Dear Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "To develop and validate the combination of 3-lncRNA for the prognosis of patients with gastric cancer" (ID: 56135). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

Comment: The paper is interesting, and presents a new method for predicting survival for gastric cancer. The methods looks promising, but the authors need to compare this method with prognostic factors already existing. Also the authors need to give some indications for the practical applicaton of the model or to describe the studies that are needed to introduce the technique in the clinical practice.

Response: It is really true as Reviewer suggested that many articles have introduced the prognostic factors of gastric cancer at present. The main methods of these articles are molecular detection by immunohistochemistry or RT-PCR. In these papers, long-rank and Cox were mainly used for survival analysis.

In this study, we obtained potential tumor-related targets through a variety of bioinformatics methods from public TCGA database. This reduces bias effectively. Secondly, when screening survivor-related lncRNAs we introduced LASSO analysis on the basis of Log-rank and Cox analysis, which could also effectively reduce bias. Finally, we validated the analytical data with clinical data from our center. This further confirms the validity and reliability of this study.

We have made correction according to the Reviewer's comments: at the end of the paper, the application prospect of this model is described.

Reviewer #2:

Comment: Unfortunately, the uploaded paper does not include Table 1. This paper cannot be judged because the patient background and stage cannot be determined.

Response: We have upload the Table 1 with the manuscript.

(1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

As we combine the figures with AI, may I upload the original figures in “PDF”? It could be edited and arranged.

(3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text;

I added this part in the end of the manuscript.

(4) I found the Table 1 is missing in the manuscript;

I added this part in the end of the manuscript.

(5) please don’t include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $^{a}P < 0.05$, $^{b}P < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used, and a third series of P values is expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$.

The corresponding content has been modified.

Reviewer #2:

1. The criteria for selecting surgical cases are not shown. It is necessary to indicate whether the samples were collected from all surgical cases or limited to some of surgical cases, and if so, what selection criteria were used. The details of adjuvant chemotherapy, diagnosis of recurrence, and treatment after recurrence are also important factors, and it is desirable to specify them in the article.

Response: It is really true as Reviewer suggested that the selection criteria is necessary. As we mentioned in the manuscript: No preoperative chemotherapy or radiotherapy was performed on enrolled patients. Gastrectomy and D2 lymph node dissection were applied to all patients. Postoperative adjuvant chemotherapy was applied to IIA and worse. In order to ensure the consistency of operation, the operator of the selected cases was the same person. The postoperative chemotherapy regimen was all first-line XELOX regimen.

2. It is a problem to include TMN stage IV cases. The patients that can be curatively resected and the patients that cannot be completely resected should not be considered together. Only the patients who were radically resected should be considered.

Response: As Reviewer mentioned that patients who did not undergo radical surgery should not be included in the study. We also evaluated the three patients during the design phase of the experiment. Because the 2 IV patients included in this study were T4bN+M0 and all accounted for R0 resection, we included them in the study. All other stage IV cases with distant metastases were ruled out. And because there were all early case, the idea of neoadjuvant chemotherapy had not yet taken shape

3. The selection of the item of 'Characteristics' in Table 1 and Table 3 should be reviewed. The item of 'Tumor histological morphology' is not required. Is the definition of 'perineural invasion' accurate? (In gastric cancer, there is not much neural invasion.) T factor and N factor should be examined rather than the TMN stage. Isn't it necessary to evaluate each surgical resection method?

Response: We have made correction according to the Reviewer's comments. The " Tumor histological morphology " section has been deleted. Besides, the record of "Perineural invasion" was the pathological report of the patients, accounting for about 25% of the total invasion in this study. This may also be associated with single-center bias. As described and practiced in this paper, the prediction of disease by a single indicator was limited, so we adopted the multi-lncRNA modeling approach. Similarly, TNM is still a recognized multi-indicator combination modeling. It is necessary for us to compare our models with the "gold standard". Since all of our patients underwent the standard D2 radical resection according to the tumor site, and we had included the tumor site in the table, it was unnecessary to include the surgery method again.

4. Item selection and validity of Multivariate analysis should be reviewed. The data of AL109615.2 and AC079385.3 are included in the 'Model'. Is it statistically valid to input them in the multivariate analysis at the same time? Isn't it appropriate to input only 'Model'? Is it appropriate to put the TMN stage? Shouldn't T factor and N factor be input, instead of TMN stage? I would like biostatistician to reconsider this part.

Response: Considering the Reviewer's suggestion, we re-did the Cox analysis. TNM and Risk-model were included simultaneously.

5. Unfortunately, the benefits of combining three lncRNAs are not highlighted. Shouldn't it be enough to consider AC079385.3 alone? The usefulness of the 'model' should be described a little

more in the discussion section.

Response: As Reviewer suggested that we have made correction and mark them in red.

6. Whether or not the ‘prognostic factor’ is useful should be considered depending on the difference in prognosis when TMN stages are aligned. Try drawing Kaplan-Meier curve for each TMN stage.

Respone: As Reviewer suggested that we have try to draw Kaplan-Meier curve for each TMN stage. Unfortunately, the data did not show a positive result. As Tab 3 showed, this model had a significant positive correlation with TNM staging, so its predictive efficacy was significant in all patients. However, it was not significant in predicting the prognosis of patients at the same stage. Thank you very much for the reviewer's opinion, and we hope to continue to explore this proposition in future studies.

7. There is no description of D and E in Figure 3.

Response: We are very sorry for our negligence of the missing of Fig 3D and Fig 3E. We have made correction according to the Reviewer’s comments and mark it in red.