World Journal of Gastrointestinal Oncology
Dear editors and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitied **Clinical significance and potential application of cuproptosis-related genes in gastric cancer** (83685). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portions are marked in red in the paper.
Thank you for your consideration of this manuscript.

Best wishes,
Sincerely,
Yongfu Shao fyshaoyongfu@nbu.edu.cn

The main corrections in the paper and the responds to the reviewers' comments are as following:

Reviewer 1：
Scientific Quality: Grade D (Fair)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
The author systematically analyzed the molecular alterations of cuproptosis -related genes (CRGs) and constructed a novel prognostic nomogram model in GC using bioinformatics technology. The findings aim to offer new insights to predict GC prognosis and provide multiple therapeutic targets for future therapy. Albeit, I consider these findings to provide new insight into cancer-related fields, I still have some suggestions.
1) The title focus on "cuproptosis"-related genes, why does the author mention "Pyroptosis" in the introduction part. For example, ……All of this evidence suggests that "pyroptosis" influences the development and distal survival time of GC. For example, ……In our study, we systematically analyzed the molecular alterations of "pyroptosis"-related genes (CRGs)…..
Answer: Thank you for your carefully review! It is our mistakes and we have corrected theme to the cuproptosis.
2) Same as Discussion part, …..The prognostic models constructed in our study consisted of three "pyroptosis"-related genes (FDX1, LIAS, MTF1). As we all know, FDX1, LIAS, MTF1 are "cuproptosis"-related genes NOT "pyroptosis"-related genes
Answer: Thank you for your carefully review! It is our mistakes and we have corrected theme to the cuproptosis.
3) Most figures and tables are highly professional; however, the authors should guide the readers to the meaning of the images and tables appropriately; otherwise, it is likely to cause misunderstandings. Therefore, I suggest the author consider revising these figures and table legends again
Answer: Your suggestion is on the mark and we have revised the figures and tables so that

they can be more appropriate to be understanded.

4) In the discussion part, the author mentions about……we explored the mechanisms of how prognosis - related CRGs influenced distal prognosis at the DNA methylation level and immune cell infiltration level. However, where is the DNA methylation-related data? Please perform pertinent bioinformatic analyses and provide examples of studies investigating miRNA alteration or DNA methylation (https://biit.cs.ut.ee/methsurv/) (PMID: 29264942, 34834441, 33437202).

Answer: Thanks for your advice and recommendation and we have added the pictures of DNA methylation-related data in Fig 4J-L and reference [7-9]. *Page 6*

5) The author demonstrated that FDX1, LIAS, and MTF1 could serve as potential prognostic biomarkers for GC patients and provide novel targets for immunotarget therapy. So far, the tumor infiltrates immune cells and is vital for patient survival. Therefore, it is worth validating their data correlated with immune cells by using the "TIMER" (http://timer.cistrome.org) analysis tool (PMID: 32442275, 34329194, 35454940).

Answer: Thanks for your comment. TIMER is a typical database to analyze the correlation between gene expression and immune cells. We have read the literatures and added the data as Supplementary Figure 1 and reference [12-14]. *Page 6*

6) Since Connectivity Map (CMap) can be used to discover the mechanism of action of small molecules, functionally annotate genetic variants of disease genes, and inform clinical trials. It would be fascinating if these data could be correlated with other clinical databases. Therefore, I suggest the authors can validate their data via CMap or proteinatlas, and discuss these methodologies and literature as well as the validated data for cancer recurrence or metastasis in the manuscript (PMID: 17008526, 29195078, 32064155).

Answer: Truly, the links of genes and treating targets have got several breakthroughs in recent years. CMap is an important database to explore the gene expression and downstream perturbagens in order to design novel clinical treatment targets. Hence, we have performed the CMap and displayed the top 10 perturbagens in Table 3. Meanwhile, we discussed the recurrence or metastasis researches in the discussion part. Thanks for your suggestions and they can make our manuscript more sufficient [18-20] [26,28,30]. *Page 7, 12, 13*

7) There are few typo issues for the authors to pay attention to; please also unify the writing of scientific terms. “Italic, capital”? The font is too small for some of the current figures; meanwhile, the manuscript also needs English proofreading.

Answer: It’s our pleasure to get this advice and we immediately amended the manuscript. We have entrusted AJE for further polishing. If something would be missed, we have provided the decomposable Figures into the PPT file, which can be further revised by editors in order to achieve the publication standards.

Reviewer 2：

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

The topic of this manuscript falls within the scope of World Journal of Gastrointestinal Oncology. The Authors explored the molecular biological mechanisms of cuproptosis-related genes in gastric cancer, and constructed a significant prognostic normogram model for gastric

cancer, and found that FDX1, LIAS and MTF1 (genes that function closely with cuproptosis) could serve as potential prognostic biomarkers for gastric cancer patients and provide novel targest for immunotarget therapy. It is a interesting manuscript that makesd a contribution to therapy for gastric cancer. It is well organized and well written.The manuscript methodologically sound well. The conclusions are supported by results. Complete the References. Tables anf Figures are good.

Answer: Thanks for your review and we have made the manuscript more suitable to be published!