

Peer Review File

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Review Comments

Major comments:

- The manuscript needs an extensive revision with editing for English language and grammar mistakes. I also recommend removal of idioms, such as “in deep water” (line 56).

Additionally, please ensure pronouns are clearly defined with corresponding nouns to provide clarity to the reader (ex. “them” in line 66).

Reply: We have revised the English language and grammar mistakes in the article. All revisions have been reviewed by a native speaker.

Changes in the text:

- BRCA molecular subtypes should be included in Table 1 and discussed. Please clarify if the data include all subtypes and how that informs your interpretation of the signature. This should also be included in the C-index calculations.

Reply: Thank you for your enquiry. The data we downloaded from TCGA including all subtypes in breast cancer, but many patients' ER, PR status are not clearly so that we could not distinguish luminal A and luminal B, so I'm sorry that we cannot add breast cancer molecular subtypes in table 1.

Changes in the text:

- Many of the figures are too difficult to read, as the axis labels are too small and blurry (Ex. Fig 4, Fig 5, Fig 7, Fig 10, Fig 11, etc). There are also several panels that appear stretched so that the text is distorted (Ex. Fig 6 A-B, Fig 9B-D).

Reply: Changes have been made to address the issue of image clarity. Figure 11 is difficult to see clearly after zooming out, so we upload the pictures in figure 11 in supplementary materials.

Changes in the text: Figure 3, figure 4, figure 5, figure 6, figure 7, figure 8, figure 9, figure 10 and figure 11 were re-uploaded.

- Several figure panels would benefit from additional description in the results section and/or figure legend, including Fig 2, Fig 3B-C. More description of what those panels are and what they show would help reader clarity.

Reply: We have added additional descriptions for mentioned figures, which we believe are able to help reader clarity.

Changes in the text: Changes have been made in line 173-175, 185-188.

- One concern is the enrichment of mutations in the high-risk group. How do you know these aren't driving the poor prognosis and the lncRNAs are an unrelated, incidental finding?

Additional preclinical mechanistic studies would alleviate this concern, but more commentary on this would also be acceptable.

Reply: Thank you for your enquiry. In the text, we firstly revealed that patients in the high-risk group faced a heavier mutation burden, indicating the potential connection between TMB and cuproptosis. In this part, there is no direct evidence proving the connection between TMB and prognosis. We only showed the distribution status of TMB between the low- and high-risk group patients and exhibited several typical mutant genes. Then, we grouped patients according to the TMB and proved its relationship with prognosis. But detailed mechanisms

are still unclear, and we did not find out if it directly derived poor prognosis or not. Besides, we have to admitted that TMB and cuproptosis are not totally unrelated. On the contrary, there must be some connections between them which we are not able to clarify in this article. After discussion, we thought that robust combination of these two factors was unacceptable in this condition. Thus, we deleted the Figure 10 E and added more commentary in the discussion.

Changes in the text: (Line 309) Besides, we discovered that patients in the high-risk group faced a higher tumor mutation burden, with PIK3CA and P53 as the most frequently mutated genes in breast cancer. Our findings suggested the potential connection between TMB and cuproptosis. Then, we grouped patients according to the TMB and proved its relationship with prognosis. Both cuproptosis and TMB serve as important prognostic factors for breast cancer patients, but we are not able to explore the detailed mechanisms in this article. More preclinical mechanical studies on this basis are wanted.

- More discussion of how the lncRNAs could affect the gene enrichment that you identified and, importantly, how all of this relates back to cuproptosis is also needed. How would this mechanism impact response to the drug sensitivity shown in Fig 11?

Reply: Changes have been made.

Changes in the text:(line 306-320) lncRNAs participate in the epigenetic modulation through complex mechanisms, which consequently have an impact on the biological behavior of cancer cells. In this study, we identified 19 cuproptosis related lncRNAs and carried out enrichment analysis, finding that they were able to influence a series of signaling pathways, which may further modulate cellular functions like immunol response and drug sensitivity. For example, the Akt signaling pathway, which was found to be enriched in this study, has been proven to be able to influence cancer cells drug sensitivity in previous studies. According to these findings, we speculate that there must be some unrevealed links between cuproptosis and these cellular functions. In this context, lncRNAs must play an integral role, but the exact mechanisms by which they are involved in are still a misery. We believe that a deeper exploration on this issue is certain to novel unprecedented discoveries, and lncRNAs may be a suitable portal for a breakthrough.

Minor comments:

- Table 1: “unknow” should be “unknown”

Reply: The change has been made.

Changes in the text: Changes have been made in table 1.

- Figure 1 needs a legend that includes any acronyms shown in the figure

Reply: The change has been made.

Changes in the text: Changes have been made in line 387-390.

- The risk score calculation (lines 177-182) belongs in the methods

Reply: The change has been made.

Changes in the text: Changes have been made in line 109-115.

- Overall, the figure legends need more detail about what is shown. For example, figure 4 has 3 graphs for each panel (A-C) but no details about what each graph is

Reply: The change has been made.

Changes in the text: Changes have been made in line 416-419.

- All figures should have figure calls in parentheses at the end of the relevant sentence (Ex. Fig 1 and Fig 4)

Reply: The change has been made.

Changes in the text: Changes have been made in line 173, 184, 195, 204, 209, 225, 241, 250, 267.

- The lack of functional studies for some of the identified lncRNAs are mentioned (line 300); is this a future direction you or others are currently pursuing? You could include more discussion on why this is important

Reply: Thank you for your enquiry, we will do more researches in lncRNA which we mentioned, lncRNAs participate in the epigenetic modulation through complex mechanisms, which consequently have an impact on the biological behavior of cancer cells. So we will do more on lncRNAs.

Changes in the text: Changes have been made in line 310-314.