Peer Review File

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Review Comments

Comment 1:

The title needs to clearly indicate the prognosis outcome to be predicted and clearly indicate the databases used.

Reply 1:

Thank you for your valuable comments on our manuscript. Considering that the title does not clearly indicate the prognostic outcome to be predicted and the database used, we hereby change the title after consultation of all authors to: *Ferroptosis and Cuproptosis Prognostic Signature for prediction of prognosis, immunotherapy and drug sensitivity in Hepatocellular Carcinoma: Development and Validation based on TCGA and ICGC databases.*

Changes in the text:

We have modified our text as advised (see page 01, line 01-04)

Comment 2:

The abstract is not adequate and needs further revisions. The background did not describe the clinical needs for this new prognosis prediction model and the potential strengths of this prediction model. In the methods, please clearly describe the outcome variable in the databases and the generation of training and validation samples. In the results, please report the AUC values in both the training and validation samples and HR and P values for the low and high risk group. The conclusion needs to briefly comment the limitations of this study and have detailed comments for the clinical implications of the findings.

Reply 2:

Thank you for the detailed review. Based on your comments, we have made the following changes to the abstract section. In the background, first, we describe the

clinical needs and potential strengths of the new model, and second, we add prognostic outcome to be predicted. In the methods, we add the outcome variables in the database, and describe the process of generating the training and test sets. In the results, we added the HR and P values of the model genes and detailed the 1-, 3-, and 5-AUCs values of the ROC curves in the training and validation sets. In the conclusion, We highlighted the importance of the model in clinical practice and pointed out the limitations of the model being constructed based on a public database. In the future, it will be necessary to collect more HCC cases and conduct many prospective clinical assessments to further evaluate the model's efficacy in clinical settings.

Changes in the text:

We have modified our text as advised (Background, see page 03, line 47-53; Methods, see page 03, line 56-59, 62-64; Results, see page 04, line 71-75, 77-81; Conclusion, see page 04-05, line 87-94).

Comment 3:

In the introduction of the main text, a brief review on existing prognosis prediction models for HCC including their predictors and comments on the limitations of known models including their limited predictive accuracy are needed. The authors need to explain why a model based on both FRGs and CRGs is more accurate for predicting the prognosis and other strengths of this new model.

Reply 3:

Thanks for your great suggestion on improving the accessibility of our manuscript. We have explained the limitations of the published model and clarified the background of the construction of the new model in accordance with the reviewers' comments. The good prediction results of the model and its clinical guidance are also illustrated.

Changes in the text:

We have modified our text as advised (see page 05-07, line 103-105, 129-131, 134-138).

Comment 4:

In the methodology of the main text, please describe the threshold values of AUC for a good predictive model and the generation of training and validation samples.

Reply 4:

Thank you for the detailed review. We describe in detail the method of dividing the training and test sets and the R packages involved. Second, combined with the published literature, we believe that a good prediction model should have an AUC value greater than 0.5, which has been added in the manuscript.

Changes in the text:

We have modified our text as advised (see page 08-09, line 171-173, 183-184).

Comment 5:

In the discussion, please compare the diagnostic accuracy of the current model with known models published before with a focus on the predictive accuracy. It seems that the predictive performance of the new model is still not good.

Reply 5:

Thank you for the detailed review. Based on the review, we reviewed the published literature on clinical models related to copper and iron death and compared their OS, AUCs, and C-index with the new model, showing that our model had the largest c-index or AUCs value. This demonstrates the good predictive performance of the new model. In addition, we added at the end the limitations of the study.

Changes in the text:

We have modified our text as advised (see page 10-11, line 220-226; page 26-27, line 333-346; page 30-31, line 422-429).