Point-by-Point Response to Reviewers

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Dear Authors, Your manuscript is very interesting, with an appropriate title, abstract, key words, and well-organised structure. Cachexia is an important problem because it is the first anti-cancer drug, particularly pancreatic cancer. You analyzed a new method for the treatment of cachexia and the role of the gut microbiome in the development and treatment of cachexia. The new method of enteral feeding with peptite-based formula is feasible and warrants further investigation, while change of the gut microbiome has potential for the treatment of cachexia and demands further investigation also.

- **We thank the Reviewer for their time in reviewing our manuscript and for providing the support to accept our manuscript.**

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: This paper focuses on cachexia in pancreatic ductal adenocarcinoma (PDAC) patients, and investigates the possible role of nutritional support and human gut microbiota in reversing PDAC cachexia. The study reported in this manuscript is very interesting and importance. The authors may further discuss the special role of systemic inflammation in the development of cachexia. Systemic inflammation as one of the main features of cachexia is mentioned by the authors several times in the manuscript. Localized transient Inflammation is the central machinery of our immune system in response to acute tissue damage [1], and such localized transient inflammation is generally protective. It helps to remove the injurious stimuli like infections, trauma and tumor cells, and initiate tissue regeneration. When there are tissue-damaging stimuli like physical injury, infectious pathogens, toxin exposure, chemical irritation, the human immune system will actively induce cell self-destruction (programmed cell deaths [2] like apoptosis, necroptosis and pyroptosis) and reuse the nutrition from the degradation of the dead cell as nutrition source (immuno-nutrition) to repair/regenerate the tissue cells. If the damaging stimuli and the destructed cell debris can be effectively and swiftly removed by inflammation and fully used for tissue regeneration, then inflammation will not be chronic or systemic, and cachexia will not be developed. Yet, when the nutrition from the destructed cells exceeds the tissue regeneration needs, the extra nutrition will be transferred into lipid intermediates and deposits on healthy non-adipose tissues like muscles, and causing lipotoxicity. Lipotoxicity will create new cell death, and leading to the destruction of

these cells. Thus, more lipid intermediates are produced by inflammation, with the expenses of lean mass. A vicious positive feedback between cell death and lipid intermediates are established, leading to cachexia, and local transient inflammation becomes systemic inflammation. So when there is cachexia, restrictive eating should be adopted by the patient [3] to avoid over-nutrition and systemic inflammation. The impact of gut microbiota on cachexia is indirect. They are playing the role of full spectrum of immuno-nutrients like essential amino acids to the human body [4]. And, as a nutrition source, if they are overgrown, they will contribute to systemic inflammation and cachexia. So although gut microbiota provide a full spectrum of essential nutrition, their abundance in the gut should also be strictly checked. Reference: 1. Greten FR, Grivennikov SI (2019) Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity 51(1):27-41. DOI: 10.1016/j.immuni.2019.06.025 2. Yang Y, Jiang G, Zhang P, Fan J. (2015) Programmed cell death and its role in inflammation. Mil Med Res. 2015;2:12. DOI: 10.1186/s40779-015-0039-0 3. Arabi YM, Reintam BA, Preiser JC (2019) Less is more in nutrition: critically ill patients are starving but not hungry. Intensive Care Med 45:1629–1631. DOI: 10.1007/s00134-019-05765-0 4. Hackmann TJ, Firkins JL (2015) Maximizing efficiency of rumen microbial protein production. Front Microbiol 6:465. DOI: 10.3389/fmicb.2015.00465

- **We thank the Reviewer for their time in reviewing our manuscript and for providing helpful comments and suggestions that we believe altogether strengthen the quality of our manuscript.**
- **We have included a new discussion in the section "MICROBIAL INTERVENTIONS AS A POTENTIAL NEW THERAPEUTIC STRATEGY FOR CACHEXIA" to further elaborate the relationship between inflammation and cachexia. We have included citations by Greten et al [19], Yang et al [20], and Arabi et al [22] as recommended by the reviewer, but we have decided not to use the reference by Hackmann et al. Instead, we cite papers by Laviono et al [21] and Al Bander et al [23] to emphasize the protective functions of the localized inflammatory response, but how cachexia represents a systemic inflammatory state whereby feeding without resolving inflammation can be detrimental. We then end this new paragraph by adding that gut microbiota have both anti- and pro-inflammatory effects and that this relationship between the microbiome and cachexia could be exploited to counteract the systemic inflammation underlying cachexia. We believe by discussing these points here, it transitions better into the next paragraph where we previously highlighted the mechanisms by which the microbiome can decrease inflammation and mitigate cachexia.**

(1) Science editor:

This manuscript analyzed a new method for the treatment of cachexia and the role of the gut microbiome in the development and treatment of cachexia. The topic of this paper is interesting which may need further research, and the article can provided some

new information. The special role of systemic inflammation in the development of cachexia may need further discussion. Also, the paper is organized well, and the language of this paper is in a high quality. Please add more references if possible.
Language Quality: Grade A (Priority publishing)
Scientific Quality: Grade B (Very good)

- **Additional references have been included in addressing Reviewer 2's comments as described above.**

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list.

- **Decomposable figures in PPT have been provided. Standard three-line tables have been provided. Figures are original with copyright information included in bottom right-hand side.**