Dear Editor, Dear reviewers

Thank you for your letter dated January 18. We were pleased to know that our work was rated as potentially acceptable for publication in the World Journal of Clinical Cases, subject to adequate revision. We thank the reviewers for the time and effort that they have put into reviewing the previous version of the manuscript. We would like also to thank you for allowing us to resubmit a revised copy of the manuscript. We hope that the revised manuscript is accepted for publication in the World Journal of Clinical Cases.

Sincerely，

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Reviewer 1：Comments to the Author

(1) First, the part Introduction in the article is similar to the research of Li et al (1). Secondly, since MUC16 encodes cancer antigen125 (CA-125), CA-125 also has a very important application in clinical work. However, they did not explore whether the MUC16 mutation would affect the expression of CA-125 at the protein level. there are protein data corresponding to gastric cancer in the TCGA database., which is regrettable that authors did not explore further.

Authors' answer: We appreciate your suggestion and we found it very useful, so we immediately browsed TCPA（https://www.tcpaportal.org/tcpa/） with the intention of downloading the relevant protein data, unfortunately, there is no data recorded in this database for CA-125. However, we still think it is a very valuable suggestion and we intend to explore the relationship between MUC16 mutation and CA-125 in more depth in our subsequent studies. Our study was also inspired by the study of Li et al. We agreed that their study was authentic, reliable and insightful, so we built on their work and explored different aspects of the MUC16 mutations using multi-omics data,

while building on this, we also tried to find which genes are actually caused by the MUC16 mutations to be differentially expressed. Using COX regression and random survival forest algorithm, we finally defined a key gene NPY1R and also discovered a possible target drug roscovitine. We think this is the meaningful part of our manuscript. We would also like to thank Li et al for the insight given by their study.

(2) The authors screened out NPY1R by using the wild type and mutant type of MUC16 as comparision, and then launched a subsequent analysis on NPY1R. What puzzles me is, does NPY1R have any important regulatory relationship with MUC16? Does this help explain why MUC16 mutations lead to a better prognosis in gastric cancer? It's just a collection of data.

Authors' answer: We thank the reviewers for their very interesting comments. In fact, when we found that patients with MUC16 mutations had a better prognosis, we wondered which genes were changed due to the MUC16 mutations, and we hypothesized that these genes might affect the prognosis, and by further screening, we finally identified NPY1R, and we found that high expression of NPY1R led to a worse prognosis, so we hypothesized that MUC16 mutations may affect the expression of NPY1R thus affecting the prognosis. Surely, in future studies, we intend to systematically investigate how the MUC16 mutations affect NPY1R.

(3) For the GSEA result of wild-type and mutant of MUC16, the authors took p53 pathway and DNA repair pathway as the explanation of why MUC16 mutations lead to a better prognosis in gastric cancer, which is reasonable. However, this is basically close to the research results of Li and Zhao (1, 2), so it is difficult to highlight its own novelty.

Authors' answer: We are very grateful to the reviewers for their approval of our results. Our study was inspired by the study of Li and Zhao et al. and we found their study very interesting. However, our study also differs from theirs. We utilized two different methods to achieve GSEA, and at the same time, we analyzed not only mRNA data but also CNV data, which we think will increase the reliability of our

results.

(4) There is basically no difference between the wild type and the mutant type of MUC16 in the immune score, and most of the 28 types of immune cells are negative results, and the regulatory mechanism of how MUC16 mutations affect immune cells is also unclear, which is difficult to make me convinced.

Authors' answer: We are grateful to the reviewers for their very interesting comments. In fact, when calculating the stromal score, immune score and tumor purity, we found that only the stromal score was different, and the immune score was not significantly different, we think a possible explanation is that the algorithm "ESTIMATE" focuses more on the overall immune score, and it is not detailed to each immune cell. When we use the algorithms "ssGSEA" and "EpiDISH" to evaluate specific immune cells, we can find that several specific immune cells in the MUC16 mutations group and the MUC16 wild group are differences. However, as the reviewer stated, only a few specific immune cells were altered, so we believe that in our subsequent studies we need to explore whether other immune cells are altered and how the MUC16 mutations affect tumor immunity.

(5) The paper is poorly written, need a clearer description of the analysis and discussion. Additional editing would help make the paper easier to read and interpret.

Authors' answer: We are very grateful to the reviewers for their suggestions to us, and we have revised and added some of the descriptions in order to increase the readability of the manuscript. Some inappropriate descriptions in the manuscript have also been corrected.

Reviewer #2: Comments to the Author

The manuscript entitled "Why MUC16 mutations lead to a better prognosis: a study based on the TCGA gastric cancer cohort" is interesting because it finds that MUC16 mutations can activate the p53 pathway and the DNA repair

pathway, in addition to also finding a potential target drug: NPY1R, and a potential drug: Roscovitine. thus, the work is interesting and deserves immediate publication.

Authors' answer: We are very grateful to have your approval and recognition of our research. We are also very pleased that you are interested in our research. As you mentioned, we have explored why patients with MUC16 mutations in gastric cancer have a better prognosis based on TCGA database using multi-omics data. At the same time, we also identified a gene, NPY1R. NPY1R is a differentially expressed gene (in the MUC16 mutations group and the MUC16 wild group), and patients with high NPY1R expression had a worse prognosis. In addition, we found a potential target drug roscovitine. Roscovitine can inhibit NPY1R expression and therefore may improve prognosis. However, there are still some problems with our study and we intend to investigate the relationship between MUC16 mutations and NPY1R in more depth in our follow-up study. Thank you again for your recognition of our study.

Science editor: Comments to the Author

Summary of the Peer-Review Report: The authors reported an interesting study. However, the authors have a large number of analysis similar to the published articles in the results, and there is no innovation in the analysis methods. Recommendation: Rejection.

Authors' answer: We are very grateful for your comments on our manuscript and we take your comments very seriously. First of all, our study was inspired by the study of Li et al, and we agree that their study is rigorous and valuable. However, our study also has novel aspects. Firstly, we have utilized multi-omics data, including mRNA, simple nucleotide variation (SNP), copy number variation (CNV) and methylation data, and extending previous studies. Secondly, we utilized multiple approaches, such as COX regression and random survival forest algorithm were applied to search for hub genes. Gene set enrichment analysis (GSEA) was used to elucidate the molecular mechanisms. Single sample Gene Set Enrichment Analysis (ssGSEA) and “EpiDISH” were used to assess immune cells infiltration, and “ESTIMATE” was utilized to

analyze the tumor microenvironment. Thirdly, we found a gene NPY1R that is differentially expressed in the MUC16 mutations group and the MUC16 wild group, and we found that high expression of NPY1R leads to a worse prognosis and was validated in an independent cohort. At the same time, we identified a potential target drug: Roscovitine, which inhibits NPY1R expression and therefore may improve patient prognosis. Of course, as mentioned by the editors, there are some issues in our study, and we intend to address these issues in more depth in our follow-up study.