Dear Editor,

I would like to thank you for the quick handling of our submission and the reviewers for thoughtful comments and suggestions to improve the quality of our manuscript. We have revised our manuscript in accordance with the reviewers' suggestions and answer the questions point-by-point. If you have any questions, please send E-mail to me .

Response to the comments of Reviewer #1

Comment: I think that authors need to discuss from their data in discussion, not only repeat the results and/or results from other manuscripts in references. Minor point There are miss-typing of the size of fonts.

Response: Thanks for your useful comments. I double-checked the discussion part of my manuscript, and all parts of the discussion are derived from data in the manuscript. There is not too much deduplication of data results. The references cited are to better explain the mechanism of LncRNA. I hope the editor can carefully consider my opinion. If it still needs to be revised, I will correct it in time. I have revised the size of fronts. thank you!

Response to the comments of Reviewer #2

Comment 1: There are many results to confirm the upregulation of HOXD-AS2 inhibits the progress of GC. We strongly recommend that the authors perform the si- HOXD-AS2 using AGS, MGC-803, and BGC-823.

Response: Thanks for the correction. I also hope that I can further use si-RNA to knock down HOXD-AS2 in GC cell lines AGS, MGC-803, and BGC-823 to further explore the effect of HOXD-AS2 on GC cells. This is also the regrettable part of the manuscript. I have already graduated and I don't have time to go to the laboratory for further verification, and the project funding is limited, so I am very sorry that this part of the experiment cannot be completed, and I hope to apply for research funding in the future to further improve the regretful part.

Comment 2: In Figure 1C, there is no explanation or definition about the high and low expression of HOXD-AS2.

Response: Thanks for the correction. We supplemented a explanation of the high and low expression of HOXD-AS2. The revised explanation are shown below.

Figure 1. HOXD-AS2 was downregulated in GC tissues and was associated with poor prognosis. A: The relative expression levels of HOXD-AS2 in GC tissues was significantly lower than those in ANTs ($P = 0.030$, $N = 79$). B: HOXD-AS2 expression levels were decreased in human GC tissues and ANTs. Bars represent the ratio between the expression levels in GC tissues and ANTs (C/N, log scale) from the 79 patients. GC tissues expressed significantly lower levels of HOXD-AS2 than ANTs in the majority of patients (62.03%). C: Kaplan-Meier survival analysis showed that patients with low HOXD-AS2 expression had a poorer prognosis than those with high expression. low: The expression level of HOXD-AS2 is lower than that of ANTs. high: The expression level of HOXD-AS2 is higher than that of ANTs. Expression levels were normalized to β-actin levels. The results are shown as the mean ± SD. $^{a}P < 0.05$, two-tailed Student's t-test.

Thank you very much for the opportunity to improve our manuscript by incorporating these changes suggested by the reviewers. We attach great importance to these comments and make serious revisions.

Sincerely,

Lin Yao

The Department of Gastrointestinal Surgery, The Affiliated Hospital of North Sichuan Medical College, The Hepatobiliary Research Institute, North Sichuan Medical College Nanchong, China

(The corresponding author)

Point-by-Point response to second-round review

I would like to thank you for the quick handling of our submission and the reviewers for thoughtful comments and suggestions to improve the quality of our manuscript. We have revised our manuscript in accordance with the reviewers' suggestions and answer the questions point-by-point.

Reviewer's comments:

The present paper by Lin Yao, described the Article, "Decreased expression of the long non-coding RNA HOXD-AS2 promotes gastric cancer progression by targeting HOXD8 and activating the PI3K/Akt signaling pathway". In this report, they demonstrated that downregulation of HOXD-AS2 significantly promotes the progression of GC cells by regulating HOXD8 expression and activating the PI3K/Akt signaling pathway. The authors should consider the following questions and answer them adequately. major 1) There are many results to confirm the upregulation of HOXD-AS2 inhibits the progress of GC. We strongly recommend that the authors perform the si- HOXD-AS2 using AGS, MGC-803, and BGC-823.

Response to the comments of Reviewer Comment:

Thanks for the correction.

1. Through the PCR data of tissues and cells, we found that HOXD-AS2 is a tumor suppressor gene in GC, and the expression of tumor suppressor genes is reduced in cells, so we used overexpression of HOXD-AS2 to verify its effect on the biological behavior of GC cells. If the tumor suppressor gene is knocked down again, we consider whether its effect on the biological behavior of GC cells is obvious.

2. I also hope that I can further use si-RNA to knock down HOXD-AS2 in GC cell lines AGS, MGC-803, and BGC-823 to further explore the effect of HOXD-AS2 on GC cells. This is also the regrettable part of the manuscript. I have already graduated and I don't have time to go to the laboratory for further verification, and the project funding is limited, and I hope to apply for research funding in the future to further improve the

regretful part.

Thank you very much for the opportunity to improve our manuscript by incorporating these changes suggested by the reviewers. We attach great importance to these comments and make serious revisions.

Sincerely,

Lin Yao

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