Specific Comments to Authors: In this study, the authors focused on “Prognostic Significance of Tumor Budding, Desmoplastic Reaction, and Lymphocytic Infiltration in Patients with Gastric Adenocarcinoma”. The research content of this paper meets the needs of clinical practice and has certain reference value for clinical guidance. However, there are still some shortcomings that need to be corrected in this study, as follows: 1.In this study, the number of cases included in this study is only 101. From a statistical perspective, the sample size is clearly insufficient. It is recommended to expand the sample size for further research. 2.As shown in Table 3, when conducting COX multivariate regression analysis, the included independent variables and dependent variables must match a large sample size in order to conduct regression analysis. However, the sample size is less than 200. I am curious about how the author obtained such a stable confidence interval? Further clarification and confirmation are needed here. 3. In this article, variable correlation analysis was conducted, and the author explained that the Pearson correlation coefficient analysis method was used. However, it was not well presented in the results section of this article. It is recommended to conduct visual analysis of the correlation between related variables. 4. The conclusion of this article. “The assessment of TB is an independent prognostic parameter in GAC patients, even in cases for whom surgical resection is not feasible. It is also more effective than DR and TILs at predicting tumor behavior.” I don't think there is sufficient evidence to support whether TB can become an independent risk factor for prognosis. I suggest revising and revising the wording in the conclusion section.

Dear Reviewer,

Thank you for your constructive comments and the time you have dedicated to reviewing our manuscript entitled "Prognostic Significance of Tumor Budding, Desmoplastic Reaction, and Lymphocytic Infiltration in Patients with Gastric Adenocarcinoma."

1. We appreciate your insights and agree that the sample size and clarity of the results are critical for the strength and credibility of our research.

a. It is important to note that our study was conducted within our single center, which naturally limits the number of available cases. Including only patients diagnosed between 2005 and 2015 was a deliberate choice to ensure accurate long-term survival analysis; hence, the sample size was confined to 101 patients. The incidence of gastric adenocarcinoma can vary significantly from region to region and from one center to another, affecting the number of available cases for study. This regional variability and our methodological choice for long-term follow-up data results in the sample size presented.
b. Nevertheless, according to your comment, we performed another search for new cases to increase the total number of cases. We detected 29 new patients (24 cases of intestinal and 5 diffuse types) with long-term follow-up suitable for further statistical analysis. We evaluated their clinicopathological findings, PTB, ITB, DR, and TILs and reanalyzed the data. Therefore, all tables and figures 3 and 4 were revised according to new results. Compared to our previous analysis, no different results were obtained other than p values.
c. This limitation is not unique to our study. For instance, the study by Pun et al. (ref no.26), entitled "Prognostic Significance of Tumor Budding and Desmoplastic Reaction in Intestinal-Type Gastric Adenocarcinoma," utilized a sample of 76 patients to explore similar prognostic features in GAC. This highlights that other studies within this domain also grapple with the challenge of limited sample sizes while attempting to yield meaningful scientific insights. Similarly, the study by Olsen et al.(ref no. 16) was conducted with 104 patients. These studies, like ours, underscore the difficulty in accruing large patient cohorts for such specialized investigations, yet they still contribute valuable findings to the field.
d. In this context, in line with your criticism regarding the results of the study, the limitations were explained as " This study has several limitations. It is conducted within a single center, limiting the sample size to remain relatively small, which might restrict the power to detect more nuanced associations or differences, particularly when stratifying the analysis by adenocarcinoma subtypes or evaluating the interaction between different prognostic factors. Moreover, potential selection biases cannot be excluded due to the retrospective nature of the study, limiting the

generalizability of the results to other populations and settings. Therefore, multicenter prospective studies and external validation are needed to confirm the findings.

Another limitation is the need for a standardized evaluation method for assessing TB, DR, and TILs in gastric adenocarcinoma, which might lead to variability in the results. Although we have employed methods consistent with current literature and guidelines, the need for universally accepted criteria for these histopathological features may affect the reproducibility and comparison of our findings with those of other studies. Additionally, the heterogeneous behavior of GAC necessitates a multifactorial analysis incorporating a wide range of potential prognostic markers. Our study focused on a select few, which, while important, do not encompass all the factors that could influence patient outcomes.

Despite these limitations, our study contributes valuable insights into the prognostic significance of TB, DR, and TILs in GAC, supporting the need for their consideration in future research and potential inclusion in pathological reporting protocols " in the last paragraph of the discussion section.

2. In the Cox multivariate regression analysis, we have included only those parameters found to be significant in the Kaplan-Meier analysis, which has led to a total of 6 independent variables in our model. For the sample size, we have adhered to a guideline suggested by Green (1991)[1] for regression analysis. This rule posits that for a model with m predictors, a minimum sample size of 50 plus 8 times the number of predictors is necessary to determine the sample size for the coefficient of determination. By this calculation, our study, with over 98 patients, provides a sample size well above the threshold for the number of independent variables we included. The inclusion of these significant parameters and the use of an appropriate sample size have contributed to the stability of the confidence interval obtained in our analysis. In the statistical analysis section, we added this study as reference 34, leading to the changes in reference number after this reference.

3. You criticized that we performed the Pearson correlation coefficient analysis method. However, we performed Spearman's correlation test as described in the materials and methods section's subheading "statistical analysis." Using this method, we analyzed the numerical values of PTB and ITB. According to your comments about the data visualization,

we added a new Figure 2 demonstrating their correlation. We investigated the correlation between categorical variables (PTB, ITB, DR, and TILs) by chi-square test. The results are presented in Table 1 and Table 4.

4. According to the comments, the conclusion of the abstract section, "The assessment of TB is an independent prognostic parameter in GAC patients, even in cases for whom surgical resection is not feasible. It is also more effective than DR and TILs at predicting tumor behavior." was revised as" Although our results support the evaluation of TB as a potential prognostic marker in GAC patients, further studies in larger series are needed to determine its role in pathology reporting protocols. Similarly, future studies are required to determine the predictive effects of DR and TILs in these tumors." The core tip also revised as '' This study investigated the relationships between tumor budding, desmoplastic reaction, and tumor-infiltrating lymphocytes in patients with gastric adenocarcinomas and assessed their influence on prognosis. Our results demonstrated that tumor budding is a promising prognostic factor in gastric adenocarcinomas. While it could also be valuable in determining survival in patients with unresectable tumors, further studies are needed to draw a conclusion. Although the desmoplastic reaction and tumor-infiltrating lymphocytes were not observed as independent parameters, their close association with tumor budding in patients with gastric adenocarcinomas suggests their value in predicting tumor behavior merits further research to clarify their roles better.'' Besides the statement about this comment at the conclusion section were also revised as '' Although the strong relationship between PTB and ITB also suggests that these two variables can be used in determining the course of the disease in patients for whom surgical resection is not feasible, especially for those with the intestinal subtype, further studies are needed to delineate their role.''

5. Because of the transfer of our manuscript to another journal, according to the new guidelines, abstract has been revised and an Article Highlights section has been added.

Sincerely yours