

Peer Review File

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Reviewer A

This is an interesting paper where the authors explore the role of mitochondrial metabolism related genes in the progression and prognosis of laryngeal squamous cell carcinoma patients with the idea to improve patient management and clinical outcomes. They constructed a prognostic model integrating MMRGs and evaluated its prognostic performance. The study design is adequate to address the scientific question. The figures are adequate.

The authors indicate that mitochondria contribute to cancer progression by modulating mitochondrial dynamics and metabolism reprogramming. Effectively, recent studies have shown that OXPHOS can be also upregulated in certain cancers.

However, molecules such as melatonin that increase OXPHOS have been shown to induce apoptosis in head and neck cancer cells (Floride et al, J Pineal Res. 2022 Oct;73(3):e12824. doi: 10.1111/jpi.12824). The authors should discuss this aspect.

Reply: We appreciate the reviewer's insightful comment regarding the pro-apoptotic potential of molecules that upregulate OXPHOS, such as melatonin, in head and neck cancers. This is indeed a critical point for understanding the complex role of mitochondrial metabolism in LSCC progression and therapeutic strategies. We have adapted the discussion to the reviewers' comments and introduced the references mentioned in the manuscript (lines 251-253).

Reviewer B

Figures

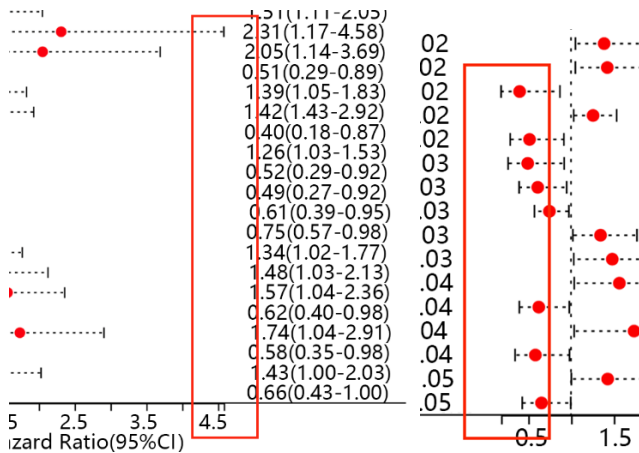
- Figure 1E: The highlighted content in the main text is **inconsistent** with that in the figure. Please check if it's necessary to revise.

Cellular compounds were mainly correlated with mitochondrion, cytosol, endomembrane system, **organelle membrane**, and vesicle (**Figure 1E**). Additionally, KEGG pathways of the 308 genes were

- mitochondrion
- cytosol
- endomembrane system
- vesicle
- extracellular region

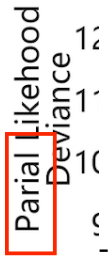
Reply: Thank you for pointing this out. We have carefully reviewed Figure 1E and the corresponding text (line 176). The highlighted content in the main text has been corrected to align with the figure.

- Figure 2A, 2C: Please **extend the x-axis**. Or the part that exceeds the horizontal coordinates should be indicated by arrows.



Reply: The x-axis of Figures 2A and 2C has been extended.

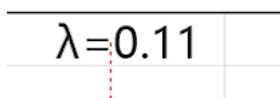
- Figure 2B, 2C: Please check if it should be **Partial Likelihood**.



Reply: After reviewing the figure legends, we have confirmed that the correct term is "Partial Likelihood," which has been updated accordingly in Figure 2B.

- Figure 2B: The following data is **inconsistent** with the main text. Please check and revise.

(**Figure 2A**). Next, using the LASSO regression analysis, 13 MMRGs were screened out, with a λ value of 0.12. The correlation coefficient change curve and cross-validation curve are presented in



Reply: We have verified and corrected the data in the main text, and the λ value should be 0.11 (line 184).

- Figure 2A: the circled hazard ratio 1.42 seems not within the 95% CI range (1.43-2.92), please verify the accuracy.

ACOT9	0.02		2.05(1.14-3.69)
NT5C	0.02		0.51(0.29-0.89)
B4GALNT1	0.02		1.39(1.05-1.83)
ARG2	0.02		1.42(1.43-2.92)
ACAA1	0.02		0.40(0.18-0.87)

Reply: We have verified the hazard ratio and 95% confidence interval (CI) in Figure 2A, it should be 1.42(1.05-1.93), we have now corrected it.

- Figure 3A, 4B: Please add a **unit** to the overall survival time.

Reply: Units for overall survival time have been added to both Figure 3A and Figure 4B.

- Figure 3A, 4B: Please indicate what L and H stand for.

Reply: The "L" means "Low", and the "H" means "High". We have revised the "L" and "H" into "Low" and "High" respectively in Figure 3A and Figure 4B.

- Figure 3B: Please revise the following to **1-Specificity**.

0.4
0.0
1-Specificities

Reply: The label in Figure 3B has been revised to "1-Specificity" as requested.

- Figure 7: Please indicate the meaning of ., -, *, **, *** and **** in the legends.

Reply: The meanings of all symbols (., -, *, **, ***, and ****) have been clarified in the figure legend.

- Please provide the full name of GDSC and FDR in Figure 9 legends.

Reply: The full names of GDSC (Genomics of Drug Sensitivity in Cancer) and FDR (False Discovery Rate) have been added to the figure legends.