

Peer Review File

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Reviewer A

This manuscript combines two important research aspects: (1) using radiomics to predict ALOX5 expression in NSCLC patients and (2) exploring ALOX5 as a prognostic biomarker for overall survival (OS). Both contributions are valuable, but their integration requires refinement to present a cohesive narrative and maximize scientific impact. Below are detailed comments addressing areas for improvement.

1. Clarity of Focus and Central Message:

- The manuscript lacks clarity on whether its primary aim is to establish ALOX5 as a significant prognostic biomarker or to demonstrate the feasibility of predicting ALOX5 expression non-invasively using radiomics. This dual focus creates ambiguity and weakens the narrative.
- Strengthening the primary objective and aligning the secondary findings to support it is essential. For example, if the study's focus is on radiomics, highlight its novelty and clinical implications. If ALOX5 is the main topic, provide a stronger argument for its prognostic relevance and practical utility.

Reply 1: We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. Our study's focus is on radiomics, according to your nice suggestions, we have made some corrections to our previous draft, the detailed corrections are listed below.

Changes in the text: In the first paragraph of the discussion section, we focused on the significance of radiomics. See Page 12, line 252-254, appear in red font in the text : "This study innovatively proposes to use CT radiomics technology to non-destructively predict the mRNA expression of ALOX5 in non-small cell lung cancer tissues, which has certain guiding significance for the judgment of prognosis and the selection of diagnosis and treatment methods."

2. Logical Connection Between Themes:

- The linkage between the radiomics model and ALOX5's prognostic value is not sufficiently developed. For instance, if ALOX5's prognostic power is modest (e.g., HR=0.453, P=0.04), the importance of predicting it becomes less compelling.
- Strengthen the connection by discussing how radiomics-based prediction can translate into actionable clinical outcomes. For instance, explain how this approach could guide therapeutic decisions, enable early risk stratification, or serve as a surrogate for invasive

tissue sampling.

Reply 2: We sincerely thank the editor and all reviewers for their valuable feedback that we have used to improve the quality of our manuscript. Our changes to the manuscript are given as follows.

Changes in the text: We highlighted the following in the discussion section. See Page 13, line 262-266, appear in red font in the text : “In the actual clinical diagnosis and treatment process, we usually use invasive tissue sampling, so in recent years, the research focus of prognostic markers has mostly incorporated the characteristics of "non-invasive". The greatest advantage of radiomics prediction model is that it is non-invasive. The use of radiomics model to predict mRNA expression and prognosis of patients can bring inspiration for clinical application.”

3. ALOX5 as a Prognostic Biomarker:

- The evidence for ALOX5’s role as an independent prognostic factor is statistically modest and under-discussed in the manuscript. Given the borderline significance and limited effect size, the practical utility of ALOX5 in guiding clinical management remains unclear.

- More robust data or additional discussion on how ALOX5 can influence treatment decisions (e.g., chemotherapy or immunotherapy) would strengthen its clinical relevance.

Reply 3: Thank you very much for the advice of the reviewers. In the current study, our cases were not followed by chemotherapy or immunotherapy. However, your suggestion gives us a very good inspiration, and we will include these patients in the follow-up study to study the guiding significance of radiomics model for patients with chemotherapy and immunotherapy.

Changes in the text: At the end of the article, see Page 14, line 307-310, appear in red font in the text : “Chemotherapy and immunotherapy are also important treatments for lung cancer. In the next part of our study, we will further analyze the significance of radiomics model in guiding the decision-making of chemotherapy and immunotherapy for lung cancer patients.”

4. Utility of the Radiomics Model:

-The radiomics model demonstrates good predictive performance (e.g., AUC=0.78 for logistic regression), but its clinical impact is not well articulated. Without a strong justification for the significance of ALOX5 prediction, the value of the radiomics approach may appear limited.

- Clarify why a radiomics-based approach to predict ALOX5 is meaningful, particularly compared to traditional methods. Emphasizing the model’s potential to reduce invasive procedures or streamline workflows could make the findings more impactful.

Reply 4: We sincerely appreciate the time and effort invested by the reviewers in evaluating our manuscript. We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

Changes in the text: See Page 14, line 301-303, appear in red font in the text. In the discussion section, we have added the clinical potential of radiomics in the discussion section: “Compared with traditional methods, our model reduces invasive procedures and simplifies the actual clinical workflow. For patients, non-invasive examinations are more easily accepted, and image data acquisition is more convenient.”

5. Choice of Machine Learning Models:

- The manuscript employs logistic regression (LR) and support vector machine (SVM) models for predicting ALOX5 expression. While these are well-established methods, they may not reflect the state-of-the-art approaches currently available in radiomics and machine learning.

