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SPECIFIC COMMENTS TO AUTHORS

The article detailedly introduces the method of predicting distant metastasis in nasopharyngeal carcinoma using a gradient boosting tree model based on detailed MRI reports. It is suggested that the authors elaborate more on the data preprocessing steps in the methods section, including how missing data were handled and how variables were selected for model training.

Response: Thanks for your professional suggestion. For the data preprocessing, we applied several techniques. For instance, we used standardization for continuous variables and one-hot encoding for categorical variables. We used a complete dataset without any missing records. Also, we adopted a well-established algorithm for the data imbalance issue, Synthetic Minority Over-sampling Technique (SMOTE), which can over-sample the minority and under-sample the majority. For the variable selection, we used the method proposed by Deng et al. (Sci Total Environ. 2021 May 20;770:144746. PMID: 33736384. DOI: 10.1016/j.scitotenv.2020.144746). Specifically, we first split the dataset into a training set and a testing set. The training set was balanced with SMOTE and used for variable selection. Additionally, we generated two types of random variables, binary and continuous. Both random variables were included in the variable selection model. Then, we selected the variables with importance scores greater than those of random variables (as the threshold of random effect). To ensure the robustness of the analysis, the whole variable selection process was repeated 20 times by using different random seeds. In this case, the selected variables had greater average impacts than the average random effects (considered as statistically significant). We have updated "**MATERIALS AND METHODS**" and "**Statistical analyses**" section in the revised manuscript (highlighted the added contents with yellow color).

The use of a gradient boosting tree model and AUC evaluation is an effective approach. However,

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further discussion on the sensitivity and specificity of the model, as well as potential overfitting issues, is recommended.

Response: Thanks for the comment. Based on the ROC curve and Youden Index, the sensitivity for the full model is 0.744 and specificity is 0.631. The sensitivity for the reduced model is 0.739 and specificity is 0.636. We have added these results in "**RESULTS**" section in the revised manuscript (highlighted the added contents with yellow color). Our models prefer sensitivity over specificity because of the severity of distant metastasis among patients with nasopharyngeal carcinoma. In another word, our models have a better ability to find a patient with potential distant metastasis, which conveys very important information for future treatment plans. The overfitting issue in machine learning models is well-known. To address this issue, we applied multiple approaches including splitting the datasets into training dataset (50%) and testing dataset (50%) and using grid search with 5-fold cross-validation for finding the best hyperparameters. From our results, we can conclude that our models did not have overfitting issues. The testing AUCs aligned with training AUCs quite well. These discussions were added in the **"DISCUSSION"** part of the revised manuscript (highlighted with yellow color).

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Additionally, comparing the performance of the gradient boosting tree model with other machine learning models (such as random forests, support vector machines, etc.) if possible, could add depth to the research.

Response: Thanks for the great suggestion. We previously compared the different combinations of classifier and feature selection methods (see attached figure). We found that the performances were quite similar among these methods. This means that no such model will significantly outperform other models. Hence, we decided to choose any one of them and in this case, we used gradient boost models. In addition, the comparison of different methods is not within the current scope of this study. We aimed to identify if our model using detailed MRI report will have better prediction power than the TN staging criteria. Further studies regarding the comparison of different methods will be considered.

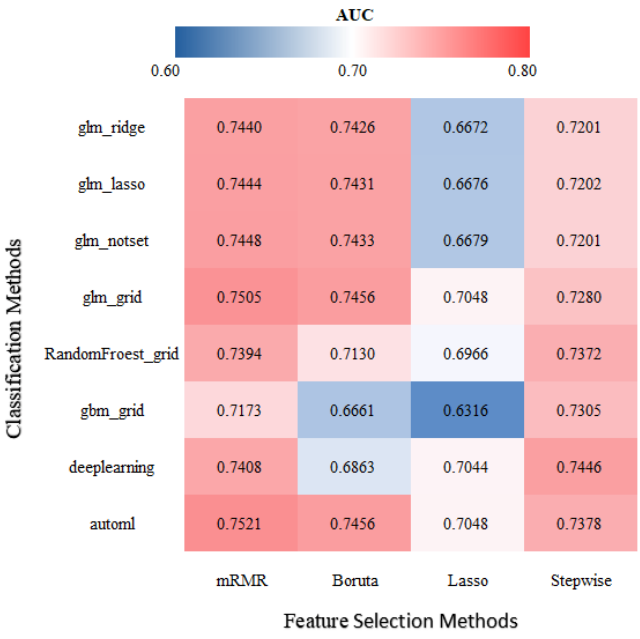

Figure S1. Comparison among different combinations of classification models and feature selection methods.

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The article successfully shows that the gradient boosting tree model outperforms the traditional tumor node staging system in predicting distant metastasis in nasopharyngeal carcinoma. The authors are encouraged to further explore why certain variables (like the number of metastatic cervical nodes) have higher relative importance in the model and discuss the potential implications of these findings for clinical practice.

