

Date: 20 February 2023

Re: Manuscript ID: 82174: Occam's razor or Hickam's dictum - COVID-19 is not a textbook aetiology of acute pancreatitis: a modified Naranjo Score appraisal

Dear Editor-in-Chief and Reviewers,

This is a revised submission of our manuscript titled: "Occam's razor or Hickam's dictum - COVID-19 is not a textbook aetiology of acute pancreatitis: a modified Naranjo Score appraisal". We are thankful to you and the reviewers for the insightful critic and comments and the conditional acceptance of our manuscript. The changes are highlighted in red.

Please see below for our point-to-point responses to the reviewers.

Reviewer 1

Comment 1: The small sample size of the study hinders the ability to generalize the results to a larger population.

Reply 1: We agree that the sample size is small with only 76 patients across the entire study period. We have added this in our limitations: “**Additionally, interpretation of this study is limited by the small sample size of 76 patients.**”

Comment 2: The insufficient diagnostic process for most patients weakens the accuracy of the diagnosis and the reliability of the study results.

Reply 2: Thank you for this comment. We agree that establishment of whether COVID-19 induced pancreatitis is related to the extensiveness of the initial work-up for causes acute pancreatitis. This was the aim of our study – to establish a scoring system to determine the probability of COVID-19 induced pancreatitis. For instance, our modified Naranjo score included a few criteria which determines whether the diagnostic process was sufficient to establish COVID-19 as an etiology:

- Criteria 5: Were all commonly known causes of acute pancreatitis ruled out? (eg, gallstones/ choledocholithiasis, alcohol, hypertriglyceridaemia, hypercalcaemia, ERCP, trauma)
- Criteria 6: Was a serum IgG4 level checked? (to rule out autoimmune pancreatitis)
- Criteria 7: Does the patient have or was the patient recently diagnosed with an infection (other than COVID-19) which could cause pancreatitis?
- Criteria 8: Was an EUS and/or MRCP performed? (eg, to rule out occult microlithiasis, pancreatic malignancy and pancreas divisum)

Comment 3: The literature review should provide a summary of important COVID-19 and healthcare trends, and should include the relevant studies in the field. The following papers are recommended: A. Artificial Intelligence and COVID-19: Deep Learning Approaches for Diagnosis and Treatment B. A conceptual deep learning framework for COVID-19 drug discovery C. Cancer Digital Twins in Metaverse

Reply 3: Thank you for the suggestions. We have included references A and B in our revision. However we did not include reference C as the reference is mainly about the use of artificial intelligence in cancer, which is beyond the scope of our study. Please let us know if there is anywhere in the manuscript which you would like us to include reference C. These references have been included in our discussion:

“Centers should continue reporting such occurrences of COVID-19-induced pancreatitis and consider incorporating of our modified Naranjo score; artificial intelligence methods may subsequently be used to diagnose COVID-19-induced pancreatitis [101, 102].”

Comment 4: The use of an untested scoring system to determine the relationship between COVID-19 and AP may limit the accuracy of the results.

Reply 4: Thank you for this comment. We agree that our scoring system is untested and has its limitations. Hence this was included in our limitations: “Firstly, given the nature of our study, prospective studies and systematic reviews were not analyzed as they lack individual patient data. Additionally, interpretation of this study is limited by the small sample size of 76 patients.” and “Fourthly, authors may not have reported cases where patients were reinfected by COVID-19. This is a potential limitation in the calculation of the modified Naranjo scoring.”

Comment 5: The absence of genetic testing to rule out hereditary AP affects the thoroughness of the diagnostic process

Reply 5: Thank you for this comment. We agree that absence of genetic testing limits the ability to exclude hereditary AP. However, this was not included in our scoring system as none of the included studies performed genetic tests for confirming or excluding hereditary pancreatitis. Addition of this into our scoring system may arbitrarily lower the score. Currently, in the evaluation of acute pancreatitis, there is no strict recommendation on the exact indications for genetic counselling and/or testing in acute pancreatitis. We have included this in our methodology as well:

“Additionally, there are no strict recommendations on the exact indications for genetic counselling and/or testing in AP, limiting its utility for inclusion in our proposed scoring system [15].”

Comment 6: The lack of investigation into other potential viral infections and the absence of certain imaging tests affects the accuracy of the diagnosis and the reliability of the results.

Reply 6: Yes we agree that the lack of investigation on other potential viral infections limit the ability to diagnose COVID-19 as an etiology of acute pancreatitis. Hence our modified scoring system included point 7: “Does the patient have or was the patient recently diagnosed with an infection (other than COVID-19) which could cause pancreatitis?” which helps to determine if acute pancreatitis was more likely to be caused by COVID-19 infection.

Comment 7: The definition of the modified Naranjo scoring system is not clearly stated and may result in misinterpretation of the results.

Reply 7: Thank you for this question and comment. This is important as our study resolves around the proposal of a new scoring system i.e. the modified Naranjo scoring system. This has been explained in our methodology under the sub-section “the modified Naranjo score” and also in Table 1. Please see if this is sufficient or requires further elaboration.

Comment 8. The conclusions drawn from the study are not strongly supported by the results and more research is needed to establish a clearer association between COVID-19 and AP.

Reply 8: Thank you for this comment. We agree that a small sample size limits the utility of our proposed scoring system. Hence, we described that “The current evidence is weak to establish a strong causal link between COVID-19 and AP, and more evidence is necessary before COVID-19 should be incorporated as a “textbook aetiology” of AP” in our conclusion. However, we have also made modifications to the conclusion: “**The use of our proposed modified Naranjo score may help to determine whether COVID-19 is a likely etiology of AP and may assist clinicians in making useful clinical decisions.**”

Comment 9: The study could have been improved with a larger sample size and more extensive diagnostic processes to enhance the accuracy and reliability of the results.

Reply 9: Thank you for this comment. While we would like to increase our sample size, this is not possible as this is a systematic review on existing evidence, for which we only found 67 articles describing 76 patients with COVID-19 induced pancreatitis. Our search was extensive which spanned across 3 databases and yielded 909 articles in our initial search.

Reviewer 2

Comment 1: Good paper, well written, good scientific soundness, methods well presented, clarity of the results. However, some references are so old must be updated

Reply 1: Thank you for this comment and we hope this article will be of utility to clinicians. We have updated one of our references – Ref 12. Other references have been kept as older references dated earlier than 2010 were relevant and have not been replaced by newer studies. Please let us know if there is any particular reference which you would like us to update.

Science Editor

Comment: The manuscript has been peer-reviewed, and it is ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Reply: Thank you for the review.

Company Editor-in-Chief

Comment: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, 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. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". 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. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles,

which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at:
<https://www.referencecitationanalysis.com/>.

Reply: Figures have been amended according to the journal requirements. Tables have also been reformatted based on the journal requirements.