Peer Review File

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Reviewer A

Comment: This work is of interest, while the authors should validate the biomarkers in well-established cancer cohort by means of IHC and calculate the correlation and survival significance. Please do not use the figures form HPA website.

Reply: Thank the reviewers for these precious comments and suggestions. We understand that IHC experiment may better reveal the difference of JAG1 between pancreatic tumor tissue and normal tissue. However, in the current research, we mainly focus on JAG1 to promote tumor tolerance to radiotherapy and chemotherapy by maintaining the dryness of tumor cells. We think that using the data in HPA may not be optimal, but it should be enough to conclude that JAG1 is more expressed in tumor tissues.

Reviewer B

Thanks very much for the comments, which are very helpful to improve the quality of this article. We have revised the manuscript and especially paid much attention to your comments and suggestions.

Comment 1: What are the biggest advantages and disadvantages of this model? What is the next research plan? It is recommended to add relevant content to the discussion.

Reply 1: Our model is accurate and reliable in predicting the prognosis of pancreatic cancer patients, which is confirmed by the retrospective data of public databases. However, our model is based on the mRNA expression level to predict the prognosis of patients, but the gene protein level may be more in line with the actual clinical situation of patients. Our next research is mainly to collect more clinical samples, use prospective real data to confirm its clinical applicability, and verify the relationship between the protein expression level of model genes and the prognosis of patients. We have explained it in the last paragraph of the discussion.

Comment 2: What is the impact of tumor microenvironment on pancreatic cancer treatment and chemo-radiotherapy resistance? Please analyze TME based on the data of this study.

Reply 2: The cancer microenvironment includes various factors such as hypoxia, immune cell infiltration, fibrosis, cytokine, oxidative stress, and acidosis. It has been shown that hypoxia-inducible factor 1α (HIF-1α) induced upregulation of retention in endoplasmic reticulum 1 (RER1) induces stemness and decreases chemosensitivity/radiosensitivity.

Changes in the text: We have modified our text as advised (see Page 4, line 8-13).

Comment 3: The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.
Reply 3: We think this is an excellent suggestion. We have indicated the clinical needs of the research focus in the background.
Changes in the text: We have modified our text as advised (see Page 2, line 9-11).

Comment 4: The discussion section is not comprehensive enough. It is suggested to increase the status and prospect of targeted drugs for pancreatic cancer.
Reply 4: Your suggestion really means a lot to us. We have added the status and prospect of targeted drugs for pancreatic cancer in the discussion section of the manuscript.
Changes in the text: We have modified our text as advised (see Page 19, line 27-33, Page 20, line 1-4).

Comment 5: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "The miR-567/RPL15/TGF-β/Smad axis inhibits the stem-like properties and chemo-resistance of gastric cancer cells, Transl Cancer Res, PMID:35117718". It is recommended to quote this article.
Reply 5: We sincerely appreciate the valuable comments. We carefully consulted the literature and added references about cancer stem cells in the introduction of the revised manuscript."During radiotherapy and chemotherapy, as long as tumor stem cells exist, they will continue to differentiate into tumor cells, even if the tumor cells are killed (PMID: 35117718)."
Changes in the text: We have modified our text as advised (see Page 5, line 12-13).

Comment 6: What are the immune genome changes caused by simultaneous radiotherapy and chemotherapy for pancreatic cancer? How to relate it to clinical results? It is recommended to add relevant content.
Reply 6: Thank you for pointing this out. After observing any changes in the immune genome caused by chemo-radiotherapy, we may be able to use specific targeted drugs to treat pancreatic cancer. However, our lack of relevant cell sequencing data makes this research beyond our capabilities.

Reviewer C

Thank you for your comments on our article. According to your suggestion, we have revised our previous manuscript, and the detailed point-by-point answers are listed below.

Comment 1: First, the title is overstated because this is only a bioinformatics analysis and an animal study and the authors mainly analyzed the prognostic role of CRRGs. The authors need to tone down the current title.

Reply: Thank you for your suggestion. We have made appropriate changes to the title.

Changes in the text: We have modified our text as advised (see Page 1, line 5-6).

