showed that exercise upregulated immune pathways and cytotoxic activity of certain immune cells and downregulated immunosuppressive pathways (38).

- 4) ERAS has served as a foundation in the call for multimodal prehab programs. Major differences are that ERAS focuses on optimization of post-surgical outcomes before, during, and after the surgery. The goal of prehabilitation is functional optimization of the patient prior to oncological treatment, whether surgical or non-surgical.
- 5) We would love to make a claim about suggestions for an HCC prehab program, however, there is currently a paucity of data within this patient population. We have extrapolated data in our narrative review from other solid organ GI malignancies, but the HCC population is unique and complex would need further studies to make a data driven claim.

Changes in the text:

(1) Added a sentence (see page 18, lines 381-383) stating that not discussing HCC patient suitability for prehab was a significant limitation of studies reviewed. Also added a comment about screening HCC for appropriateness for prehab (see page 12, lines 249-250)

(2) ?

(3) As cancer pain can be a major barrier in prehabilitation, we added a comment about the role CR could play in treating cancer pain (see page 12, lines 249-251) and about how future studies could include comparing pain management strategies within a prehab model (see 19, lines 385-387).

(4) We added a sentence highlighting how ERAS differs but can be an example for prehab programs (see page 17, lines 351-353).

(5) (See page 18, lines 377-380) We included a sentence explaining the difficulty in making evidence-based suggestions for HCC prehabilitation programs.