**Peer Review File**

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**Reviewer A**

**Comment 1:** First, the title could be specific to the prediction of OS since the current study did not test other prognosis outcomes. I also suggest the authors to emphasize the combination of RBPs and clinical factors since the prediction model was not RBPs-based only.

**Reply 1:** We thank the reviewer for this suggestion. Our model is not solely based on RBPs, but rather incorporates both RBPs and clinical factors. Readers can find this in the abstract and subheadings of the article. In addition, OS is an important indicator of prognosis. Similar titles have been used in other articles (PMID: 33828074; 35561270).

**Comment 2:** Second, the abstract needs some revisions. The background did not explain the clinical needs for this prediction model and why RBPs-based model could potentially accurately predict the prognosis. The methods did not describe the generation of training and validation samples, the clinical factors in the dataset, and the statistical methods for assessing the predictive accuracy. The results need to briefly describe the clinical sample used to generate the prediction model and report the accuracy AUC indicators from both the training and validation samples. The conclusion needs more detailed comments for the clinical implications of the findings.

**Reply 2:** We thank the reviewer for this suggestion. We have carefully considered your comments and tried to make the necessary revisions to improve the abstract. However, the abstract should be concise and clear, and the specific content has been clarified in the methods and conclusion part of the text.

**Changes in the text:** see Page 1, line 30, 33-35; Page 2, line 44-46, 48

**Comment 3:** Third, the introduction was poorly written. The authors need to extensively review known prognosis prediction models in ESCA including their clinical and biological markers and accuracy, have comments on their limitations, and explain why there is a need for the RBPs-based prognosis prediction model. The authors need to further explain why RBPs-based prognosis prediction model is potentially accurate.

**Reply 3:** Thank you for the reviewer's feedback on the introduction of our manuscript. The purpose of our manuscript was not to compare the RBPs-based prognostic model with other prognostic models. There have been different prognostic models of esophageal cancer based on other gene families, such as ferroptosis-related genes, autophagy-related genes and etc. (PMID: 35121801; 37405477). Given the important role of RBPs in cancer, we aimed to explore whether RBPs could also be used to predict the prognosis of esophageal cancer.

**Changes in the text:** see Page 3, line 89-97

**Comment 4:** Fourth, in the methodology of the main text, the authors need to describe the generation of training and validation samples, the clinical sample and clinical factors in the dataset, and threshold AUC values for a good prediction model. Please explain why the authors combine both clinical factors and RBPs to develop the model.

**Reply 4:** We greatly appreciate the reviewer's attention to detail. We used the R package "caret" to generate the training set and test set, which was previously described on Page 4, line 134-135. In clinical practice, patients' age, gender, and tumor stage would also affect the prognosis of patients. Therefore, we combined the RBPs-based model with clinical factors to establish a more effective predictive model. In addition, we have refined the explanation of AUC according to your suggestion.

**Changes in the text:** see Page 5, line 162-164

**Comment 5:** Finally, please consider to cite and review some related papers: 1. Luan L, Lu F, Wang X, Wang Y, Wang W, Yang Y, Chen G, Yao H, Shi X, Yuan Z, Zhou G, Zhang H, He S. The predictive value of RNA binding proteins in colon adenocarcinoma. J Gastrointest Oncol 2021;12(4):1543-1557. doi: 10.21037/jgo-21-318. 2. Liu X, Lv Q, Jing Z, Long X, Yi R, Yang D, Zhao X. Construction of a prognostic risk model of colorectal adenocarcinoma through integrated analysis of RNA-binding proteins. Transl Cancer Res 2021;10(5):1962-1974. doi: 10.21037/tcr-21-40. 3. Wang N, Qiao H, Hao J, Deng C, Zhou N, Yang L, Zeng M, Guan Q. RNA-binding protein ENO1 promotes the tumor progression of gastric cancer by binding to and regulating gastric cancer-related genes. J Gastrointest Oncol 2023;14(2):585-598. doi: 10.21037/jgo-23-151. 4. Pu Y, Lu X, Yang X, Yang Y, Wang D, Li M, Guan W, Xu M. Estimating the prognosis of esophageal squamous cell carcinoma based on The Cancer Genome Atlas (TCGA) of m6A methylation-associated genes. J Gastrointest Oncol 2022;13(1):1-12. doi: 10.21037/jgo-21-686. 5. Lin S, Lin J, Weng J, Su W, Weng G, Chen Y, Hirahara N, Min YW, Chen X, Zhu K, Lin K. Combination of neutrophil-to-lymphocyte ratio and albumin concentration to predict the prognosis of esophageal squamous cell cancer patients undergoing esophagectomy. J Thorac Dis 2023;15(4):2224-2232. doi: 10.21037/jtd-23-333.