Comment 2: Second, the abstract needs some revisions. The background did not indicate the knowledge gap on CRRGs in pancreatic cancer and the potential clinical significance of this research focus. The methods need to describe the clinical factors and prognosis outcomes in the database, how the independent prognostic role of CRRGs was ascertained, and the development and validation of the nomogram-based prognosis prediction model. The results need to quantify the findings by providing statistics such as P value of log-rank test and AUC values of the prediction model. The conclusion needs more detailed comments for the clinical implications of the findings.

Reply 2: It is an excellent suggestion to us. The clinical needs of the research focus have been pointed out in the background. Kaplan-Meier survival analysis and ROC (receiver operating characteristic curve) are used to evaluate the accuracy of the model. Univariate and multivariate independent prognostic analysis was used to explore whether risk score can be an independent factor to predict the overall survival of pancreatic cancer patients. Using correlation analysis to study the relationship between risk score and clinical characteristics; The performance of the prognostic risk model was comprehensively evaluated by drawing Decision Curve Analysis (DCA) and nomogram. The ROC curve shows that the prognostic risk model can accurately predict the prognosis of pancreatic cancer patients.

Due to the limitation of the number of abstract words, These contents have not been added to the manuscript.

Changes in the text: We have modified our text as advised (see Page 2, line 9-11).

Comments 3: Third, in the introduction of the main text, the authors need to review known prognostic biomarkers in pancreatic cancer, have comments on their limitations, and explain why CRRGs relative to other biomarkers deserve to be studied. The authors need to explain the differences between prognostic biomarkers and therapeutic targets because it seems that the authors used the two terms interchangeably.

Reply 3: We sincerely appreciate the valuable comments. We have added the prognostic biomarkers in the introduction section of the manuscript. Prognostic biomarkers refer to biomarkers used to determine the possibility of clinical events, disease recurrence or progression in patients with related diseases or medical conditions. The therapeutic target is the malignant phenotypic molecule pointing to tumor cells, which can act on specific cell receptors and signal transduction channels that promote tumor growth and survival, angiogenesis and cell cycle regulation, thus achieving the anti-tumor effect of inhibiting tumor cell growth or

promoting apoptosis. Thank you very much for your suggestion. We have revised it in the manuscript.

Changes in the text: We have modified our text as advised (see Page 4, line 13-19， Page 3, line 5, Page3, line 27).

Comments 4: Fourth, in the methodology of the main text, please have an overview of the research procedures of this study, as well as their corresponding questions to be answered. The authors need to describe the clinical and prognosis outcomes in the databases. The authors need to explain why they developed the nomogram to predict the prognosis by using clinical predictors and CRRGs-based risk scores. The authors only need to examine the prognostic role of CRRGs. In statistics, please ensure P<0.05 is two-sided.

Reply 4: Your suggestion really means a lot to us. We have added the research procedures in the methods section of the manuscript. In this part, we explain why these studies are needed.

Changes in the text: We have modified our text as advised (see Page 11, line 12-30).

Reviewer D

Comment 1：Figure 1

a) Please explain GEM in the legend.

b) As there are no symbols "*, **, #, ##" in the figure, please delete the explanations in the legend.

Reply 1： We have explained the meaning of GEM in the footnote in Figure 1, and deleted the redundant symbols.

Changes in the text: We have modified our text as advised (see Page 30, line 5-6).

Comment 2: Figures

Please explain ALL abbreviations of the figure/legend in the legend. Such as CRRGs, TCGA, OS, GEO etc.

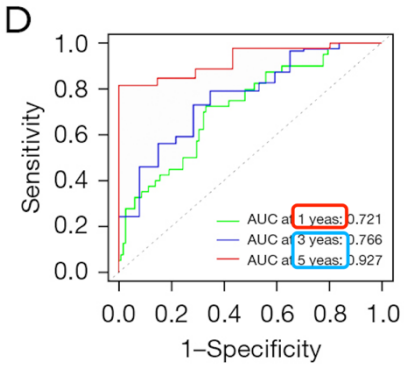
Reply 2: We have explained all the abbreviations of the figures/legends in the legend.

Changes in the text: We have modified our text as advised (see Page 30, line 6, 23-25, Page 31, line 3-5, 13-14, 20-21, Page 32, line 5-8, 20-24).

