The paper titled "APOBEC mutational signature predicts prognosis and immunotherapy response in nonsmoking patients with lung adenocarcinoma" is interesting. The results established a comprehensive view of APOBEC3 mutations in nonsmoking LUAD patients. Our review provides new insights into using the APOBEC3 mutation to predict prognosis and improve the immunotherapy response for future applications. However, there are several minor issues that if addressed would significantly improve the manuscript.

**Comment1**: This study emphasizes the relationship between APOBEC3 mutation characteristics and smoking or non-smoking lung adenocarcinoma patients. Is there a correlation between APOBEC3 mutation characteristics and cancer risk in different regions? What is the relationship between? Please explain in the discussion.

Replay1: Thank you for your suggestions. As described in our discussion: The APOBEC3 family of enzymes has been considered a major endogenous source of somatic mutations found in more than 75% of cancer types and approximately 50% of all cancer genomes, which means that APOBEC mutagenesis pattern is widespread in human cancers and makes equal contribution in cancers with different tissue origins, different ethnicity, or different regions (more detail in our cited references 31-35).

In addition, Chen YJ, et al. performed a proteogenomic study in east Asia cohort and derived a similar conclusion to ours.

Reference: Chen YJ, et al. Proteogenomics of Non-smoking Lung Cancer in East Asia Delineates Molecular Signatures of Pathogenesis and Progression. Cell. 2020 Jul 9;182(1):226-244.e17.

**Comment2**: All figures are not clear enough. It is recommended to provide clearer figures again.

Replay1: Thank you for your suggestions. In accordance with the requirements of Editorial Office of Translational Lung Cancer Research, we provided the low-resolution version of preview images in manuscript for review. Meanwhile, we submitted the high-resolution version of original image (PNG/JPEG/TIF format) to Submission website.

**Comment3**: In the introduction of the manuscript, the author needs to increase the core role of APOBEC3 in tumor genesis and development.

Replay1: Thank you for your suggestions. we have added the core role of APOBEC3 in tumor

genesis and development in introduction.

**Comment4**: In the discussion section, the authors need to extensively review the tumor immune microenvironment of LUAD and how to reduce the probability of recurrence after surgery.

Replay1: Thank you for your suggestions. Given the highlights described in our manuscript, we should need to extensively elaborate on the tumor immune microenvironment of LUAD and how to reduce the probability of recurrence after surgery. We added and reinforced the discussion of the relevance of the t tumor immune microenvironment of LUAD and immunotherapy.

**Comment5**: The abstract is not adequate and needs further revisions. The background did not indicate the clinical needs for this research focus.

Replay1: Thank you for your suggestions. Following your suggestions, we have adapted and rewritten the abstract, especially the background.

**Comment6**: Please consider to cite the below related paper: APOBEC3B deletion polymorphism and lung cancer risk in the southern Chinese population. Ann Transl Med. 2021 Apr;9(8):656. doi: 10.21037/atm-21-989.

Replay6: Thank you for providing the article by Ben X et al. we have carefully studied the article which demonstrated the complementary interactions with A3B deletion polymorphism, smoking and gender would increase susceptibility to NSCLC, and provide us with valuable information. we cited the article as reference 14.

**Comment7**: What are the possible associations of genomic profiles of LUAD with tumor mutation burden, PD-L1, and the immune cell infiltration landscape? It is suggested to add relevant contents in the discussion.

Replay1: Thank you for your suggestions. In our discussion, we have demonstrated in the possible associations of genomic profiles of LUAD with tumor mutation burden, PD-1(not PD-L1), and the immune cell infiltration landscape in three paragraphs.

Part1demonstrated that the APOBEC score was more significantly correlated with APOBEC mutation signature than each individual APOBEC expression, and the average mutation number of high-APOBEC3 score patients is significantly higher than low-APOBEC3 score patients; Part1demonstrated that the vast majority of somatic mutations or TMB in the nonsmoking samples could be categorized as APOBEC-associated mutations; Part3 demonstrated that Tumor mutational burden (TMB) generate mutant tumor peptides (immune-reactive neoantigens), which could be recognized by cytotoxic T cells in the TME, CD4 memory T cells and CD8 T cells accumulated in the TME, anti-PD-1 agents pembrolizumab and cemiplimab will reactivate the cytotoxic T cells immune response against tumor cells. APOBEC3 score

could serve as a promising biomarker for ICB during nonsmoking LUAD therapy.

