Dear Editors,

We would like to thank you again for your kind invitation to write a review on acute pancreatitis and pancreatic cancer. We highly value the considerate feedback provided by the reviewers and editors on our manuscript entitled “Pancreatitis and pancreatic cancer: a case of the chicken or the egg” (manuscript ID 62753).

In this response we would like to share our reply to both your editorial comments as well as the useful comments of the reviewers. Below, you can find our detailed responses to all editorial remarks and commentary by the reviewers. The adjusted manuscript, together with adjusted additional files, has been uploaded.

We believe that with the substantial contributions of the reviewers, we have been able to make considerable improvements to the manuscript.

On behalf of all of the co-authors, I would like to thank you again for your invitation and your critical assessment of our manuscript.

Yours sincerely,

Devica Umans

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Differentiation between pancreatitis and PDAC still be difficult ,author discussed the relationship between acute or chronic pancreatitis and pancreatic cancer, explain the causality and diagnostic methods of AP,CP and PDAC. A systematic document retrieval in this field was conducted to review and explain the relationship from the perspectives of background, clinical case, the relationship between AP,CP and PDAC and how to differentiate (imaging and biomarkers). Minor revision: 1 the author present the educational case , however we cannot conclude the tail of pancreatic cancer on MR was originated from the first time onset of AP, is any similar or different imaging finding on the tail of pancreas. The first time onset is on the head of pancreas, but the second time is on the tail of pancreas. Does the tumor was exist on the onset of first time? 2The references need to be updated, only 17 of 49 references were published in the last 5 years, which made the current value of this review doubtful.

Authors: We would like to thank the reviewer for his/her valuable time and considerate feedback. With regards to the first question on the educational case: the reviewer is correct to point out the fact that a definitive causal relationship between acute pancreatitis and pancreatic cancer is difficult to ascertain in individual cases. We can also not be sure that the pancreatic cancer would have been diagnosed sooner, had the patient undergone additional imaging after the first episode of acute pancreatitis. This case is therefore a true reflection of the difficulty of management of patients with idiopathic acute pancreatitis and the uncertainty clinicians face when treating patients with idiopathic acute pancreatitis. Thus, although a causal relationship cannot be definitively determined, we think this case serves as an insightful educational case.

With regards to the second question on the references: thank you for pointing out the publication year of the references. For this review, we have ran several databases searches to ensure we had the most up to date data available. However, we were slightly disappointed to find that the evidence on some of the subjects in this review is – at best – limited. We have made sure to include the current state-of-the-art practice in this field in the review as well as the currently most promising research fields. Yet, we also emphasized the need for further evidence, particularly on the strategy for differentiation between pancreatitis and pancreatic cancer. We hope this is adequately reflected in our review. Our review gives an clear overview of not only the latest advances but also the current common practice on this subject, and thus, we believe this review is of value to current clinicians.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Dear Editor, thank you very much for the invitation. Some considerations: This review article was very well written, designed and updated for the proposed theme. Recent and detailed bibliographic review. Images with good resolution. I believe that a smaller and less repetitive conclusion would be more appropriate. Congratulations for the excellent work. Regards,

Authors: We would like to thank the reviewer for this kind and helpful feedback. The reviewer pointed out that the conclusion could be shorter and we agree with this assessment. We have shortened the conclusion while trying to retain the most relevant information. The current conclusion is as follows:

"AP can be a first symptom of underlying PDAC, especially in patients with presumed idiopathic AP, between the ages of 56 and 75 and those who had a diagnosis of new-onset DM or CP. Additional imaging to exclude PDAC in these patients should at least be considered. EUS seems to be the preferred imaging modality.

CP, particularly hereditary CP, may lead to PDAC through oncogenic mutations caused by long-standing pancreatic inflammation, and CP patients may be exposed to overlapping risk factors for CP and PDAC. In patients with PRSS1-mediated CP or a history of autosomal dominant hereditary CP without known mutations, surveillance for PDAC can be considered, although the efficacy and modalities of surveillance are still up for debate.

(Chronic) pancreatic inflammation may present as a focal mass on imaging. Specific findings, such as the duct-penetrating sign (MRCP) and the duct-to-parenchyma ratio (EUS), may aid in the differentiation between pancreatitis and PDAC.

Currently, considerable effort is focused on finding a biomarker or machine-learning methods as a superior discriminant between CP and PDAC. Unfortunately, no clinically useful technique has yet emerged. Improving the possibility to differentiate between CP and PDAC, as well as identifying patients at risk of underlying or future PDAC, may give clinicians the opportunity to enhance the diagnostic process."

Reviewer #3:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Please replace MRI image to MRCP image since the image does not clearly show dilatation of the pancreatic duct.

Authors: We would like to the reviewer for this valuable addition to the review. We agree that the pancreatic duct dilatation is not clearly shown on the MRI slide. Therefore, we have added the MRCP image. Figure 3 now consists of a "figure 3a" and figure 3b" and shows abdominal magnetic resonance imaging (figure 3a) of the pancreas and magnetic resonance cholangiopancreaticography (figure 3b). A hypo-intense lesion (shown in figure 3a) is causing a pancreatic duct stenosis with upstream dilatation of the pancreatic duct (shown in figure 3b).

(1) ***Science editor:***

1 Scientific quality: The manuscript describes an evidence review of the pancreatitis and pancreatic cancer. The topic is within the scope of the WJG. (1) Classification: Grade A, Grade B and Grade B; (2) Summary of the Peer-Review Report: The authors found a very well written, designed and updated review. However, the references should be updated. The questions raised by the reviewers should be

answered; and (3) Format: There 1 table and 4 figures. (4) References: A total of 49 references are cited, including 9 references published in the last 3 years; (5) Self-cited references: There is 1 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A, Grade A and Grade A. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) Please obtain permission for the use of picture(s). 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. 6 Recommendation: Conditional acceptance.

Authors: We would like to thank the science editor for their in-depth analysis of our review. Please see our response to reviewer #1 for our explanation for the publication date of our references.

Thank you for including additional information on how to submit the images. We have now arranged the original images in a PowerPoint file, which we will upload separately.

The patient described in the case has given informed consent for collecting his medical data and using this medical data for scientific publications (anonymously). He has signed an informed consent form (in Dutch). If requested, the informed consent form containing can be submitted, although to ensure anonymity, any identifiers of the patient will be blacked out on the form.

(3) ***Company editor-in-chief:***

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, the author(s) must add a table/figure to the manuscript.

Authors: We thank the company editor-in-chief for thoroughly reviewing our manuscript. We have indeed added a figure to our manuscript. Please see our response to reviewer #3 for a description of the added image.