In this study titled "Identification of a Prognostic DNA Repair Gene Signature in Esophageal Cancer," the authors tried to identify novel DNA repair-related genes and their prognostic implications in esophageal cancer. Overall, the study lacks novelty and there are major defects preventing the study in current form from reaching the main conclusion claimed by the authors.

Comment 1: The study is not novel. The overall design, methods, and even some the exact same results, have already been reported in the following study:

Wang L, Li X, Zhao L, Jiang L, Song X, Qi A, Chen T, Ju M, Hu B, Wei M, He M, Zhao L. Identification of DNA-Repair-Related Five-Gene Signature to Predict Prognosis in Patients with Esophageal Cancer. Pathol Oncol Res. 2021 Mar 30;27:596899. doi: 10.3389/pore.2021.596899. PMID: 34257547; PMCID: PMC8262199.

The authors need to search the existing literature extensively before implementing any new projects to avoid repetition of already published studies, without providing any meaningful new information.

Reply 1: We would like to express our sincere gratitude for reviewing our manuscript and providing valuable feedback. You have raised a valid concern regarding novelty. Upon reviewing the reference study, I acknowledge significant similarities in the general framework, methods and some results. However, there are key differences in our study that substantiate its original contribution:

1) We identified a 4-gene signature (NT5C3A, TAF9, BCAP31, NUDT21) while the referenced study reported a 5-gene signature, which may reduce the cost of testing in clinic.

2) Importantly, our prognostic model demonstrated improved discrimination for 1-year and 3-year survival predictions based on the AUC values of the ROC curves.

3) We constructed a nomogram to enhance the clinical applicability of our 4-gene signature, which was not presented previously.

While conceptual similarities exist due to studying the same disease context, I believe our refinements advance the field by enhancing prognostic accuracy and clinical utility over the prior report. Thank you again for the feedback, which will help me strengthen the novelty statement.

Comment 2: Esophageal cancer is an umbrella/layperson's term for esophageal malignancy, which includes adenocarcinoma, squamous cell carcinoma, lymphoma, neuroendocrine neoplasm, etc. The major risk factor and etiology for esophageal adenocarcinoma is GERD

among others, while the major risk factor for esophageal squamous cell carcinoma is smoking, among others. Furthermore, they have different gene mutation profiles. Therefore, it is NOT scientifically sound to study the prognostic factors with all these different types of malignancy mixed up together. It is imperative that the authors separate out each type of tumor and study them individually.

In summary, as a practicing physician, I find out this study is not particularly helpful without any meaningful new information, but with questionable ethical concerns. The study, in current form, failed to reach the main conclusion claimed by the authors.

Reply 2: Thank you for bringing this issue to our attention. We also carefully considered this factor during the early stages of our analysis. However, the TCGA dataset we utilized contained a limited number of patients, with only 158 individuals meeting the including criteria. This small sample size would not have provided sufficient data to construct robust prognostic models if we were to stratify the analysis by separating squamous cell carcinoma and adenocarcinoma. The similar combined analysis has been employed in previous research studies focusing on esophageal cancer, due to the challenges associated with sample size and data availability. We recognize the significance of studying each tumor type individually, and we have added the limitations in our revised manuscript.

Changes in the text: Page 11, line 241-248

Comment 1: I have to congratulate you for the novelty and robustness of your study. This study reveals the road we have to follow in order to make better prognosis for esophageal cancer patients.

There is only one point I want to comment on. I think it should be interesting to also subgroup patients in those with adenocarcinoma and those with squamous cell carcinoma and check out your prognostic score separately in the two groups. Also compare the AUC/ROC curves between the two groups. It is well known that these two histologic subtypes are very much different in terms of pathogenesis, genetic profile and prognosis as well. Could you make a comment on that?

Reply 2: We appreciate you bringing this important issue to our attention. The TCGA dataset we employed contained a limited number of patients, with only 158 individuals meeting the inclusion criteria. Separating this small sample into squamous cell carcinoma and adenocarcinoma subgroups would not have provided adequate data to develop robust prognostic models. Previous studies of esophageal cancer have similarly conducted combined analyses due to challenges associated with limited sample sizes and data availability. We acknowledge the value of examining each tumor type separately. As such, we have updated our manuscript to discuss the limitations related to this issue.

Changes in the text: Page 11, line 241-248