Author's response letter

Reviewer #1:

In this paper, Petrov provides an excellent review about the potential role of post-pancreatitis diabetes mellitus (PPDM) and excess intra-pancreatic fat deposition (IPFD) as specific harbingers of pancreatic cancer. This is an interesting topic with recent promising findings that could offer new strategies for the early detection of pancreatic cancer. The manuscript is very well written and includes the most important recent evidence in this field. The author is to be congratulated for a complete and concise review.

Response: Thanks very much for the time taken to peer-review the manuscript. Your feedback was truly helpful.

I have the following minor comments: - The author suggests that a combined approach (history of pancreatitis/PPDM and variables of END-PAC score) might ultimately make screening for pancreatic cancer cost-effective and achievement-appropriate. Some questions that could be of interest to address regarding this statement arise. How could be the clinical application of such screening? Who is the population that must to be screened? All patients with history of pancreatitis/PPDM and New-onset Diabetes? Which is the proposed screening strategy and why it might be cost-effective? Any consideration regarding these questions, if possible, could add some value and provide future perspectives for the screening implementation.

Response: The manuscript understandably raises many questions regarding operationalising of the proposed approach. It can probably be applied to all middle-aged and older adults after an attack of pancreatitis who develop new-onset diabetes and unintentional changes in body composition (including but not limited to weight loss) during follow-up. In the revised manuscript, I have commented on the above aspect and highlighted the need for purposely-designed studies to compellingly address this aspect.

The author provides a complete explanation about the relationship between IPFD, pancreatic cancer, pancreatitis and pre-malignant lesions. However, could the author suggest which patients could benefit from assess IPFD for estimate de risk of pancreatic cancer in clinical practice? Only patients with a history of pancreatitis and pre-malignant lesions? Could any strategy to perform a sequential assessment for detect IPFD changes during follow-up be justified? Do patients with incidentally found fatty pancreas disease benefit from a special follow-up for early detection of pancreatic cancer? Could any screening strategy in patients with excess IPFD be suggested with the current evidence?

Response: At this stage, it appears that that only patients with history of pancreatitis or pancreatic pre-malignant lesions would justify a regular follow-up. The idea of regular follow-up of all people with fatty pancreas disease in the general population is appealing. However, given that fatty pancreas is common (in fact, it is even more common than type 2 diabetes!) and taking into account that pancreatic cancer is a rare disease, screening all people with fatty pancreas disease is unlikely to be cost-effective. But, hopefully, future studies will identify a subgroup of people with fatty pancreas disease that is at high risk for pancreatic cancer. The above points have been incorporated in the revised manuscript.

- Spacebar in "adenocarcinomaarising" (page 9).

Response: This has been corrected. Thank-you.

- Reference 10: "before" instead of "defore".

Response: This has been corrected. Thank-you.

- I do not consider essential to address all these minor questions because of the good quality of the paper is equally obvious. Nevertheless, it could try to offer a practical approach that could be of interest for clinicians. If recommendations for routine clinical practice cannot be yet made, it could be of interest also to explain it.

Response: The questions the reviewer raised were very worth addressing and I have done my best to touch on them in the revised manuscript as much as our current (limited) knowledge allows us!

Science editor:

(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.

Response: This has been done.

(2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Response: This has been done.

(3) Please obtain permission for the use of picture(s).

Response: I can confirm that the figure is original.

Company editor-in-chief:

There are 28 self-cited references. The self-referencing rates should be less than 10%. Before final acceptance, you are requested to keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If you fail to address the critical issue of improper self-citation, the editing process of your manuscript will be terminated.

Response: The number of cited articles from my group has been reduced to 4 in the revised manuscript.