Response: Thank you very much for your suggestion. In this study, we found that number of metastatic cervical nodes played a substantial role in predicting DM in NPC patients, with a much higher relative importance score than other variables based on GBT models. This finding was consistent with that of our previous study (Radiother Oncol 2020; 151: 40-46. PMID: 32679310 DOI: 10.1016/j.radonc.2020.07.02), in which, by using Cox model, we found that positive lymph nodes number was an independent risk factor for DM-free survival in NPC patients and was superior to other nodal factors (such as location and laterality of positive LNs, used in AJCC TNM staging). The present study confirmed the prognostic importance of metastatic nodal number in NPC patients. The importance of metastatic nodal number may be explained as follows: In NPC patients, LN metastases often follow an orderly manner from upper to lower level LNs, so the number of metastatic LNs was adequate to simultaneously reflect the location and laterality of positive LNs, and can better reflect the metastatic lymph node burden of patients. The current difficulty is that counting the number of metastatic lymph nodes on MRI can be a laborious task when a patient has too many lymph nodes. With the application of artificial intelligence in medical imaging, the counting of lymph nodes will become relatively easy. Nevertheless, we hope that the importance of metastatic nodal number could attract the attention of clinicians, and its potential clinical value, such as usage in selecting patients who may benefit from the additional chemotherapy, requires further study.

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Overall, the article is well-structured, but the authors are advised to check and correct any inaccuracies or unclear points in language.

Response: Thanks for the suggestion. We have sent our revised manuscript to a professional English language editing company (Editage) to perform further language polishing.

Additionally, introducing some figures to visually present model performance comparisons and variable importance might make it easier for readers to understand the results.

Response: Thanks for your professional suggestion. We presented the model comparison among different combinations of models and variable selection methods in supplemental Figure S1. In addition to showing the variable importance (Figure 1), we added the partial difference plots to show the association between top 5 selected variables and the outcome (supplemental Figure S2).

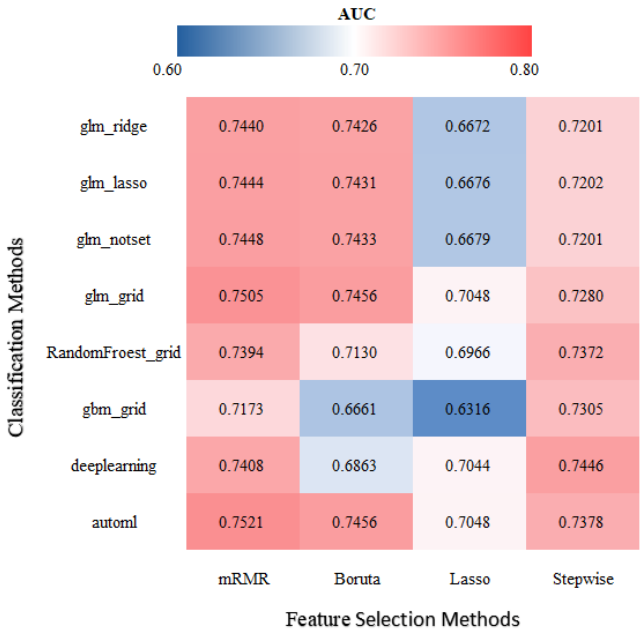

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Figure S1. Comparison among different combinations of classification models and feature selection methods.

