Dear editor,

We are grateful for the opportunity of revising our manuscript entitled "**Mitophagy-related gene signature predicts prognosis, immune infiltration and chemotherapy response in colorectal cancer.**" We thank the editors and reviewers for their critical comments and invaluable suggestions which greatly help us to refine this work. As you and the reviewers may see, we have taken a great effort to address all the points raised by reviewers, and all the revisions has been highlighted in the manuscript. Specific point-by-point responses to the comments editor are described below and revised words and sentences have been highlighted.

Considering the contribution of authors during the revision stage, the author list has been changed. We sincerely believe that the substantial revision has greatly enhanced the quality of this paper. We would like to submit the revision along with the point-by-point responses to the reviewers' comments, and would appreciate your consideration for review and eventually publication of this important report in ***World Journal of Gastrointestinal Oncology***.

Best regards,

Sincerely,

Jingping Lin, MD

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Reviewer #1: Comments：

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors aimed to develop a mitophagy-related gene signature to predict the survival, immune infiltration, and chemotherapy response of

CRC patients. There are, however, a number of problems with this study.

1. In recent studies, there have been reports that autophagy genes are associated with colorectal cancer. What are the advantages and differences between your research and theirs?

Response: In this present study, we for the first time identified three molecular clusters with different clinicopathological features and prognosis in CRC based on mitophagy-related gene expression. In addition, we analyzed the prognostic value of mitophagy-related genes comprehensively and a novel prognostic signature with good predictive ability was developed and validated in this study.

2. Why did the authors not use the TCGA database for analysis since their research focuses on tumors?

Response: Thank you very much for your suggestion. We used TCGA database as an external validation set. By applying the prognostic signature in TCGA cohort, it was found that patients were successfully separated into two groups with significantly different overall survival (supplementary Figure S1B). In addition, survival ROC showed that the developed mitophagy-related gene signature performed good in predicting prognosis (5-year AUC = 0.72, supplementary Figure S1C).

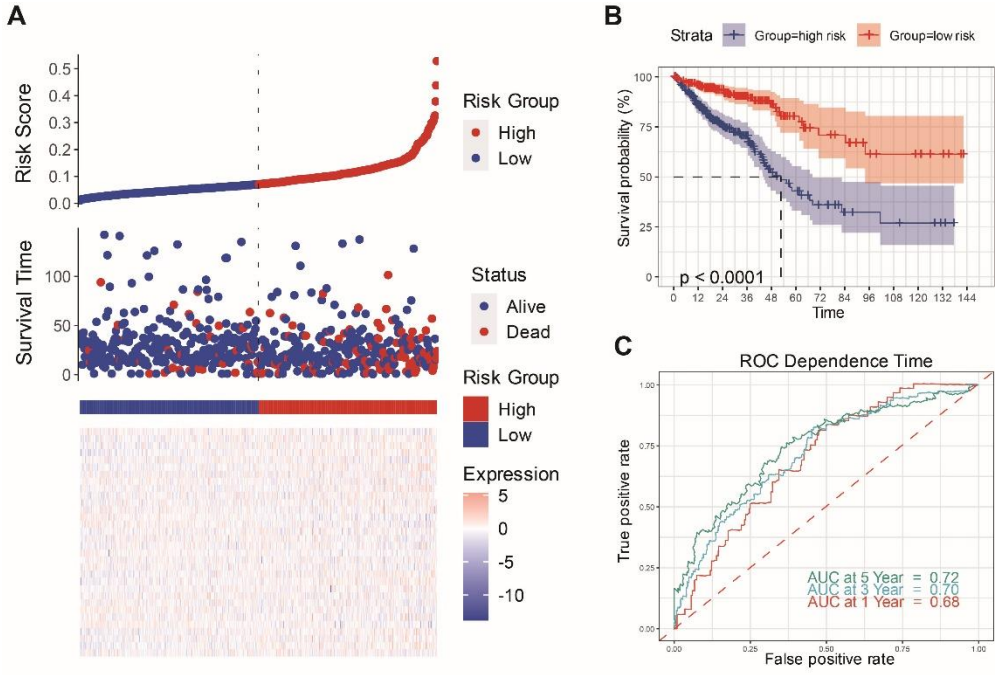

Figure S1

3. In addition to the training set and validation set, the authors should add at least one more cohort for the validation set.

Response: As mentioned in question 2, TCGA database has been set as an external validation set in this study. The predictive ability and prognostic accuracy of the developed signature were successfully validated in TCGA cohort.

4. A detailed description of the version of the R package should be provided.

Response: According to your suggestions, the detailed version of each R package used in this study have been described in the method part.

5. There are 36 genes in the signature, but they may be too many, making it difficult to use in clinical practice.

Response: Thank you very much for your concern. Before the signature can be applied as a clinical-grade assay, further steps are needed according to the established guidelines: firstly, identification of an appropriate approach to quantify expression (microarray); secondly, design of specific probes based on the sequences tested in the microarray chips; thirdly, validation in independent cohorts of patients with full clinical annotation available. Once an established signature was successfully validated, the procedure of calculating relapse or death risk will be intelligentized and automated with the development of bioinformatics and artificial intelligence. Therefore, we believe that the number of genes identified in a panel will not be an obvious obstacle when applying prognostic signature in clinical practice.

