Reviewer comments-Reviewer A

Comment 1: What is the relationship of cuproptosis-related lncRNAs and immune microenvironment in ccRCC? It is recommended to add relevant content.

Reply 1: Thank you so much for your kindly and professional advice. We added the sentence "Cuproptosis-related lncRNAs have been found to be important in assessing immune function and tumor microenvironment in ccRCC patients. Chi H et al. found that cuproptosis-related lncRNAs can predict the immune microenvironment of patients with Pancreatic adenocarcinoma (24). Therefore, we examined the power of the 5-CRLs signature to detect the immune characteristics of ccRCC patients. GSEA function enrichment analysis between the high- and low-risk groups showed that there were significant differences in in the levels of multiple metabolic pathways among different populations. Interestingly, there were also significant differences in immune function. The ssGSEA results suggest that there are differences in various immune characteristics among different risk populations, such as immune checkpoints. Therefore, we analyzed the levels of immune checkpoint expression across groups and found that there were significant differences in immune checkpoint expression. The correlation analysis between immune infiltration and risk score showed that macrophages M0 and Tregs cells were significantly positively correlated with risk score. This suggests that the high-risk group has more dormant macrophages and more immunosuppressive Tregs. These analyses suggest that patients in the high-risk group may have a higher probability of immune escape, thereby contributing to the development of neoplastic disease." in the Discussion (See Page 15, line 478).

Changes in the text: See Page 15, line 478.

Comment 2: What are the roles of cuproptosis-related lncRNAs in predicting immunotherapy response? It is recommended to add relevant contents.

Reply 2: Thank you so much for your kindly and professional advice. We added the sentence "Cuproptosis-related lncRNAs have also been identified as important in guiding clinical treatment of tumor patients. Chen S et al. found that cuproptosis-related lncRNAs can predict drug therapy response in hepatocellular carcinoma (25)." in the Discussion (See Page 15, line 495).

Changes in the text: See Page 15, line 495.

Comment 3: Does copper-induced cell death take part in tumorigenesis or tumor progression? What are the potential roles of cuproptosis-related lncRNAs? It is recommended to add relevant

contents.

Reply 3: Thank you so much for your kindly and professional advice. We added the sentence "Recently, cuproptosis has been discovered to be a novel type of cell death regulation, similar to ferroptosis. This pattern has been found to influence the progression of cancer disease. A review by Jiang Y et al. showed that copper ions can exert anti-tumor effects, suggesting that copper death may play a key role in the treatment of tumor diseases (22). Some studies have suggested that copper death-related genes play a key role in predicting clinical outcome in renal clear cell carcinoma (23). However, few studies have investigated the function of cuproptosis-related CRLs in ccRCC." in the Discussion (See Page 14, line 443).

Changes in the text: See Page 14, line 443.

Comment 4: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Comprehensive analysis of cuproptosis-related long noncoding RNA immune infiltration and prediction of prognosis in patients with bladder cancer, Front Genet, PMID: 36186475", "Identification of a combined lncRNA prognostic signature and knockdown of lncRNA MANCR to inhibit progression of clear cell renal cell carcinoma by bioinformatics analysis, PMID: 36217399".   It is recommended to quote this article.

Reply 4: Thanks for your careful review and thoughtful comments. We added the sentence "Xue S et al. found that the mitotically-associated lncRNA MANCR could play an important influence on the progression of ccRCC by constructing a prognostic lncRNA model (15). In addition, Zhang Y et al. found that the cuproptosis-associated lncRNA signature could be used to predict the immune infiltration and prognosis of bladder cancer patients by systematically analyzing the expression characteristics of cuproptosis-associated lncRNA (16)." in the Introduction (See Page 3, line 95).

Changes in the text: See Page 3, line 95.

Comment 5: It may be more meaningful to suggest to increase the functional research of related key lncRNAs.

Reply 5: Thank you so much for your kindly and professional advice. Your comment is very professional, and we also hope to conduct functional research to fully explain the mechanism of related key lncRNAs in ccRCC tumors. This is what we have always wanted to do, but due to tight time and lack of funds, we only performed some in vitro experiments, and did not perform functional research. The further research will be certainly conducted in the future. We added the sentence "In addition, the mechanism of key lncRNA contained in the 5-CRL signature in ccRCC needs to be verified by more in vivo and in vitro experiments in the future." in the "limitation" section of Discussion (See Page 16, line 527).

Changes in the text: See Page 16, line 527.

Comment 6: The biological characteristics of cuproptosis-related lncRNAs and its research

progress in tumors should be added to the discussion.

