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Dear Editors,

Thank you very much for giving us the opportunity to revise our manuscript entitled, "**Validation and head-to-head comparison of four models for predicting malignancy in intraductal papillary mucinous neoplasm of the pancreas: a study based on endoscopic ultrasound findings**". We also thank the reviewers for their valuable and constructive comments. We have carefully considered these comments, and our replies are provided below.

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Responses to the reviewers' comments:

Responses to the comments of Reviewer #1:

The authors conducted a study in which they performed a head to head comparison of several models used to predict pancreatic cancer in patients with IPMN. The study is based on surgically resected specimens and therefore the diagnosis of benign and malignant lesions is well documented. The authors conclude that the PSC model is the best in predicting malignancy. The study is well done and the manuscript is well written. However, the implications of the study for gastroenterologists dealing with IPMN are not obvious. The authors need to present an algorithm for working up a patient with IPMN and for taking a decision to operate or not to operate based on their findings. They also need to clarify how their algorithm is similar or

different from current guidelines of practice in patients with IPMN.

Response: Thank you very much for commending our work and for providing such valuable comments. The main purpose of our study is to validate and compare existing prediction models. We found that the PSC model has the best performance characteristics for predicting malignancy in our IPMN cohort. Therefore, we believe that the PSC model should be considered the best tool for assessing an individual's risk for malignant IPMN in current clinical practice. However, the PSC model still has room for improvement due to the lack of preoperative CA19-9 levels. To this end, we have also developed a nomogram on the basis of our institutional data (see Supplementary Figure 3). The optimal cut-off value for the probability of malignancy using our nomogram was 0.65; patients with values above this threshold were considered at high risk for malignancy, and those with values lower than this threshold were considered low risk for malignancy (see Supplementary Figure 4). Our nomogram may facilitate the clinical evaluation of IPMN malignancy and decision-making regarding surgical and follow-up strategies. In addition, since this nomogram was constructed using our own data from IPMN patients, the predictive accuracy was relatively sound (see Table 2 in the revised manuscript). An external validation using a multi-institutional cohort is needed to further confirm the clinical benefit of our nomogram.

We hope that this explanation is satisfactory. In addition, we are very

grateful for your expertise and your thorough review of our manuscript.

Responses to the comments of Reviewer #2:

I would recommend the author strengthen the introduction by highlighting that nomograms lead to individual risk stratification and individualized/personalized medicine. This is in contrast to guidelines where all patients are treated uniformly.

Response: We appreciate this suggestion. We have added this content to the INTRODUCTION section in the revised manuscript (highlighted in yellow).

Figure 2 is not necessary since morphologic classification of mural nodules was not significant on univariate, multivariate analysis nor used in any of the nomograms.

Response: We appreciate this suggestion. We have moved this figure and renamed it Supplementary Figure 1 (see Supplementary Material).

Figure 6- I honestly have not seen this kind of figure before but it was a helpful display of the data but perhaps should be switched to supplementary figures.

Response: We appreciate this suggestion. We have moved this figure and renamed it Supplementary Figure 2 (See Supplementary Material).

Supplementary Figure 1- why didn't the authors compare their nomogram to the other four nomograms? The authors should report the sensitivity, specificity, NPV, PPV and accuracy of their nomogram.

Response: Thank you for this valuable comment. The sensitivity, specificity, PPV, NPV, and accuracy values of our nomogram were 0.839, 0.840, 0.830, 0.849, and 0.840, respectively. We have included these data in Table 2 in the revised manuscript (highlighted in yellow).

I would suggest an additional table that includes all the factors for each of the four models the authors are comparing. This might be helpful for readers who are not as familiar with all 4 models. This could be a supplementary figure.

Response: We appreciate this suggestion. We have added a supplementary table depicting the factors used in the four examined models (please see Supplementary Table 1).

The biases and limitations of the study were discussed, however missing data is another bias that should be discussed in the limitations and transparency of how the authors dealt with missing data in the methods would be beneficial.

Response: Thank you for raising this issue. In this study, only patients with available preoperative endoscopic ultrasound records and pathologically confirmed IPMN were included. By searching our prospectively maintained institutional database, we identified 195 patients who fulfilled the inclusion criteria. After reviewing pathological reports, 14 cases with concomitant pancreatic ductal adenocarcinoma (PDAC) were excluded from the analysis due to a lack of histological transition between IPMN and PDAC. Patient demographic, clinical, laboratory, and pathological data were collected by reviewing electronic medical records. In our department, preoperative tests

for serum tumor markers including CA19-9 and CEA are routinely performed in surgical populations. As no missing data were observed in this patient cohort, we did not report how we dealt with missing data. We hope that the above explanation is satisfactory. Thank you for taking valuable time out of your schedule to review our manuscript.

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We would once again like to thank the editorial board for giving us the opportunity to respond to the reviewers. We hope that the above explanations are sufficient and satisfactory. If there is anything in the reviewers' comments that we misunderstood or that were not addressed to your satisfaction, we would appreciate the opportunity to respond accordingly. We look forward to hearing from you regarding your final decision.

Yours sincerely,

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