

## Response to the reviewers' comment

<b>Reviewer 1</b>	<p><b>Moderate concerns:</b></p> <ol style="list-style-type: none"> <li>1. The manuscript is overwhelmingly citing meta-analysis results. While solid meta-analysis studies can offer higher statistical power, this type of study comes with its own weakness. The references in this manuscript should be more balanced in citing more single studies.</li> <li>2. Figure 1 only depicts the possible mechanisms of pancreatic cancer leading to the development new-onset diabetes in pancreatic cancer. There should be another panel depicting the potential mechanisms of long-standing type 2 diabetes leading to PDAC.</li> <li>3. The manuscript is under-weighted on the discussion of early detection of pancreatic cancer in patients with diabetes. Discussion on biomarkers for early detection and/or screening of PC in T2DM should be expanded.</li> </ol> <p><b>Minor concerns:</b></p> <ol style="list-style-type: none"> <li>1. On page 3, the authors stated that pancreatic cancer is an epidemic. Please confirm and cite the reference.</li> <li>2. Add references for this statement: "the reported relative risk (RR) for developing PDAC in long-term diabetes varies between 1.4 and 2.1" on page 4.</li> <li>3. Revise this sentence: Diabetes is often the result of the underlying endocrine dysfunction from a pancreatic exocrine disease, known as type 3c diabetes.</li> <li>4. Check grammar: "The hypothesis</li> </ol>	<ol style="list-style-type: none"> <li>1. Thank you, Sir for your comments. Many single studies have been cited in appropriate places as suggested by you.</li> <li>2. Another figure was added to the manuscript to depict potential mechanisms of long-standing type 2 diabetes leading to PDAC.</li> <li>3. A separate section on early detection of pancreatic cancer was added. Discussion on biomarkers for early detection and/or screening of PC in T2DM were also expanded.</li> <li>1. The sentence have been modified and the reference was added.</li> <li>2. The reference was added.</li> <li>3. The sentence has been revised.</li> </ol>
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	<p>includes" on page 8.</p> <p>5. Revise this sentence: "Recent experimental studies have pointed towards the role of PDAC-associated exosomes in inhibiting the PI3K-Akt-FOXO1 pathway down the insulin receptor signalling causing IR in skeletal muscle" on page 9.</p> <p>6. Multiple typos, punctuation, and grammar issues throughout the manuscript.</p>	<p>4. The grammar was checked.</p> <p>5. The sentence has been revised.</p> <p>6. We have thoroughly checked for all the errors and modified accordingly.</p>
<p><b>Reviewer 2</b></p>	<p>1. A brief conclusion about definition and classification of diabetes is lacking in the introduction, especially to focus on type 2 diabetes, long-standing diabetes and new onset diabetes. In addition, the introduction section is too brief, so you should add more background information, such as the main clinical treatment strategies of diabetes and pancreatic cancer, as well as main obstacles and difficulties during the diagnosis and treatment.</p> <p>2. Please list some research papers or reviews to confirm the consistent risk association between PC and diabetes, but not only depend on the meta-analysis.</p> <p>3. Please briefly introduce the definition of chronic pancreatitis (CP).</p> <p>4. "In a meta-analysis including fifteen studies (8970 patients) the incidence of NOD was 30% and the prevalence increased after 5 years of CP diagnosis." Please note the references of this sentence.</p>	<p>1. Thank you, Sir for your comments. The definition and classification of diabetes has been added in the manuscript. Introduction section has also been expanded as suggested by you.</p> <p>2. A significant proportion of citations of meta-analysis has been removed and replaced with original studies.</p> <p>3. The definition was added.</p> <p>4. The reference was added.</p>

	<p>5. Please ensure your table fonts are capitalized.</p> <p>6. Please ensure the clarity of the text in the picture, and you can add more pictures in appropriate position to summarize the interaction between diabetes and PC.</p> <p>7. "Currently the evidence is clear that diabetes has an unfavorable impact on the overall outcome of PC, particularly after surgery. Both long-standing diabetes and NOD are associated with poor prognosis." Please note the references of these points.</p> <p>8. In the last summary and conclusion section, you should add more discussion about the clinical application potential based on the above discoveries. For example, how to use the epiphenomenon of different types diabetes to generate an effective screening tool for PC. Besides, how to halt or delay the occurrence or progression of PC in a patient with diabetes also should be discussed. Please revise the contents to improve the sections.</p>	<p>5. The table fonts were capitalized.</p> <p>6. One more figure was added to describe the relationship between long standing DM and PC.</p> <p>7. The statement has been modified with reference.</p> <p>8. Summary has been expanded.</p>
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