- Recent advancements in deep learning, such as convolutional neural networks (CNNs) or transformer-based architectures, have shown significant improvements in processing and analyzing medical imaging data. These models could potentially capture more complex patterns in radiomics features and improve predictive performance.

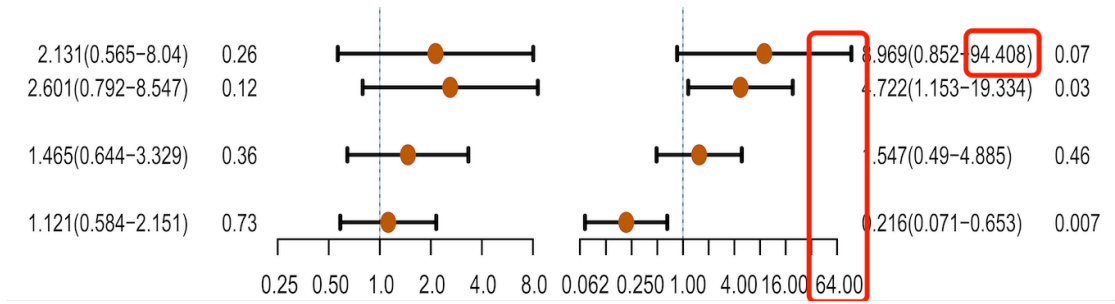
Reply 5: Many thanks to the reviewers for their professional suggestions. The two deep learning methods proposed by the reviewers do have good potential in research. There are many deep learning models. At present, our research uses LR and SVM methods, which are highly used, and the models have good performance. The two models proposed by the reviewers give us a valuable idea, which we may continue to study in the following studies using both methods.

Changes in the text: At the end of the article, see Page 14, line 310-313, appear in red font in the text, we added: “There are many deep learning models, recent advancements in deep learning, such as convolutional neural networks (CNNs) or transformer-based architectures, have shown significant improvements in processing and analyzing medical imaging data. Comparing different deep learning models and finally selecting the best model is also our next research direction.”

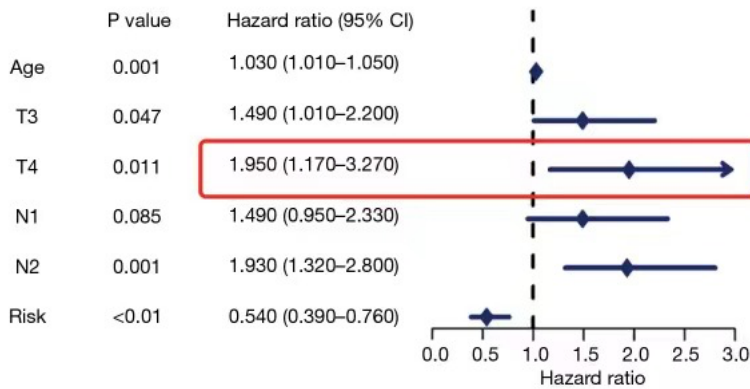
Reviewer B

1. Figure 2

To standardize the results, the part that exceeds the horizontal coordinates should be indicated by arrows.



Please see the example below:



Reply 1: Thank you very much for pointing out our problem. In our actual analysis, in order to better visualize all the characteristics of the data and avoid the influence of individual extreme values on the visualization, log₂ was taken for HR in the process of drawing. However, some values still exceed the horizontal coordinates after log₂ processing. In the original forest diagram of the article, we did not clearly mark the X-axis, which caused the misunderstanding of the reviewer. We are very sorry, and we have modified Figure 2、Figure S1 and Figure S2.

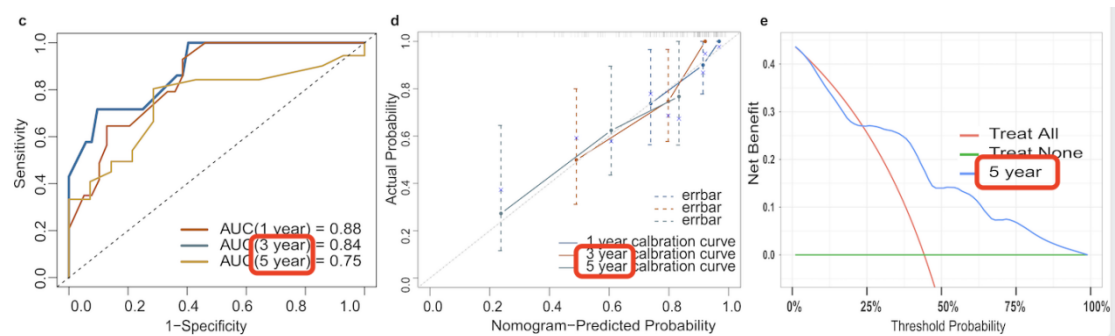
2. Figure 5

Please send the latest version of figure 5, the current version was damaged.