Reply 6: Thank you so much for your evaluation of our manuscript. We added the sentence "Subsequently, we verified the results through experiments, which showed that AC015912.3, AC026401.3, AC103706.1 and AC134312.5 were highly expressed in tumor tissues, while EMX2OS was poorly expressed in tumor tissues. Wang Y et al. found that lncRNA can enhance the resistance of hepatocellular carcinoma to targeted drugs through related pathways (29). Chen ZH et al. confirmed that overexpression of EMX2OS can inhibit the growth of Wilms 'tumor in vitro (30). These findings suggest that the key lncRNAs we have identified may play an important role in the progression of a variety of tumors, but the regulatory mechanisms in ccRCC need further study." in the Discussion (See Page 16, line 513).

Changes in the text: See Page 16, line 513.

Comment 7: This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.

Reply 7: Thank you so much for your kindly and professional advice. Your comment is very professional and we would like to add some in vivo and in vitro experiments to fully illustrate the role of key lncRNAs in ccRCC. Unfortunately, due to some irresistible factors, we are unable to complete these contents for the time being, and we will add functional experiments of these key lncRNAs in the future to demonstrate the mechanism more fully. We added the sentence "In addition, the mechanism of key lncRNA contained in the 5-CRL signature in ccRCC needs to be verified by more in vivo and in vitro experiments in the future." in the "limitation" section of Discussion (See Page 16, line 527).

Changes in the text: See Page 16, line 527.

Reviewer comments-Reviewer B

Comment 1: There are some stylistic mistakes are presented in the text. For example, in the abstract the word «analysis» is used 2 times in a row.

Reply 1: Thanks for your careful review. We have modified our text as advised (See Page 2, line 43).

Changes in the text: See Page 2, line 43.

Comment 2: I do not agree with the authors' statement that 50% of patients after radical nephrectomy have metastases. What stage of the disease are we talking about. This statement does not correspond to the world statistics on kidney cancer.

Reply 2: Thank you so much for your kindly and professional advice. We checked the latest literature and found that our description was indeed wrong. We added the sentence "For surgical treatment, 30% of patients with localized ccRCC (i.e., stage I-III) develop recurrence and

metastasis after surgical tumor resection (4)." on Page 3, line 73. And we added reference "4. Li QK, Pavlovich CP, Zhang H, et al. Challenges and opportunities in the proteomic characterization of clear cell renal cell carcinoma (ccRCC): A critical step towards the personalized care of renal cancers. Semin Cancer Biol. 2019;55:8-15." on Page 18, line 581.

Changes in the text: See Page 3, line 73& Page 18, line 581.

Comment 3: It is not entirely clear how the tissue of the kidney tumor was taken for analysis: whether it was a biopsy or a postoperative specimen.

Reply 3: Thank you so much for your kindly and professional advice. We added the sentence "These tissue samples were taken from postoperative specimens of these patients." on Page 4, line 129.

Changes in the text: See Page 4, line 129.

Comment 1: Figure 1

Please provide an editable version of the flow chart (figure 1) in DOC/PPT.

Reply: Thanks for your careful review. We have provided an editable version of flow chart in the email attachment (See Figure1.pptx).

Changes in the text: See the email attachment.

Comment 2: Figure 2

Since the data is out of range (>1.0), please extend the scale of x-axis.

Reply: Thank you for your careful review. We have modified our figure as advised (See Figure 2-revised.jpg).

Changes in the text: See the email attachment.

Comment 3: Figure 4

Since the data is out of range (>0.6), please extend the scale of y-axis.

Reply: Thank you for your careful review. We have modified our figure as advised (See Figure 4-revised.jpg).

Changes in the text: See the email attachment.

Comment 4: Figure 5

a) To standardize the results, the part that exceeds the horizontal coordinates should be indicated by arrows.

b) Please double check if the order is correct. Usually, it should be I, J, K, and L.

Reply: Thank you for your careful review. We have modified our figure as advised (See Figure

5-revised.jpg).

Changes in the text: See the email attachment.

Comment 5: Figure 6

Please revise the x-axis, it should be T1-2, T3-4.

Reply: Thank you for your careful review. We have modified our figure as advised (See Figure 6-revised.jpg).

Changes in the text: See the email attachment.

Comment 6: Figure 8

Please revise "1-years-DCA, 3-years-DCA, 5-years-DCA" to "1-year-DCA, 3-year-DCA, 5-year-DCA".

Reply: Thank you for your careful review. We have modified our figure as advised (See Figure 8-revised.jpg).

Changes in the text: See the email attachment.

Comment 7: Figure 9

Please explain GSEA in the legend.

Reply: Thank you for your careful review. we have modified our text as advised (See Page 24, line 780).

Changes in the text: See Page 24, line 780.

Comment 8: Figure S1

To standardize the results, the part that exceeds the horizontal coordinates should be indicated by arrows.

Reply: Thank you for your careful review. We have extended the scale of x-axis to include all values (See Figure S1-revised.jpg).

Changes in the text: See the email attachment.

Comment 9: Table S1

Please explain HR in the table footnote.

Reply: Thank you for your careful review. we have modified our text as advised (See Page 31, line 821).

Changes in the text: See Page 31, line 821.