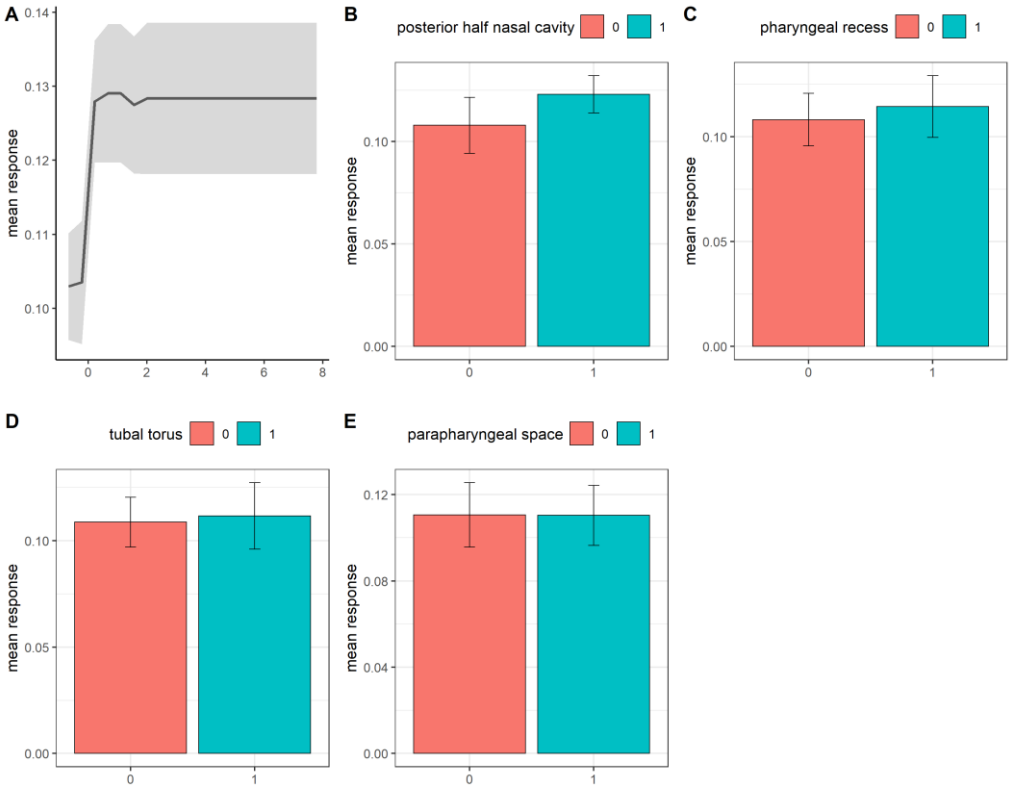

Figure S2. Partial difference plot for top 5 selected variables. A is the number of cervical nodes; B is Posterior half nasal cavity; C is Pharyngeal recess; D is Tubal torus; and E is Parapharyngeal space.

Although the article briefly discusses the study's limitations, a more comprehensive discussion on how these limitations impact the interpretation of the results is recommended, along with suggestions for future research directions, especially on how to overcome these limitations.

Response: Thanks for your professional suggestion. We agree with your comments. In

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this retrospective study, we did not compare other machine-learning methods in this study. Instead, we used cross-validation and grid search to tune the parameters of the models, and the performance of our models was good. Further studies comparing other methods to this type of model are warranted in the future. We did not add any clinical data (include age, sex, EBV-DNA and so on) in the model, because this study focused on the imaging variables got from the detailed MRI reports. Model combining imaging data and clinical data was needed to be further studied in future, especially in large sample, multi-center and prospective studies. These limitations have been added in the limitation part of the revised manuscript.

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PEER-REVIEW REPORT

SPECIFIC COMMENTS TO AUTHORS

This paper addresses the problem of distant metastasis in nasopharyngeal carcinoma patients. The study proposes a predictive model based on detailed MRI reading reports using the gradient boosting tree model to investigate the most significant contributors of metastasis in nasopharyngeal carcinoma. The paper is well written including the abstract, the key words and the background. Methods and results are well described, and the discussion also takes up the work of the literature. Have the populations been adjusted for age? A p-value test could be used to check this point.

Response: Thanks for the great question. We agree with the your opinion that demographics may impact the results. Unfortunately, we did not add age in the model because the current scope in this study focused on the entire population instead of certain sensitive subgroups. Our biggest concern was the detailed MRI reports -- the imaging variables, such as tumor invasion, lymph nodes metastasis, and so forth. More over, our previous studies showed that age was not associated with distant metastasis in NPC patients ($p<0.05$) (J Magn Reson Imaging 2021; 53: 152-164. PMID: 32860315 DOI: 10.1002/jmri.27339 and Radiother Oncol 2020; 151: 40-46. PMID: 32679310 DOI: 10.1016/j.radonc.2020.07.02). Models combining imaging data and clinical data (include age, sex, EBV-DNA and so on) need to be further studied in future, especially in large sample, multi-center and prospective studies. We added the limitation in the Discussion.

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Did authors compare the performance of the Gradient Boosting Tree model to other existing models in the literature?

Response: Thanks for the great question. We compared the performance of our Gradient Boosting Tree model to other existing models in the literature in the DISCUSION section. Our model outperformed a previous report using a multivariate COX model to predict distant metastasis in NPC patients (Front Oncol 2020; 10: 616. PMID: 32547935 DOI: 10.3389/fonc.2020.00616). In that article, a nomogram for DMFS was established in NPC patients with detailed MRI reading and hematological characteristics (plasma EBV DNA) and TN-staging system (concordance index was 0.718 in validation cohort). The predictive performance of our model was comparable to another machine learning model using MRI-based tumor burden features and all clinical factors (concordance indexes were 0.766 and 0.760 in internal validation and external validation sets). (Oral Oncol 2021; 118: 105335. PMID: 34023742 DOI: 10.1016/j.oraloncology.2021.105335).

Does the sex of the populations have an impact on the results?

Response: Thanks for the great question. We agree with the your opinion that demographics may impact the results. Unfortunately, we did not add sex in the model because our biggest concern was the detailed MRI reports -- the imaging variables, such as tumor invasion, lymph nodes metastasis, and so forth. More over, our previous

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studies showed that sex was not associated with distant metastasis in NPC patients ($p<0.05$) (J Magn Reson Imaging 2021; 53: 152-164. PMID: 32860315 DOI: 10.1002/jmri.27339 and Radiother Oncol 2020; 151: 40-46. PMID: 32679310 DOI: 10.1016/j.radonc.2020.07.02). Models combining imaging data and clinical data (include age, sex, EBV-DNA and so on) need to be further studied in future, especially in large sample, multi-center and prospective studies. We added the limitation in the Discussion.