Reply 2: Figure 5, Figure 2, Figure S1, Figure S2 have been sent separately in the attachment.

3. Figure 6

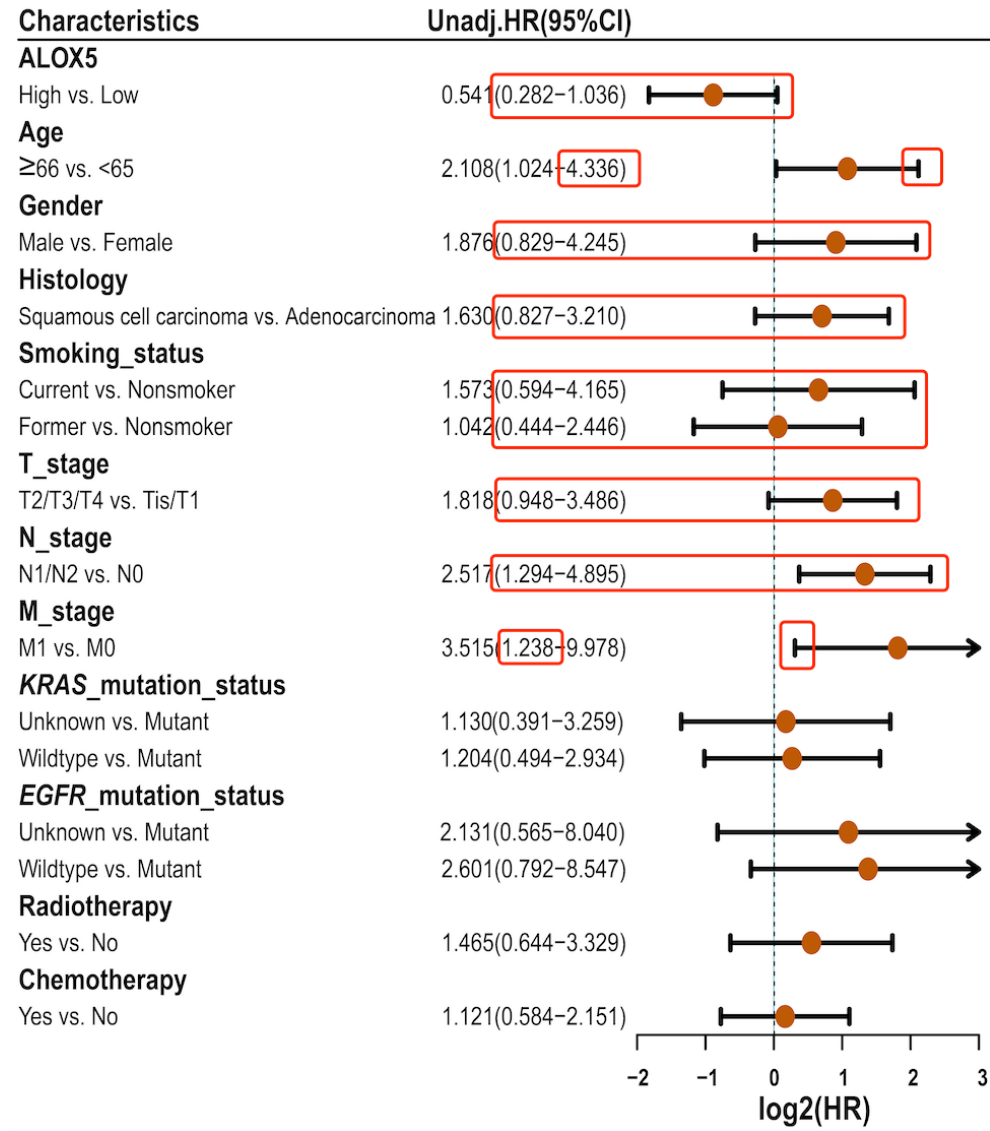
Please revise “3 year/5 year” to “3 years/5 years”.



Reply 3: Thanks for your meticulous work. We have advised Figure 6 and sent separately in the attachment.