**Reply 5:** We thank the reviewer for this suggestion. After reading the corresponding articles, references were added and described in our manuscript. Although the fifth article is also related to the prognosis of esophageal cancer, it has little relationship with RBPs, thus it was not cited in our manuscript.

**Changes in the text:** see Page 3, line 89-94; Page 9, line 297-299

## Reviewer B

The paper titled "Development and validation of a prognostic model based on RNA binding proteins in patients with esophageal cancer" is interesting. The study provides a potential

prognostic model for predicting the prognosis of ESCA patients. The prognostic nomogram could improve individualized outcome predictions for patients with ESCA, therefore providing novel insights into future diagnosis and treatment. However, there are several minor issues that if addressed would significantly improve the manuscript.

**Comment 1:** There have been many studies on ESCA. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.
**Reply 1:** We greatly appreciate the reviewer's attention to detail. There have been several articles focusing on the construction of the prognostic model for esophageal cancer patients. However, there are few studies based on RBPs in esophageal cancer. Our study is the first to establish the RBPs-based prognostic model for esophageal cancer, providing new insights into the treatment of esophageal cancer. We have made the corresponding revisions in the introduction.
**Changes in the text:** see Page 3, line 90-97.

**Comment 2:** Can the comprehensive analysis of RNA binding proteins better understand the origin of diseases? How to provide new insights into the treatment of ESCA based on the content of this study? It is recommended to add relevant content.
**Reply 2:** We identified five key RBPs associated with the prognosis of patients by Cox regression analysis. These hub RBPs may play important roles in the progression of esophageal cancer. The intervention of the five RBPs, or the exploration of new targeted drugs, is expected to improve the prognosis of patients. In addition, the enrichment analysis of RBPs could provide potential signaling pathways to help further explore the regulatory mechanism of RBPs.
**Changes in the text:** see Page 11, line 349-352.

**Comment 3:** Some fonts need to be enlarged, as shown in Figure 2.
**Reply 3:** We greatly appreciate the reviewer's attention to detail. Fonts were enlarged as possible. However, due to the large number of proteins in Figure 2(A), the font size that is too large could not be accommodated. We have previously used high-resolution images so that readers could see clearly.

**Comment 4:** This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.
**Reply 4:** Thanks for the reviewer's suggestion. We are sorry that we did not perform experimental research for RBPs in our established model in the limited time. We plan to conduct these experiments in the future study to explore the underlying mechanisms of RBPs in the esophageal cancer.

**Comment 5:** It may be more meaningful to add functional research on key RNA binding proteins.
**Reply 5:** Thanks for the reviewer's suggestion. We understand the significance of functional research on key RBPs. In our study, we explored the underlying function of RBPs through GO and

KEGG enrichment analysis but did not perform specific functional experiments on key proteins. We also plan to conduct further research to explore the regulatory mechanism of RBPs in esophageal cancer. This is one limitation of our study and has been identified as such under the discussion section (Page 11, line 357-360).

**Comment 6:** The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Prognostic model construction and immune microenvironment analysis of esophageal cancer based on gene expression data and microRNA target genes, Transl Cancer Res, PMID:37304542". It is recommended to quote the article.

**Reply 6:** We greatly appreciate the reviewer's attention to detail. We have carefully read the paper suggested and refer it in our manuscript.

**Changes in the text:** see Page 3, line 96-97

**Comment 7:** It is necessary to further accumulate clinical cases and conduct larger sample, multi-center, randomized, and controlled clinical trials.

**Reply 7:** Thanks for the reviewer's suggestion. Clinical trials are necessary for the further clinical application of the prognostic model. We would like to add validation experiments and conduct more detailed experiments in the near future work. In addition, we also hope to further accumulate esophageal cancer patients and validate our model in the clinic. We have added this limitation in the discussion part in the revised version.

