

Dear editors,

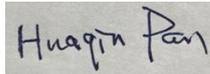
Re: Resubmission of manuscript

Thank you for the opportunity to allow our research group to revise our manuscript entitled " COVID-19 and its effects on the digestive system". Your comments were highly insightful and enabled us to greatly improve the quality of our manuscript. We dedicated enough effort to respond in accordance with the comments. The changes to the text are given in red font. The following pages contain our point-by-point responses to each of the comments.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *World Journal of Gastroenterology*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

A rectangular box containing a handwritten signature in black ink that reads "Huaqin Pan".

Huaqin Pan, MD, PhD

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## **Responses to the comments of Reviewer**

1. All key words reflect the focus, other than “mechanisms”. Mechanisms are not sufficiently described in the manuscript.

It has been already mentioned in “Mechanisms of gastrointestinal tract involvement”. Now, this part is revised accordingly.

2. References have been cited adequately. Though the numbering of referencing needs to be rechecked.

We have rechecked the references and revised accordingly.

3. Yes, manuscript is well-organized with appropriate language for the most part. In some sentences, percentage of patients are stated as “were dead”. It should be replaced with “died”.

We have revised accordingly in red font.

4. Page 5: Please confirm whether it is 7th or 8th. Some research articles have counted previous coronaviruses with human infection capacity to be 7, making this the 8th one. [Reference: Zheng J. SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. *Int J Biol Sci.* 2020;16(10):1678-1685. Published 2020 Mar 15. doi:10.7150/ijbs.45053]

We have revised accordingly in red font.

5. Page 7: Highlight importance of gastrointestinal health for COVID-19 patients for correction of albumin deficiency, which has been correlated with higher risk of mortality. Albumin can be improved more meaningfully through dietary protein intake compared to albumin infusion. [References: (1) Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and comorbidity. *J Med Virol.* 2020;92(10):2152-2158. doi:10.1002/jmv.26003 (2) Anna E. Thalacker-Mercer, Craig A. Johnson, Kevin E. Yarasheski, Nadine S. Carnell, Wayne W. Campbell, Nutrient Ingestion, Protein Intake, and Sex, but Not Age, Affect the Albumin Synthesis Rate in Humans, *The Journal of Nutrition*, Volume 137, Issue 7, July 2007, Pages 1734–1740, <https://doi.org/10.1093/jn/137.7.1734>]

We have added a separate section in “Malnutritional risk and nutritional

intervention in COVID - 19 patients” accordingly.

6. Page 8: *Impact of malnutrition on disease progression should be highlighted. (1) Micronutrients are essential for proper functioning of immune system; (2) Insufficient protein intake and absorption can lead to further drop in albumin level; (3) Several anti-inflammatory active constituents contained in foods such as Ginger, Cinnamon and Turmeric that may provide some degree of relief from cytokine storm will not be consumed or absorbed in case of decreased appetite or gastric complications. [Reference: (1) Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients*. 2020;12(1):236. Published 2020 Jan 16. doi:10.3390/nu12010236 (2) Anna E. Thalacker-Mercer, Craig A. Johnson, Kevin E. Yarasheski, Nadine S. Carnell, Wayne W. Campbell, *Nutrient Ingestion, Protein Intake, and Sex, but Not Age, Affect the Albumin Synthesis Rate in Humans, The Journal of Nutrition, Volume 137, Issue 7, July 2007, Pages 1734–1740, <https://doi.org/10.1093/jn/137.7.1734> (3) Khan MA, Khan ZA, Charles M, Pratap P, Naeem A, Siddiqui Z, Naqvi N, Srivastava S. Cytokine Storm and Mucus Hypersecretion in COVID-19: Review of Mechanisms. *J Inflamm Res*. 2021; 14:175-189 <https://doi.org/10.2147/JIR.S271292>**

We have added a separate section in “Malnutritional risk and nutritional intervention in COVID - 19 patients” accordingly.

7. Page 8: Delete “Patients with ”

We have revised accordingly.

8. Page 9: *Epigallocatechin Gallate (an active constituent of Green Tea) has been identified as a potential inhibitor of this domain and other proteins of SARS-CoV-2. You may suggest that effect of green tea consumption may be explored for inhibition of spike proteins domains to prevent its binding with ACE2. This may be particularly effective in the gastrointestinal tract, as oral route implies maximum availability in the digestive tract. [Reference: Mohammad Faheem Khan\*, Mohsin Ali Khan, Zaw Ali Khan, Tanveer Ahamad and Waseem Ahmad Ansari, “In-Silico Study to Identify Dietary Molecules as Potential SARS-CoV-2 Agents”, *Letters in Drug Design &**

*Discovery* (2021) 18: 1. <https://doi.org/10.2174/1570180817999201209204153>

Page 9: You may suggest that in the absence of TMPRSS2 inhibitor, effect of green tea consumption may be explored for inhibition of spike protein domains to prevent its binding with ACE2.

We have revised accordingly.

9. Page 10: Include prevalence of hypoalbuminemia in COVID-19 patients, as it has been seen to be associated with higher risk of COVID-19 severity and mortality. You have briefly mentioned it in Figure 1, so it should be described here.

We have added a separate section in “Malnutritional risk and nutritional intervention in COVID - 19 patients” accordingly.

10. Other spelling mistakes and inappropriate expressions pointed by the reviewer have been amended.