

On behalf of all the contributing authors, I would like to express our sincere appreciations of your letter and reviewers' constructive comments concerning our article entitled "GATIS score for predicting the prognosis of rectal neuroendocrine neoplasms: A Chinese multicenter study of 12-year experience" (ID: 93779). These comments are all valuable and helpful for improving our article. According to the associate editor and reviewers' comments, we have made extensive modifications to our manuscript. In this revised version, changes to our manuscript were all highlighted within the document by using yellow-colored text. Point-by-point responses to the nice associate editor and three nice reviewers are listed below this letter.

Reply to Reviewer #1:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

Comments: "*The study of rectal neuroendocrine neoplasms is very impressive.*"

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript.

Sincerely,

The Authors.

-----End of Reply to Reviewer #1-----

Reply to Reviewer #2:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your clear and detailed feedback.

Comments: *"This study is interesting, but there are some points to revise before publishing."*

We hope that the explanation has fully addressed all your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses.

To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

Comment 1: *In present study, more than 90% of patients were NET. The prognosis of NET and NEC are very different. Therefore, authors should reexamine excluding NEC and MANEC.*

Response 1: We sincerely thank you for careful reading. According to your comment, we reexamine the predictive value of GATIS score for the prognosis of NET patients, and the results showed that GATIS score could accurately predict the prognosis of NET patients, and the predictive efficacy was superior to TNM stage in all time period, and a higher net benefit compared with TNM stage could be obtained (Figure 1).

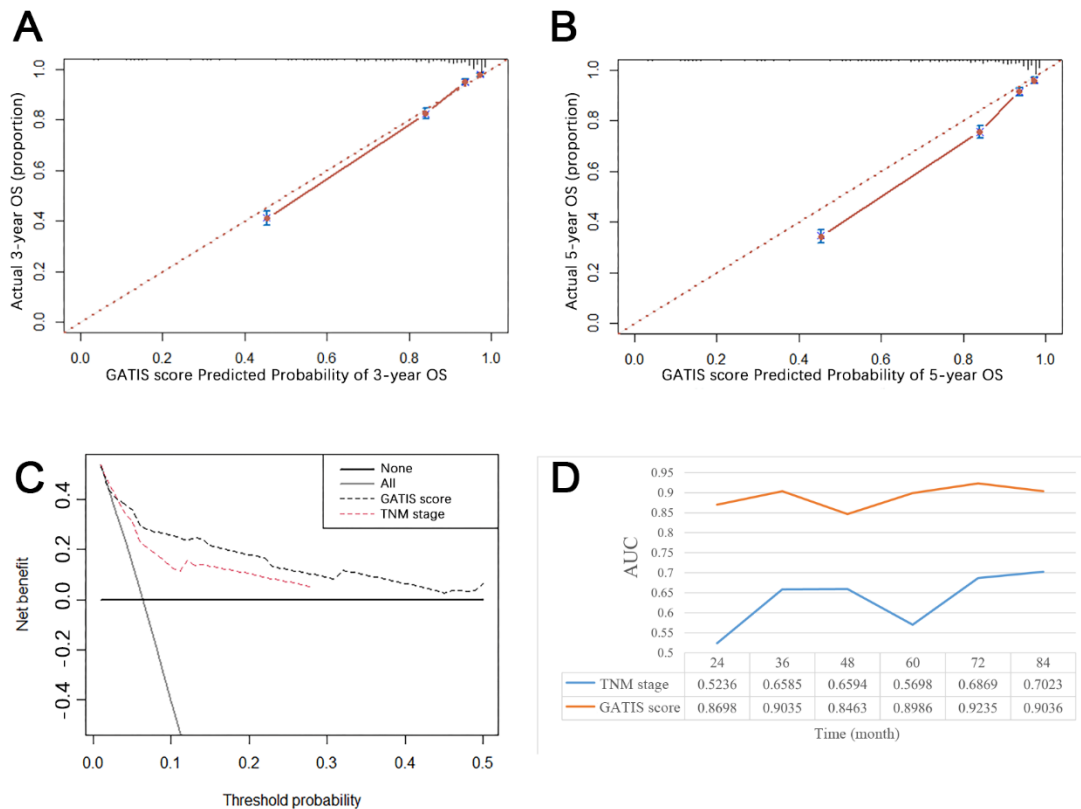


Figure1. Model validation for NET patients. (A) Calibration plot of 3-year overall survival. (B) Calibration plot of 5-year overall survival. (C) The decision curve analysis. (D) Time-dependent area under the receiver operating characteristic curve analysis.