**Changes in the text:** see Page 11, line 358

**Reviewer C**

**1. References**

a. The citations of references (25, 26, 27) are missing. References should be cited consecutively and consistently according to the order in which they first appear in the text. Please check and revise.

**Reply 6.1:** Thanks for the editor's attention to detail. During the modification process, the references were deleted by mistake. We have made the corrections.

**Changes in the text:** Page 9, line 314

b. The authors mentioned "studies...", while only one reference was cited. Change "Studies" to "A study" or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

*According to previous studies, RBPs are abnormally expressed in colorectal cancer, affecting the translation of mRNAs into proteins and leading to carcinogenesis (6).*

**Reply 6.2:** Thanks for the editor's attention to detail. We have made the revisions as suggested.

**Changes in the text:** Page 3, line 91

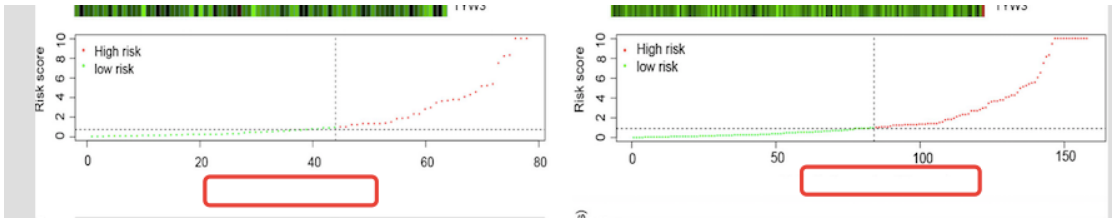
2. **Figure 2A** is not clear enough for publication. It would be much appreciated if you could provide it with a higher resolution as possible as you could. The preferred format is JPG or TIFF.

**Reply 6.2:** Thanks for the editor's attention to detail. We have made the revisions as suggested. However, the size of the image with a higher resolution is too large and we provide two different sizes of Figure 2 for the editor to choose.

**Changes in the text:** Figure 2-reivised-1; Figure 2-revised-2.

**3. Figure 5**

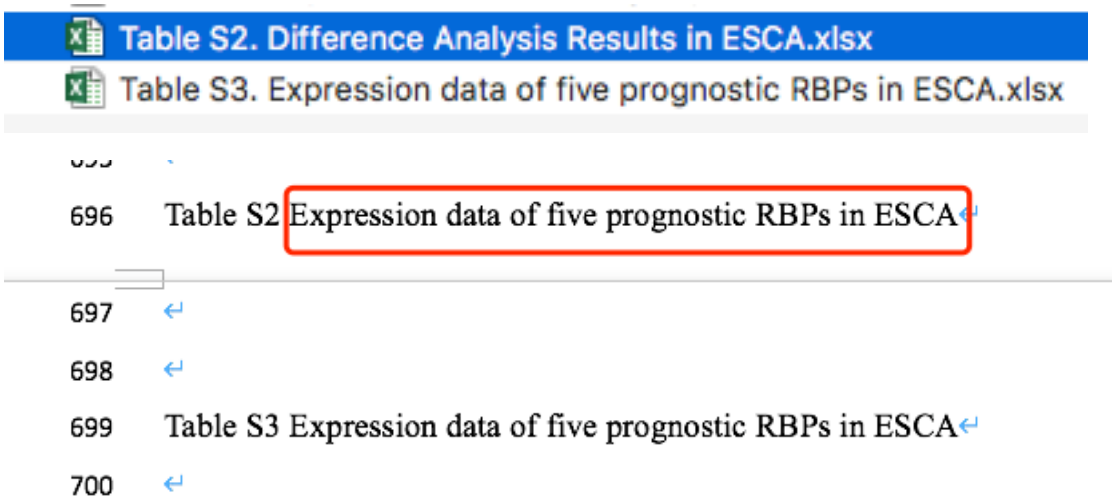
Please add the description of the X-axis.




**Reply 8:** Thanks for the editor's suggestion and we have added the description of the X-axis.

**Changes in the text:** Figure 5-revised

4. The title of **table S2** does not consistent. Please check and revise.




**Reply 9:** Thanks for the editor's attention to detail. We have checked and revised the title of table S2.

**Changes in the text:** Page 20, line 714