Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-2554A

Reviewer A:

Comment 1: In line 34, the author should provide the full name of "TCGA" and "GTEx" when the abbreviations first appearance.
Reply 1: Thank you for your advice. We supplemented the full names of "TCGA" and "GTEx" in the revised manuscript.
Changes in the text: We have modified our text as advised (See Lines 39-40).

Comment 2: An abbreviations list should be offered behind the "Key words".
Reply 2: Thank you for your valuable recommendation. We admit the necessity of adding an abbreviation list as you advised.
Changes in the text: We have modified our text as advised (See Line 61-92).

Comment 3: The authors should list the full name of "PD1" here given that it is the first time mentioning this word in the manuscript.
Reply 3: Thank you for your suggestion. The full name of PD1 has been added in the revised manuscript.
Changes in the text: We have modified our text as advised (See Line 111).

Comment 4: Also, in line 71, the authors should give a detail incidence of pancreatic cancer in the article. The author said "the incidence of pancreatic cancer has increased annually, but I think this maybe not accurate.
Reply: Thank you for your thoughtful suggestion. We thought that adding the detailed incidence of pancreatic cancer would be meaningful according to your advice. Moreover, after a team discussion, we decided to use the annual percent change (APC) to describe the annual increase in the pancreatic cancer incidence, which is a more accurate and professional index. According to some well-conducted studies, the incidence of pancreatic cancer has increased annually since 1994 and is projected to increase in the coming years(1,2).
Changes in the text: We have modified our text as advised (See Line 107-108).

Comment 5: Line 72 to 73: Pancreatic cancer is figured as a "immunotherapy-cold" tumor. The authors are expected to quote the recent publication (PMID: 32188939, published in March 2020) that reported pyroptosis-induction combined with ICIs potently suppress tumor development even in "Immunotherapy-cold" tumor.
Reply: Thank you for your constructive advice. Quoting the recent publication that you suggested is helpful to provide more interesting information for readers.
Changes in the text: We have modified our text as advised (See Line 113, citation No.

14).

Comment 6: Line 110: Please explain the implication of Log2FC.
Reply: Thank you for your thoughtful suggestion. Adding a clear definition of Log2FC is helpful for readers who are not familiar with statistics.
Changes in the text: We have modified our text as advised (See Lines 149 to 150).

Comment 7: Line 165 to 167, according to guidelines for authors, this part is not required and to some extent meaningless for presentation in main-text. Please delete this part.
Reply: Thank you for your suggestion. After a team discussion, we thought that your viewpoint is correct and deleted this part as you advised.
Changes in the text: We have deleted the part "Role of the funding source" as you suggested.

Comment 8: Line 154 to 156, I believe the R package for depicting the ROC curve was not presented, please added the information.
Reply: Thank you for your advice. Supplementing related information for the R packages is essential for readers to replicate our study.
Changes in the text: We have modified our text as advised (See Lines 196).

Comment 9: Line 210 to 211, please list the full name of these cohorts.
Reply: Thank you for your comments. Adding the full names of these cohorts is important for readers to replicate our study.
Changes in the text: We have added the full names of these cohorts according to your advice (See Lines 253 to 255).

Comment 10: Line 224 to 225, The authors only used one GEO dataset to explore the differential expression of ferroptosis regulators. Although the outcome is statistically significant, the authors should try to elaborate their retrieval strategy in case of some unexpected missing of useful dataset.
Reply: Thank you for your valuable recommendation. Elaborating a well-designed retrieval strategy for GEO datasets is of great importance as you pointed out. According to your suggestion, we re-retrieved the GEO datasets based on a combination of key words: "Pancreatic cancer" OR "PDAC". In addition, species is limited to human beings. We found that the dataset that we included is representative with a sufficient sample size. Thus, the validation by this dataset is relatively reliable.
Changes in the text: Not applicable.

Comment 11: The authors wrote in Line 201-203 that "NCOA4 and CISD1 were upregulated in pancreatic cancer but in few other cancer types, suggesting that they play roles specifically in the pathophysiology of pancreatic cancer and these few other cancers through ferroptosis regulation." Then, why not discuss some existing knowledge about NCOA4 and CISD1 in the "discussion" section?

Reply: Thank you for your thoughtful advice. Adding related information to the manuscript is helpful to improve the quality of our manuscript. The corresponding content has been added to the revised manuscript.
Changes in the text: We have modified our text as suggested (Lines 412 to 417).

Reviewer B:
Comment: The term ferroptosis was coined in 2012 to describe an iron-dependent regulated form of cell death caused by the accumulation of lipid-based reactive oxygen species; this type of cell death was found to have molecular characteristics distinct from other forms of regulated cell death. Features of ferroptosis have been observed periodically over the last several decades, but these molecular features were not recognized as evidence of a distinct form of cell death until recently. Current studied suggested that ferroptosis is a process driven by accumulated iron-dependent lipid ROS that leads to cell death, which is a distinct regulated cell death comparing to other cell death. The lethal metabolic imbalance resulted from GSH depletion or inactivation of glutathione peroxidase 4 is the executor of ferroptosis within the cancer cell. Small molecules-induced ferroptosis has a strong inhibition of tumor growth and enhances the sensitivity of chemotherapeutic drugs, especially in the condition of drug resistance. These evidences have highlighted the importance of ferroptosis in cancer therapeutics, but the roles of ferroptosis in tumorigenesis and development remain unclear.

Based on this, in this study, a lot of work has been done to discuss the role of ferroptosis regulators in the prognosis, immune activity and gemcitabine resistance of pancreatic cancer. Obviously, plenty of results and conclusions are produced through a great many works, this really is something worth celebrating. The authors collected RNA sequencing data of 31 cancers from TCGA and GTEx. Then, they performed a nomogram integrating patients' clinical information and risk score based on the expression levels of ferroptosis regulators. Finally, the correlation between the activity of immunity-associated gene sets, immune score and infiltrating immune cells and key ferroptosis regulators were further assessed. The article integrates and utilizes a large number of database resources. The manuscript is well written and very clear. Finally, I hope the authors could consider a further polishing to improve the literary beauty of the language and check the manuscript according to the submission checklist for authors point by point for publishing.

Reply: Dear reviewer, thank you for your generous compliment. We have polished the language of our revised manuscript with the help of an expert in English (Company: AJE, Number: S1FFJ582).

1. Gordon-Dseagu VL, Devesa SS, Goggins M, et al. Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data. Int J Epidemiol 2018;47:427-39.
2. Siegel RL, Miller KD. Cancer statistics, 2020. 2020;70:7-30.