Comment 2: *Why authors use 2 statistical soft?*

Response 2: Thanks for your comment. In this study, SPSS version 25.0 (IBM, Armonk, New York, NY) was used for descriptive analysis, t-test, Mann-Whitney U-test, Log-rank test and Cox proportional hazard model. X tile software was used for determining the optimal cutoff value of continuous variables for predicting survival data. Both random forest and nomogram models were conducted using R 4.0.0. In addition, in order to avoid missing

important predictors and improve the accuracy of the model, we used Cox proportional hazard and random forest model for the screening of predictors, and the results suggested that the predictive power of the model was satisfying. Thanks again for the careful check.

Comment 3: OS of patients with NET are good. So, if authors use OS for primary endpoint, you should use longer follow-up data. If you do not use those data, you change the primary endpoint, such as progression free survival, and so on.

Response 3: Thanks for your careful checks. Based on your comment, we analyzed PFS in patients with R-NENs, and the results showed that tumor grade, T stage, tumor size, age, and PNI were also important predictors of PFS. Thus, we constructed a GATIS score for predicting PFS, and the model validation results suggested that the C-index was 0.908 (95% CI, 0.872 – 0.944), with good predictive efficacy, high accuracy, and a net benefit higher than all single clinicopathological indicators. We have added the aforementioned information on page 10-11 to support our conclusion.

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We hope you will find this revised version satisfactory.

Sincerely,

The Authors.

-----End of Reply to Reviewer #2-----

Reply to Reviewer #3:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

Comments: "*The authors have conducted a rigorous analysis on the overall survival of rectal neuroendocrine neoplasms. I have some additional comments, that could potentially strengthen the study.*"

We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses.

To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

Comment 1: *Could you also conduct a survival study for progression-free survival, apart from overall survival? Progression-free survival is of important interest in the oncology community, to study the efficacy of the current line of therapy being administered to the patients.*

Response 1: Thanks for your careful checks. Based on your comments, we analyzed PFS in patients with R-NENs, and the results showed that tumor grade, T stage, tumor size, age, and PNI were also important predictors of PFS. Thus, we constructed a GATIS score for predicting PFS, and the model validation results suggested that the C-index was 0.908 (95% CI, 0.872 – 0.944),

with good predictive efficacy, high accuracy, and a net benefit higher than all single clinicopathological indicators. We have added the aforementioned information on page 10-11 to support our conclusion.

Comment 2: Could you also study the relevance of tumor volume, spiculation, as well as the change in tumor size and volume over time (i.e., a longitudinal analysis)? The change in characteristics of tumor regions over the treatment period and subsequent follow-ups is important to study the efficacy of treatment, if it was useful in preventing future recurrences and so on.

Response 2: We sincerely thank you for careful reading. As you said, the change in characteristics of tumor regions over the treatment period and subsequent follow-ups is important to study the efficacy of treatment. However, in this multicenter study, we did not collect information on tumor volume, spiculation, as well as the change in tumor size and volume over time, so relevant studies could not be carried out. Thank you very much for your suggestion, and we will perform relevant analysis in the subsequent study in order to provide more reliable reference for the diagnosis and treatment of R-NENs.

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We hope you will find this revised version satisfactory.

Sincerely,

The Authors.

-----End of Reply to Reviewer #3-----

Reply to Revision reviewer:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits.

Comments: "*Authors revised my comments. Therefore, there are no adding comments for this article.*"

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript.

Sincerely,

The Authors.

-----End of Reply to Revision reviewer-----

We tried our best to improve the manuscript and made some changes marked in yellow in revised paper which will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope the correction will meet with approval. Once again, thank you very much for your comments and suggestions. If you have any queries, please don't hesitate to contact me at the address below.

Xinyu Zeng, MD

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