4. Figure 2

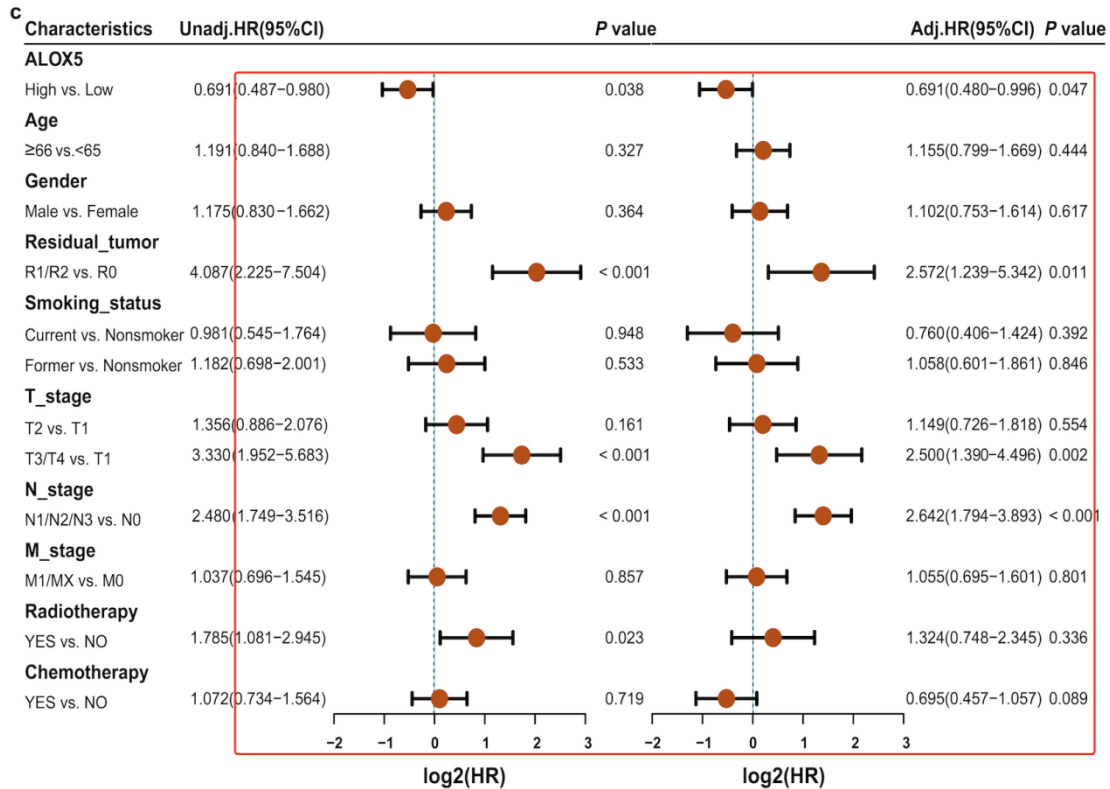
We point out some data below, which is not matched with the x-axis, please check the whole figure again.



Reply 4: Thanks for pointing out and providing feedback on the details of the figures. We have rechecked the figures and adjusted the matching of the coordinate axes and data points. It should be particularly noted that the x-axis values in the figures are $\log_2(\text{HR})$, and the corresponding HR values have been clearly listed in the table. To express clearly and reduce misunderstandings, we have improved the scale of the X-axis.

5. Figure S1

The data below is not matched with the x-axis, please check the whole figure again.



Reply 5: Thank you. Similar to the above issue, we have also improved the X-axis scale of Figure S1 and S2. The revised Figure 2, Figure S1, Figure S2 will be sent to the editor's email in the form of attachment.

6. Tables

a) ALL abbreviations used in each table or table description should be defined in a footnote below the corresponding table. Please check and revise.

b) Please provide the header of the first column.

Table S2 · Regression coefficient of feature in LR model

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.160642518	0.334625359	-0.480066777	0.631179911
original_shape_Flatness	-1.076946783	0.410015712	-2.626598815	0.008624295
original_glszm_SizeZoneNonUniformity	-1.915813063	0.74581873	-2.568738201	0.010206954
original_firstorder_Minimum	-0.894156152	0.781893626	-1.143577748	0.252798794
original_gldm_LargeDependenceH	1.328802785	0.660241068	2.012602443	0.04415647

Reply 6: We have revised the tables based on comments.

7. References/Citations

Please check if the author's name matches with the citation.

tumors; Melstrom LG et al. (7) found that inhibiting 5-LOX in an in vivo colon cancer xenograft model suppressed tumor growth. A study by Jianjun et al. (8) indicated that the overexpression of ALOX5 activates gastric cancer cells. Zhou et al. (9) reported that ALOX5 mediates the growth and migration of breast cancer cells. Currently, the

al. (17) indicated that ALOX5 is a differentially expressed gene related to ferroptosis in patients with LUSC, and it is closely related to its prognosis. According to Zhao QQ et al. (18), normal lung tissue expresses ALOX5 at higher levels than NSCLC tissues and impacts the prognosis of patients with NSCLC, consistent with our findings.

Reply 7: We have checked all references and citations. Thank you.