Comment 3：Figure 3

a) Please revise "1 yeas" to "1 year".

b) Please revise "3/5 yeas" to "3/5 year"



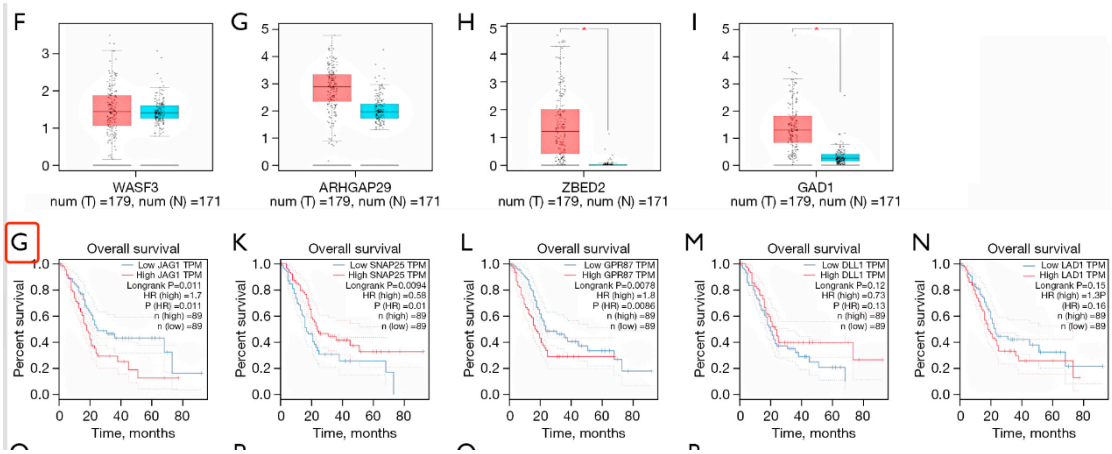
c) Please explain "*, ***" in the legend.

Reply 3: In figure 3D, we have changed "years" to "year". We also explain "*, * *" in Legend 3.

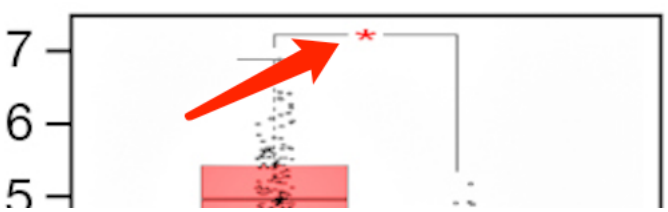
Changes in the text: We have modified our text as advised (see Page 31, line 2-3).

Comment 4: Figure 4

a) Please check if here should be J.



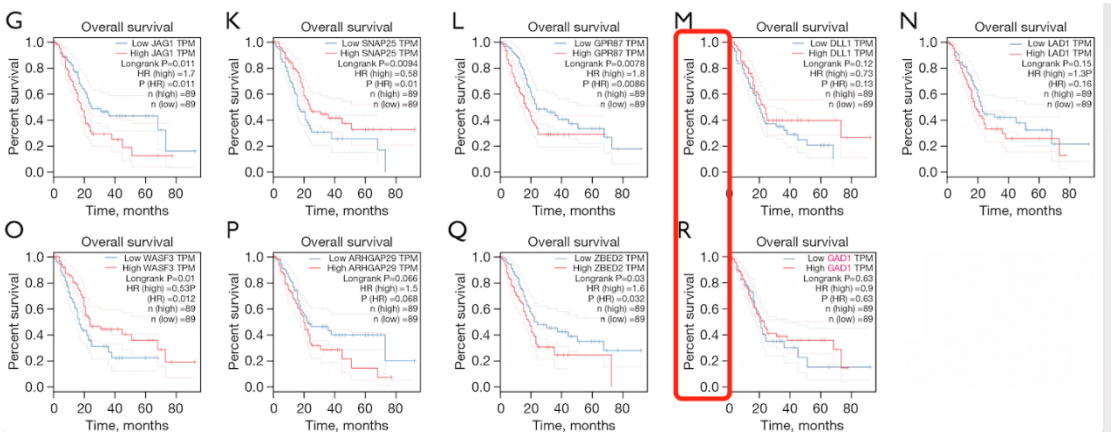
b) Please explain "*" in the legend.



c) As there are no symbols "**, ***," in the figure, please delete the explanations in the legend.

d) The correct format for the y-axis should be one of the following, please revise.

