Cover Letter

Dear Editors and Reviewers,

Thank you very much for your efficient work and thank you for your letter and comments. Accordingly, we have revised the manuscript entitled *"A three-miRNA indicator predicts prognosis of gastric cancer patients with bioinformatics analysis" (Manuscript NO: 37473),* and would like to resubmit it for your consideration. We have addressed the instructive comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers' comments are listed for your consideration. We would like to express our sincere thanks to the editors and reviewers for the constructive and meaningful comments.

We are so grateful that you have offered us this opportunity to resubmit our manuscript. We hope that the revised version of the manuscript is now acceptable for publication in your journal.

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We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

Dong-Qiu Dai

Reviewer # 1 (Number ID: 03317069)

Comment 1: The authors found that a novel three-miRNA indictor could be used for predicting the prognosis of GC patients. This is a carefully done study and the findings are of considerable interest. For the benefit of the reader, however, a number of points need modifying. These are given below: Major comments: Three DEMs used this study seem to be associated with many target genes. They have essential roles during cancer progression. Therefore, it is difficult to understand actual roles or function of these DEMs. The authors should evaluate the signal change by overexpression or suppression analysis of three DEMs by in vitro study

Response 1: We are grateful for your meaningful comments. However, our present study aims to identify multiple miRNAs for predicting the prognosis of gastric patients with the methods of bioinformatics analysis. Besides, the role of miR-125b-5p and miR-99a-5p in gastric cancer have been studied *in vitro* by other researchers and the studies indicated that the two miRNAs act as oncogene role in gastric cancer. Interestingly, the role of miR-145-3p in gastric cancer is unclear and we would focus on this tissue in our future study. Hopefully, this may address your concerns.

Comment 2: Minor comments 1. (Abstract, Page 2, Line 12-15) bovious→obvious.

Response 2: We are so grateful for your meaningful comments, and we fully agree with you and feel sorry for this spelling mistake. Accordingly, we have corrected the spelling in the Abstract. (See in the Abstract Section). Hopefully, this may address your concerns.

Comment 3: Minor comments 2. (Results, Page 5, Line 26-28) What's the meaning of ranking the three DEMs by the median of expression? The authors should mention the roles of each DEMs, especially miR-145-3p.

Response 3: Thank you for your meaningful comments, and we fully understand and agree with you. The meaning of ranking the three DEMs by the median of expression is to divide the 361 patients with gastric cancer into two groups, patients of the three DEMs' expression under median value were classified to the group of low risk. Otherwise, classified to the group of high risk. Then, a survival analysis with the Kaplan–Meier method and log-rank test was conducted between the two groups. As a result, we found that patients in high risk group tend to have a poorer prognosis than patients in the low risk group. As described in the manuscript, we explained the role of these three DEMs in the Discussion. (See in the Discussion Section). Interestingly, we found a novel miRNA (miR-145-3p) which was not studied in the field of gastric cancer. Our finding with the methods of bioinformatics analysis indicated that miR-145-3p was overexpressed in gastric cancer tissues compared with normal adjacent tissues. Based on this finding, we suppose that miR-145-3p may act as an oncogene in the tumorigenesis and development of gastric cancer and we will pay more attention to this hypothesis in future study. Hopefully, this may address your concerns.

Comment 1: It is suggested that miRNAs may serve as diagnostic and prognostic factors in oncologic disorders. The expression of specific miRNAs can indicate beingn or aggresive course of disease. The authors (Zang et al.) identified a three-miRNAs indicator for predicting the prognosis of patients with gastric cancer and analyzed potential signaling pathways in the development and progression of GC.

Response 1： Thank you very much for your meaningful comments and we are fully appreciative for your understanding and approval to our study. Hopefully, this may address your concerns.