Reviewer#1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Kalliopi Michoglou et al. uncovered an interesting topic regarding PDAC. Points to be addressed:

1) The rationale of why the authors came up with this research is scanty and is related to a lack of novelty: please highlight what this manuscript might add. - This article will review the suggested biological link between depression, anxiety and pancreatic cancer, with the aim to identify potential biomarkers, which could be implemented in a more individualized and targeted approach in pancreatic cancer treatments.

2) What is the information that is not exactly available that motivated the authors to come up with this information. What are the current caveats and how do the authors highlight the current research in answering them? If not they need to address in background and in future directions. - Future design of prospective clinical trials, which could suggest new treatment strategies, including antidepressant pharmacological agents and implementing pre-existing depression as a stratification factor. The challenge remains on whether these new treatment strategies could be translated into survival benefit in this group of patients. The current field lacks biomarker-driven targeted therapy. Furthermore, genomic stratification factors should be implemented in future clinical trials, as selected patients could be chosen based on genetic alterations in order to achieve maximal benefit from treatment and improve survival outcomes. It is also fundamental that future research follows a more holistic approach, highlighting the importance of multidisciplinary team support, and early involvement of mental health professionals.

3)State of the art figures are required: scale bar should be provided in high resolution. – Figure provided demonstrating the suggested theories about pancreatic cancer and biological association with depression.

4)The authors could provide a little more consideration of genomic directed stratifications in clinical trial design and enrolments. - The current field lacks biomarker-driven targeted therapy. Furthermore, genomic stratification factors should be implemented in future clinical trials, as selected patients could be chosen based on genetic alterations in order to achieve maximal benefit from treatment and improve survival outcomes.

5)The underlying message here is that more precision and individualized approaches need to be tested in well-designed clinical trials – a challenge, but I would be interested in their perspective of how this might be done. If beyond the scope of the manuscript, this should be highlighted as a limitation – As above.

6) The authors need to highlight what new information the review is providing to enhance the research in progress – Review of the latest literature and suggesting design of new clinical trials with implementation of depression screening tools. The link between pancreatic cancer and depression could be a biomarker itself.

7) Did the author check for gaussian dinstribution of the data? – Out of the scope of this article

7) this reviewer personally misses some insights regarding the immune landscape of PDAC: Genetic alterations, especially the K-Ras mutation, carry the heaviest burden in the progression of pancreatic precursor lesions into pancreatic ductal adenocarcinoma (PDAC). The tumor microenvironment is one of the challenges that hinder the therapeutic approaches from functioning sufficiently and leads to the immune evasion of pancreatic malignant cells. Mastering the mechanisms of these two hallmarks of PDAC can help us in dealing with the obstacles in the way of treatment. InThe direct targeting of the involved signaling molecules and the immune checkpoint molecules, along with a combination with conventional

therapies, have reached the most promising results in pancreatic cancer treatment. Please refer to PMID: 33918146 and expand the introduction/discussion sections. - Have adjusted the introduction/discussion sections based on comments above.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: In terms of the association between pancreatic cancer and depression, it does open up a new direction in the connection between pancreatic cancer and psychiatric symptoms, and more importantly extends the study of the occurrence and progression of pancreatic cancer to the nervous system. The authors examined the relationship between pancreatic cancer and psychological symptoms in patients with pancreatic cancer before diagnosis. According to the content in the manuscript, the author should provide more recent relevant literature reports. The literature listed is old and lacks the latest research results. The biological relationship between pancreatic cancer and depression mentioned in the paper is extremely important and is also the focus of research on the diagnosis of early pancreatic cancer. However, according to the content in the paper, the biological association between pancreatic cancer and depression lacks in-depth research, especially in the aspect of biomarkers. The author should introduce more recent research results and reports to support the reliable biomarkers between pancreatic cancer and depression. Pancreatic cancer has a very low 5-year survival rate of less than 10 percent. The drug therapy of pancreatic cancer after diagnosis has not been satisfactory. Therefore, combined treatment of pancreatic cancer with depression may lead to improved treatment of pancreatic cancer. Therefore, the authors should combine the latest literature reports, conduct detailed analysis and comparison, and make a new breakthrough for the drug therapy needs of pancreatic cancer. The bottom line is that the link between depression and pancreatic cancer is a biomarker, and it is key to seek biomarkers that are strongly associated with pancreatic cancer. – Manuscript adjusted including latest research results.