- If the description is "Percent survival", the numbers should be 0-100.
- If the description is "Survival", the numbers should be 0-1.0.



Reply 4:

a) We have changed it to J in Figure 4.

b) We have explained "*" in the legend.

c) We have deleted the symbols "**, ***," from the legend.

d) We have changed the format of the y axis to "survival" in Figure 4.

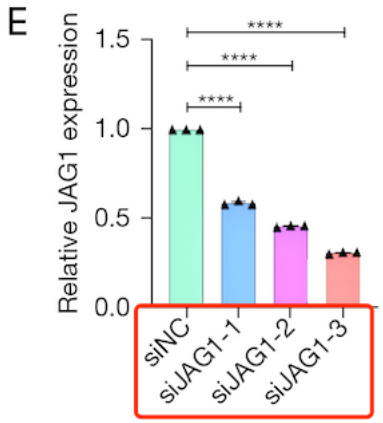
Changes in the text: We have modified our text as advised (see Page 31, line 13).

Comment 5: Figure 6

a) As there is no symbol "*" in the figure, please delete the explanation in the legend.

b) It seems that the legend is different with the figure, please check.

27 *JAG1*. (E) The expression levels of *CD24*, *CD44*, and *EPCAM* in PANC-1 cells
28 transfected with *JAG1*-targeting siRNA (si*JAG1*) were assessed with qRT-PCR
29 experiments. (F) The protein expression level of *JAG1* in pancreatic cancer and normal



Reply 5:

a) We have deleted the symbols "*" from the legend.

b) We have checked the legend and the figure, and completed the revision at the same time.

Changes in the text: We have modified our text as advised (see Page 31, line 28-33, Page 32, line 1, 4).

Comment 6: Figure 7

As there is no symbol "*" in the figure, please delete the explanation in the legend.

Reply 6: We have deleted the symbols "*" from the legend.

Changes in the text: We have modified our text as advised (see Page 32, line 19).

Comment 7: Table 1

Please explain GEO and TCGA in the table foonote.

Reply 7: We have explained GEO and TCGA in the footnotes of the table, and we will send you Table 1 as one of the attachments.

Comment 8: References/Citations

a) Please double-check if more studies should be cited as you mentioned "studies". OR use "study" rather than "studies".

that *DLL1* induces tumor vessel normalization (47). Some studies have also revealed that *DLL1* passes nuclear factor kappa-B (NF-κB) pathway increases the resistance to DNA damage and cell death, and plays a key role in promoting the progression, metastasis, and chemoresistance of invasive breast intraluminal tumors (48).

autism (62). Studies have shown that *GAD1* expression is associated with pleural invasion, vascular invasion, and advanced stages of non-small cell lung cancer (NSCLC) (63).

b) All the cited articles should be cited numerically (in round brackets) and consecutively in the order of appearance, NOT indicate the PMID. Please revise all the ci rations in the main text, if the studies are not included in the reference list, please also update the current version.

(PMID: 30630537). Commonly used tumor markers related to the diagnosis of increased in other digestive system tumors, and were not specific (PMID:28315907) (PMID:28197876). Therefore, there is an urgent need to explore new prognostic

continue to differentiate into tumor cells, even if the tumor cells are killed (PMID: 35117718). Therefore, understanding the genes that influence resistance to therapy may

inhibitors.(PMID: 25366685) There are new drugs, such as NTRK inhibitor for NTRK

people to find new treatment schemes in different subgroups of PC patients through genetic testing. (PMID:34358103)

Reply 8:

a) We have changed the "studies" in these two places to "study".

Changes in the text: We have modified our text as advised (see Page 17, line 9, Page 18, line 8).

b) We have revised the contents of the article, updated the references and cited these articles in numerical order.

Changes in the text: We have modified our text as advised (see Page 22-29).