Peer Review File

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Reply to Reviewer

#Comment 1: 1. Title;
Because there are no experiments demonstrating the possible targets for cancer therapy, "provide new therapeutic targets" is not suitable for the contents of the manuscript.
Reply 1: We sincerely appreciate this valuable comment. We have changed the title of the paper to: Anoikis-related gene signatures predicts prognosis of lung adenocarcinoma patients and reveals immune infiltration. (see Page 1, line 2-3)
Change in the text: Anoikis-related gene signatures predicts prognosis of lung adenocarcinoma patients and reveals immune infiltration.

#Comment 2. Page 3, line 75;
"UAMP" should be "UMAP".
Reply 2: We are really sorry for our careless mistake, thank you for your reminder. We have modified our text as advised. The "UAMP" has been corrected on "UMAP". (see Page 3, line 76)

Change in the text: Then, we verified the reliability of the clustering by unified modal approximation and projection (UMAP) using the "ggplot2" R package.

#Comment 3: In the text;
There are no indication of "Figure 1C" in the text.
Reply 3: Thanks for your kind reminder. We have added this in the text. (see Page5, line 137)
Change in the text: Additionally, the network diagram revealed the relationships among the first 32 genes in terms of gene expression levels (Figure 1C).

#Comment 4: Page 5, line 146-7;
The authors described "As shown 147 in Figure 2E, S100A7 may be a good prognostic factor", however, it is difficult to realize the result from Figure 2E. An explanation should be necessary.
Reply 4: We think this is an excellent suggestion. We have re-written this sentence according to the Reviewers' suggestion. (see Page 5, line 149-151)
Change in the text: The result plots of UMAP and tSNE showed that at k = 2, the two clustering subtypes were clearly distinguished (Figure 2C, D). The heat map depicted in Figure 2E illustrates a low expression of S100A7 in the majority of the two subtypes,

suggesting that S100A7 may be a good prognostic factor.

#Comment 5: Page 5, line 155-6;
The authors described "significantly lower proportion of activated CD4 and CD8 T cells in population B than in population A", however activated CD8 cells looks similar in population B and population A.
Reply 5: Thanks for your kind reminder. We have modified our text as advised. (see Page 5, line 160-161)
Change in the text: Moreover, single sample gene set enrichment analysis (ssGSEA) results showed a significantly lower proportion of activated CD4 and regulatory T cells in population B than in population A (Figure 3B);

#Comment 6: Page 5, line 158--- and Figure 4A, B;
Here the authors selected 6 ARGs using the Lasso-penalized Cox method (Figure 4A, B). This should be the most important point in the manuscript, however, there are no explanation how they chose the 6 from 64 ARGs. There are also no indications in the Figure 4A, B. The authors should explain how they chose the 6 ARGs in detail and should indicate which is the 6 ARGs in Figure 4A, B.
Reply 6: Thank you for pointing this out. In Figure 4A the vertical coordinates demonstrate the coefficients of 64 genes, while in Figure 4B, the dotted line on the left side represents λ min, indicating the optimal model fit at that λ value. We have modified our text as advised. (see Page 5, line 163-167)
Change in the text: In the univariate Cox regression analysis, we identified seven ARGs associated with the OS rate using the least absolute shrinkage and selection operator (LASSO) analysis (Figure 4A, B). In the ensuing multivariate Cox regression analysis, six ARGs were independently selected as predictors for the prognosis of LUAD, establishing the risk model.

#Comment 7: Page 5, line 160;
The "risk scores" here in the sentence "the final risk scores for the 6 ARGs characteristics are listed" seems to be different from the other "risk scores" in the text; for example, in the sentence "the risk scores are clearly different in the two subtypes" (Page 6, line 1). This is confusing.
Reply 7: We thank the reviewer for bringing this to our attention. We have modified our text. (see Page5, line 167-168)
Change in the text: In Supplementary Table S2, the correlation coefficients based on the six ARGs characteristic are listed.

#Comment 8: Page 5, line 160;
"prognostic index (PI)" seems to be the same as "risk scores". This is also confusing.
Reply 8: We sincerely thank the reviewer for careful reading. We have corrected the "prognostic

index (PI)" into "Riskscore" (see Page 5, line 168-169)

Change in the text: The risk score is calculated as follows: Riskscore = (0.300* level of PDGFB expression) + (0.160* level of HMOX1 expression) + (0.521* level of GDF2 expression) + (0.582* level of LDHA expression + (0.068* level of S100A7 expression) + (0.232* level of CDX2 expression).

#Comment 9: Page 6, line 188;

The authors should explanation the "immune scores", "stromal scores", and "estimate scores (Figure 5F)".

Reply 9: Thanks for your suggestion. We have modified our text as advised. (see Page 6, line 196-200)

Change in the text: Moreover, in examining the stromal cell component of the tumor microenvironment, assessing immune cell infiltration levels, and estimating tumor purity, we computed immune scores, stromal scores, and estimation scores for the high-risk and low-risk groups based on the estimation of expression profiling scores (Figure 5F).

#Comment 10: Page 6, line193-196, and Figure 6A;

The explanation should be described about the nomogram model in Figure 6A. It is difficult to be understood.

Reply 10: Thank you for pointing this out. We have modified our text as advised. (see Page 6, line 205-210)

Change in the text: The nomogram construction relies on regression coefficients' magnitudes for all predictors, establishing a scale that assigns scores based on each predictor's value. In instances with multiple predictors, a cumulative score is calculated, facilitating the subsequent computation of the probability of correlation with the occurrence of a clinical outcome for each patient, determined by their total score.

#Comment 11: Page 7, line 220-221;

The authors described "the novel prognostic model we developed with 6 ARGs can improve the early diagnosis of LUAD", however the model they developed is for prognosis prediction, so that the model does not lead to the improvement of the early diagnosis of LUAD.

Reply 11: Thanks for your kind reminder. We have modified our text as advised. (see Page 7, line 237)

Change in the text: However, although the novel prognostic model we developed with six ARGs had good predictive performance, the number of markers used is insufficient.

#Comment 12: Figure 3A and B;

What does the asterisks at the top of the figures mean?

Reply 12: Thank you for pointing this out. Asterisks are assigned based on the p-value, following a standard convention: one asterisk indicates a significance level of less than 0.05, two asterisks for less than 0.01, and three asterisks for less than 0.001. This labeling system

provides a clear indication of the statistical significance associated with each result.

Change in the text: -