Dear editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript “The proteomic signatures of infiltrative gastric cancer by proteomic and bioinformatic analysis” for publication in the World Journal of Gastrointestinal Oncology. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in red, for a point-by-point response to the reviewers’ comments and concerns.

Reviewer 1

This article described proteomic signatures of infiltrative gastric cancer (IGC). They found the top 10 up-regulated proteins (MRTO4, BOP1, PES1, WDR12, BRIX1, NOP2, POLR1C, NOC2L, MYBBP1A, and TSR1) and the top 10 down-regulated proteins (NDUFS8, NDUFS6, NDUFA8, NDUFA5, NDUFC2, NDUFB8, NDUFB5, NDUFB9, UQCRC2, and UQCRC1). The study design is well, and exciting article. However, there are some concerns about this article. 1. The authors could describe the flow chart of this study methods. In addition, the authors cold present the figure of high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to understand general readers. 2. The number of pairs of IGC and adjacent normal tissues was too small to generalize the result of this study. 3, The authors could describe how this result was applied clinically.

Response: We are grateful for the suggestions. From suggestion 1, the flow chart of this study methods and HPLC-MS/MS were added in figure 1.

The entire process of HPLC–MS/MS is briefly summarized and shown in Fig. 1.

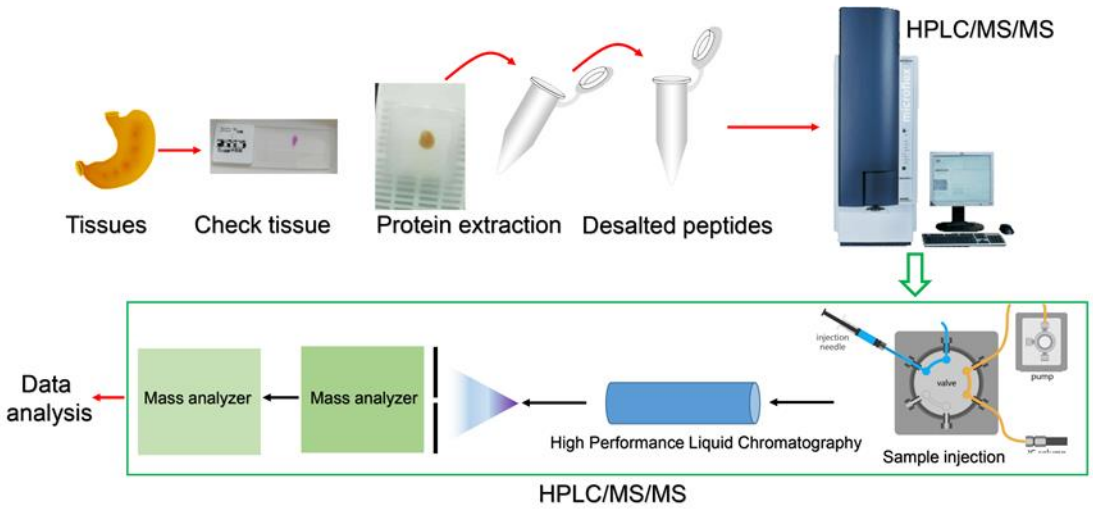

Figure 1. Schematic diagram showing the brief procedure of HPLC–MS/MS for proteomic analysis

From suggestion 2, limitations of the number of samples were added in the discussion.

"This study had several limitations. First, the number of pairs of IGC and adjacent normal tissues was not enough. In the follow up study, we plan to increase the sample size and conduct a multi-center study. Second, the number of verified proteins was also not perfect, we will use Mass Spectrometry Imaging method to verified more proteins at same time."

From suggestion 3, the clinical application of this result was described in the discussion.

"The significant DEPs were potentially diagnostic biomarkers and therapeutic targets of IGC. The proteomic signatures of IGC will contribute to precision medicine for more accurate diagnosis and better treatment effect."

Reviewer 2

Institutional review board approval document is not in english. Biostatistics review certificate is not correctly signed. Institutional animal care and use commite approval document is not signed, it is only two sentence in a Word document that anyone could have written. It is important to keep the same font type and size with concordance. In some sections they change.

Response: we deeply appreciate the reviewer's suggestion. Institutional review board approval document in English has been revised according to the suggestion. Biostatistics review certificate has been correctly signed. Institutional animal care and use commite approval document was revised to keep the same font type and size with concordance.

Reviewer 3

Stomach cancer (GC) is the fourth most prevalent malignancy worldwide and ranks third in terms of mortality and its molecular mechanism pathways is not completely understood. Proteomic methodology has the potential to provide new avenues for diagnostics and for the development of novel personalized therapeutic targets. Zhang Lihua et al. analyzed the proteomes of infiltrative gastric cancer (IGC) and normal gastric frozen tissue samples using high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) aiming to identify the differentially expressed proteins (DEPs). Twelve pairs of IGC and adjacent normal tissues were collected, and their proteomes analyzed by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). The key proteins were screened and functionally annotated by gene ontology (GO) and KEGG pathway analyses. The Statistical methods and software used were appropriate. They found that the proteins involved in cell cycle regulation, DNA replication and mismatch repair, and metabolism were significantly altered in IGC, and the proteomic profile may enable the discovery of novel biomarkers. Presented representative figures included volcano map of significantly differentially expressed proteins/ signature, gene ontology and pathways are complicated but followable, particularly the Western blotting was extremely

helpful. Furthermore, the proteomic signatures of IGC provide insights into the possible mechanisms underlying IGC progression, which involve DNA replication, cell cycle, mismatch repair, and energy metabolism pathways. I find this clinical study intriguing and of educational value and it may help unravel the molecular mechanisms and novel biomarkers of IGC as it lays the foundation for the discovery of potential diagnostic and prognostic markers as well as therapeutic targets in IGC. The significant DEPs identified in this study will have to be validated in a large cohort from multiple centers to provide justification for further clinical investigation. NB: In the future, authors are advised to upload the Institutional Review Board (IRB) approval letter translated in English.

Response: we appreciate the reviewer's positive evaluation of our work. Institutional Review Board (IRB) approval letter in English has been revised according to the suggestion.