1. You've mentioned "stud<span style="color:red">ies</span>", while only one reference was cited in this sentence. Please check.

> Recent studies have also demonstrated that overexpression of APOBEC3B can induce heteroclitic neoepitopes, which promotes sensitivity to ICB in a mouse model of melanoma, and APOBEC activity promotes T cell infiltration in HER2-driven mouse mammary tumors (40). In order to investigate the relationship between APOBEC-

Reply: checked, we have changed.


2. Please check if there're any references missing here since you've mentioned "Recent studies".

> endogenous mutations in human cancers. Recent studies have shown that the APOBEC3 family was a major cause of APOBEC mutation, and a combination of mutations (including TCA to TTA or TGA, TCT to TTT or TGT) in the TCW pattern can indicate the status of APOBEC mutations. Therefore, we calculated TCW counts

Reply: checked, we have changed.


3. Figure 1
a. Please supplement the descriptions of X-axis for Figure 1A, 1C-1D.
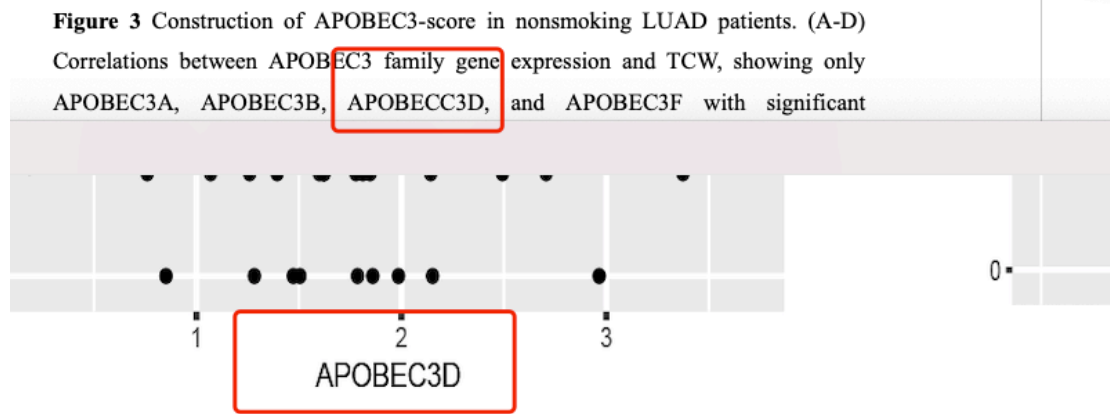b. Please also check if the X scale is missing in Figure 1B.
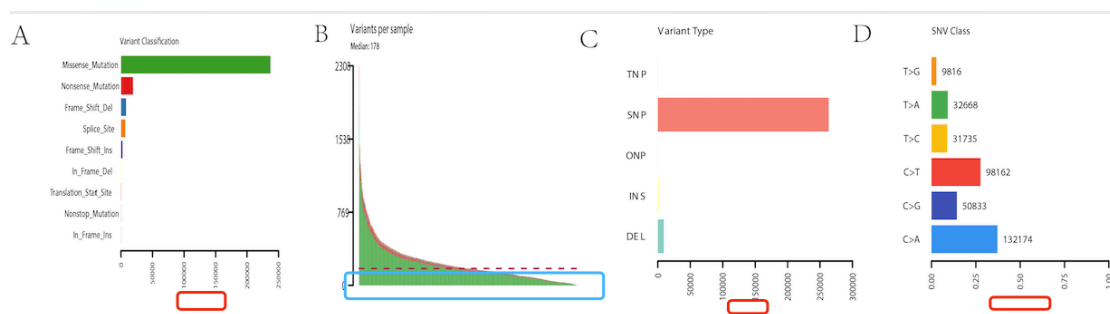


Reply: checked, we have changed. X axis in Figure 1B indicates each sample, and there is no scale, just like figue 1E and figue 1G.