6. The authors wrote in Figure 1D that the three clusters are clearly separated, but the 1D figure does not show them. Additionally, there is no obvious connection between Cluster III and early stage in the Fig.1F.

Response: We are sorry for our carelessness. We have added the legend in figure 1D. After carefully analyzing the correlation between clusters and tumor stage, no significant connection was detected, suggesting that the gene cluster may be an independent prognostic factor. We have revised the description and interpretation of

fig.1F in the result.

7. It is recommended that authors revise and polish their writing.

Response: According to your suggestion, we have used a professional language editing company to polish our writing and the language editing certificate has been submitted as a supplementary file.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This novel predictive model developed in this article is of interest in the field of clinical cancer research, which probably can be clinically applicable in the future. Generally, I believe the results can help clinicians further understand the prognostic role of mitophagy-related genes in CRC and that could be relevant and valuable in a clinical setting. However, there are some minor questions that the authors should address before publication:

1. The predictive tool showed outstanding performance in predicting prognosis of CRC patients. I want to know whether this tool can be applied to predict the therapeutic response of immunotherapy in these patients?

Response: Based on the results presented in this study, we concluded that an epigenetic signature that was capable of predicting postoperative outcomes and may also serve as potential biomarker for immunotherapy responses has been successfully developed for CRC. Actually, we are preparing clinical trial to test the value of signature in guiding immunotherapy. We hope we can publish this result in the near future.

2. The 95%CI of AUC calculated in this study should be provided.

Response: According to your suggestions, the 95%CI of all the calculated AUC has been added.

3. Though the result was vividly visualized in this manuscript, more detailed interpretations of how to read the nomogram should be made.

Response: We have made revision according to the reviewers' suggestions. Nomograms have been successfully applied to a variety of malignancies for the purpose of improving oncological outcome prediction and provide patients and physicians with a more intelligible outcome measure when making treatment-related decisions. Upon using nomogram, it can be interpreted by summing up the weighted score assigned to each variable, which is indicated at the top of scale. The total score can be converted to predicted probability of death and recurrence or metastasis for a patient in the lowest scale. A higher total points was associated with a worse survival.

4. Language should be checked throughout the manuscript to avoid odd formulations

Response: The language of this manuscript has been revised by a professional language editing company.

Round 2

Dear editor,

We are grateful for the opportunity of revising our manuscript entitled "**Mitophagy-related gene signature predicts prognosis, immune infiltration and chemotherapy sensitivity in colorectal cancer.**" We thank the editors and reviewers for their critical comments and invaluable suggestions which greatly help us to refine this work. As you and the reviewers may see, we have taken a great effort to address all the points raised by reviewers, and all the revisions has been highlighted in the manuscript. Specific point-by-point responses to the comments editor are described below and revised words and sentences have been highlighted.

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Best regards,

Sincerely,

Jingping Lin, MD

Department of Critical Care Medicine, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou 350014, China;

E-mail: ljpccm@163.com

1. Specific Comments To Authors:

(1) The final screened genes should be marked in Figure S1A.

Response: According to your suggestion, the screened genes have been added in Figure S1A.

(2) The authors have noticed the problem with the PCA graph in Figure 1D, but they have not changed the previous issue (Can the PCA graph in Figure 1D clearly distinguish the 3 clusters?

Response: After carefully re-checking the data input when performing PCA, a wrong expression file was used. We are extremely sorry for our carelessness and we have corrected the data input and provided the revised PCA graph. As illustrated in the Figure 1D, these three clusters were notably discriminated

(3) The title of each part of the results should be improved.

Response: We have improved title of each part of the results according to your suggestion.

2. We suggest that change the manuscript type into "Meta-Analysis" if the clinical ethical files can't been provided (fill in PRISMA_2009_Checklist).

Response: Thank you for your suggestion. As this study is a retrospective analysis based on public database and all the data were downloaded from GEO and TCGA databases. Therefore, the Institutional Review Board of our hospital suggested that the Ethical Approval was not needed for this study. After repeatedly communicating with the Institutional Review Board of our hospital, we have successfully passed the ethical application and the clinical ethical files for this study has been provided. We really hope our study can be accepted as original article.

3.The labeling of P value in the figures does not meet the requirements of WJGO, 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 aP <0.05, bP <0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP <0.05 and dP <0.01 are used, and a third series of P values is expressed as eP <0.05 and fP <0.01.

Response: We have revised our manuscript according to the requirements of WJGO.

4. Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted

figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Response: We are extremely sorry and it is really difficult to re-organize all the figure into PowerPoint file. Instead, we have provided the PDF version of each figure and all the texts and elements in each figure can be edited directly by using **Adobe Illustrator** without losing image pixels. We sincerely hope you can accept this type of figure file.

5. Your manuscript has been checked by CrossCheck. Please read the attached CrossCheck report for details. Our editorial policy states the overall similarity should be less than 30%, the overlapped section should be less than 5% in single papers, including author's own work.

Response: We have revised our manuscript comprehensively based on the similarity result.