June 26, 2020

Dear editor and reviewers:

Thank you for your careful consideration of our manuscript entitled "Meta-analysis reveals an association between acute pancreatitis and the risk of pancreatic cancer" (Manuscript NO: 56551). We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. The following are our replies to the comments of the reviewers. We have incorporated all of the changes suggested by the reviewers into our revision, and we have provided a point-by-point response to these suggestions below.

We hope that you find this revised manuscript suitable for publication in World Journal of Clinical Cases. We look forward to hearing from you.

Sincerely,

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To Reviewer #1:

We thank the reviewer for the kind comments, these have been taken into consideration and used to improve our manuscript. We have carefully proofread the document and corrected all spelling mistakes. In addition, we have deleted the sentence “Generally it takes decades…….. AP diagnosis” from the discussion, and instead elaborated on the possible mechanism for the relationship between acute pancreatitis and pancreatic cancer, especially in the first year.

To Reviewer #2:

We thank the reviewer for the valuable comments.

Answer #2-1:

We agree with this idea, our meta-analysis is just a statistical finding and cannot prove the cause-relation between AP and PC. However, we believe that some patients are misdiagnosed with AP, when in fact they were at initial stages of PC. Therefore, a spuriously strong overall association occurs in patients misdiagnosed with AP. We believe that this is an important finding, and have subsequently incorporated it in the discussion.

Answer #2-2:

Our metanalysis revealed an association between AP and PC risk. Based

on results from subgroup analyses, AP is unlikely to be a causal factor for PC, although its occurrence might be an opportunity for identifying PC. The clinical significance of our findings lies in improving strategies for prevention and early screening of PC patients, especially at onset of AP diagnosis. We have therefore elaborated on why AP is not a direct risk factor for PC, using possible mechanisms in the discussion section.

Answer #2-3:

Some of the articles included in our meta-analysis were too old. We have maintained them in the study and added newer references to improve the discussion.

To Reviewer #3:

We appreciate the valuable comments and recommendation given by this reviewer.

This meta-analysis is based on some authoritative articles, such as Munigala et al. Clin Gastroenterol Hepatol 2014; 12(7):1143-1150.e1; and Kirkegård et al. Gastroenterology 2018; 154(6):1729-1736; Pang et al. PLoS Med 2018; 15(8):e1002618. In these prospective cohort study, AP was defined by International Classification of Diseases (ICD), ensuring

that investigators included only patients with acute pancreatitis. However, we believe that a pre-existing pancreatic cancer might go undetected, since it clinically manifests as acute pancreatitis. We agree with the idea that AP might not be a direct cause of PC risk, and its occurrence could be an opportunity for PC detection. Furthermore, we have clarified the association between AP and PC risk in the discussion section and included the limitations of our meta-analysis.

To Reviewer #4:

We thank the reviewer for the kind comments and questions.

Answer #4-1:

This meta-analysis is based on some authoritative articles, such as: Munigala et al. Clin Gastroenterol Hepatol 2014; 12(7):1143-1150.e1; Kirkegård et al. Gastroenterology 2018; 154(6):1729-1736; Pang et al. PLoS Med 2018; 15(8):e1002618. In these prospective cohort study, AP was defined according to the ICD (International Classification of Diseases), ensuring that investigators included only patients with incident acute pancreatitis. However, we believe that a pre-existing pancreatic cancer might go undetected, which clinically presented as acute pancreatitis. We agree with the idea that AP might not be a direct cause of PC risk and the occurrence of AP might be an opportunity to find out PC.

Answer #4-2:

We have deleted the controversial sentence: “ paying more attention to the relationship between AP and PC”, and replaced it with “ more focus should be directed to improving PC prevention approaches, key among this being early screening for patients at onset of AP.”

Answer #4-3 and #4-4:

We have presented the limitations of our study. In addition, we have listed several possible reasons, in the discussion section, to justify the strong relationship between acute pancreatitis and pancreatic cancer in the first year.

To Reviewer #5:

We thank the reviewer for the pertinent comments.

Our meta-analysis included 11 studies, instead of 12, and was based on o some authoritative articles, such as Munigala. Clin Gastroenterol Hepatol 2014; 12(7):1143-1150.e1; Kirkegård. Gastroenterology 2018; 154(6):1729-1736; and Pang. PLoS Med 2018; 15(8):e1002618. These studies have revealed a strong association between AP and PC risk, within 1 year of AP diagnosis, and further shown a declining trend after

long-term follow-up. From our findings, we believe that pancreatic cancer (PC) may initially manifest symptoms similar to those observed in mild acute pancreatitis (AP) cases, indicating that it may be misdiagnosed as AP. Based on these, AP might not be a direct risk factor for PC, but its occurrence could be an opportunity for PC diagnosis. We have revised the corresponding conclusions, to guide future research.