4. Please define "**, ****, ns" in Figure 2 legends.
Reply: checked, we have changed.


5. Figure 3:

a. Please check both the figure and the legends, they do not match.

Figure 3 Construction of APOBEC3-score in nonsmoking LUAD patients. (A-D) Correlations between APOBEC3 family gene expression and TCW, showing only APOBEC3A, APOBEC3B, APOBECC3D, and APOBEC3F with significant
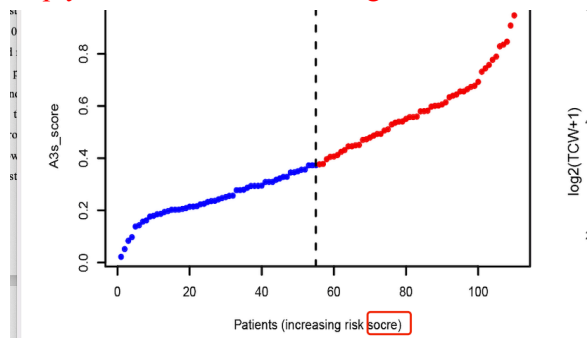
Reply: checked, we have changed.

b. Legends of Figure 3K are missing, please check.
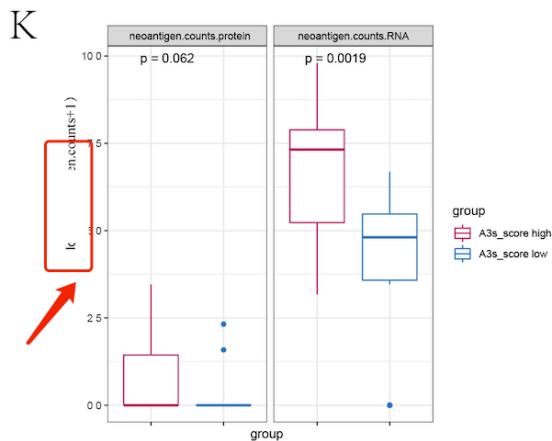
Reply: checked, we have changed.

c. Please check and revise the typo.

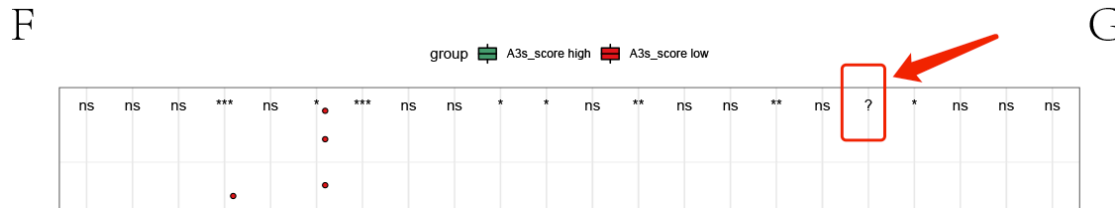Reply: checked, we have changed.

d. Figure 3K: Information missing, please check.

Reply: checked, we have changed.

6. Figure 4

a. Please check the question mark.



Reply: checked, we have changed.

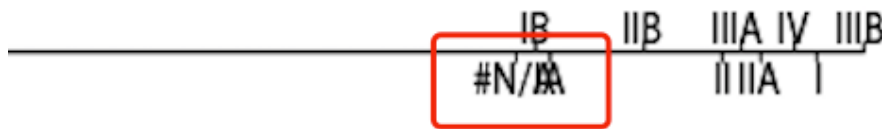b. Please define "*, **, ***, ns" in figure legends.

Reply: checked, we have changed.

7. Figure 5:

a. Legends of Figure 5I are missing, please check.

Reply: checked, we have changed.

b. The words got covered, please check.



Reply: checked, we have changed.

c. Please define "*, **" in figure legends.

Reply: checked, we have changed.

8. Please define all abbreviations in Figure S2 legends.

Reply: checked, we have changed.

9. Figure S3: Please check the typo.

<span style="color:red">Reply: checked, we have changed.</span>

10. Figure 2I was not cited in your paper, please cite it consecutively in text.

<span style="color:red">Reply: checked, we have changed.</span>