

## Reply to reviewers

Reviewer 1:

Dear Reviewer,

First of all, thank you very much for carefully reviewing my manuscript and giving valuable comments. The progress and efficiency of manuscript review seems to have exceeded my expectations. So far, I have carefully read your comments. It is true that my manuscript has the related problems you mentioned. These suggestions are all worth taking. Thanks for your patience. We have thoroughly revised the manuscript based on all your suggestions. Your suggestions are very meaningful and professional.

1) This is a comprehensive review on the mechanism of Ferroptosis and its impact on EC and immunotherapy.

**Reply: Thank you for your approval of this review.**

2) There are only some spellings and the initials that should be checked and corrected. For example, the "squamous cell carcinoma (ESCC)" appears TWICE in this manuscript. The first "squamous cell carcinoma (ESCC)" is present in the INTRODUCTION part, and it appears the second in the "The prognosis of EC predicted by ferroptosis-related genes (FRGs)" part.

**Reply: Thanks for the careful review and reminder. As you can see, I ignored these details. I have corrected some spellings and the initials in the revised manuscript. The occurrence of the same definitions appeared twice has been corrected in the revised version, such as ESCC, EA, LOX, ICIs. The definitions of GPX4 and IFN $\gamma$  were also supplemented in the process.**

3) In the "CONCLUSION" part: Based on the keywords "esophageal cancer" and "ferroptosis", we searched the PubMed database. However, there wre limited reports in this area." is not appropriate.

**Reply: Thank you for your reminder. Your suggestion is good. I have deleted the sentence "Based on the keywords "esophageal cancer" and "ferroptosis", we searched the PubMed database. However, there wre limited reports in this area." in the "CONCLUSION" part.**

Reviewer 2

Dear Reviewer,

First of all, thank you very much for carefully reviewing my manuscript and giving valuable comments. The progress and efficiency of manuscript review seems to have exceeded my expectations. So far, I have carefully read your comments. It is true that my manuscript has the related problems you mentioned. These suggestions are all

worth taking. Over the past month I have carefully revised my manuscript based on your suggestions. Below are responses to your doubts and revisions.

1) It is innovative to investigate the role of ferroptosis in the immunotherapy of esophageal cancer.

**Reply: Thank you for your approval of this review.**

2) First-line immunotherapy for advanced esophageal cancer has been recommended by the guidelines, but this article lacks an update.

**Reply: Thanks for the careful review and reminder. As you can see, I have updated the first-line immunotherapy for advanced esophageal cancer in the review. For example, I added "Pembrolizumab (the PD-1 inhibitor) plus chemotherapy (cisplatin and 5-fluorouracil) was approved for the first-line treatment of advanced EC" in the "The prognosis of EC predicted by ferroptosis-related genes (FRGs)" part, whereas deleted "ICIs are approved for the second-line treatment of patients with advanced EC". In the same time, I added "PD-1 inhibitors have been reported as first-line immunotherapy for advanced metastatic EC" in the INTRODUCTION part, whereas deleted "PD-1 inhibitors KEYNOTE-181, ATTRACTION-3, and ESCORT have been used as second-line therapy for patients with advanced EC". You can review this replacement in the revised manuscript.**

3) The research on ferroptosis in tumor immunotherapy is still in its infancy, which can also be reflected in this review. If more clinical data are available, the discussion may be more convincing.

**Reply: Thanks for your suggestion. I have added "The research on ferroptosis in tumor immunotherapy is still in its infancy." In the CONCLUSION part. Unfortunately, I didn't find more clinical data.**