Peer Review File

Reviewer A

The manuscript is well prepared and written in clear English. The Authors construct and validate ferroptosis-related gene signature in lung cancer samples. In addition to in silico analysis, the Authors included experimental validation. Technical value of the results is high, and the results are conclusive.

I have only minor concern below:
line 385: "navitoclax which inhibited Bcl-2" - Bcl-2 is written in italics, however, the Authors mention protein. Please correct (gene names should be written in italics, protein names should not). In addition, Navitoclax is not a BCL-2 selective inhibitor.

We do agree with the reviewer's comment and have corrected the written BCL-2 in line 356. Navitoclax (ABT-263) was regarded as a BCL-2 gene family inhibitor including BCL-2 according to the reference "Tse C, Shoemaker AR, Adickes J, Anderson MG, et. al. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res. 2008 May 1;68(9):3421-8", and we edited navitoclax here as "the BCL-2 gene family inhibitor".
Changes in the text: line 356.

Reviewer B

The manuscript titled' Construction and validation of a novel ferroptosis-related prognostic signature for lung adenocarcinoma' is an interesting manuscript in the field of metabolic rewiring in LUAD. However, the manuscript has several limitations specifically the mechanistic role of different ferroptosis-related genes in LUAD. The strength of the manuscript are the patient data validated with ferroptotic genes. My comments follow below,
1. Line 275-280 'Validation of the ferroptosis signature' section Figure 2 is wrongly named.

Thank you for the good suggestion. The name of the section Figure 2 is changed to "Development and validation of prognostic signature."
Changes in the text: line 627.

2. Line 280, Figure 2F is missing.

Thank you for the good suggestion. Line 299 is related to the supplemental figure 2F. It has been modified as Figure S2F in line 299.
Changes in the text: line 299.

3. Authors need to add the molecular weight of ACSL3 and PRDX6 western blots. Additionally, it would be nice to have positive control blots for ACSL3 and PRDX6.

We do agree with the comment and the molecular weight of ACSL3 and PRDX6 is added in Figure 6 and Figure 7. The expression of ACSL3 and PRDX6 was confirmed in cell lines with siRNA-related gene knockdown to confirm the special band position. Then, the expression of ACSL3 and PRDX6 was confirmed in the tissues with the corresponding molecular weight. Changes in the test: Figure 6 and Figure 7.

4. Figure 7D labeling is wrong please check.

Thank you for the good suggestion. The labeling of Figure 7D has been changed in lines 376. Changes in the test: lines 376.

5. Concentration used for ferrostatin-1 (Fer-1) is missing.

Thank you for the good suggestion. The concentration of Fer-1 is added in the method part. Changes in the text: line 204.

6. The role of GPX4 the main regulator of ferroptosis has not been mentioned in the author's analyses. The authors need to comment on this. Since RSL3 GPX4 inhibitor induces ferroptosis in lung cancer cell lines.

Thanks for the good suggestion. We added the role of GPX4 in ferroptosis in the part of the discussion. "GPX4 was considered a primary enzyme in anti-ferroptosis progression. RSL3, a GPX4 inhibitor, leads to increased levels of uncontrolled lipid peroxidation and ferroptosis. However, opposing PUFA activation and incorporation into membrane PLs may prevent PUFAs from oxidized and ferroptosis following GPX4 inhibition."
Changes in the text: Lines 431-437.

7. Patient data information also missing in the method section.

We appreciate for the suggestion and the patient data information was added to the supplemental table1.
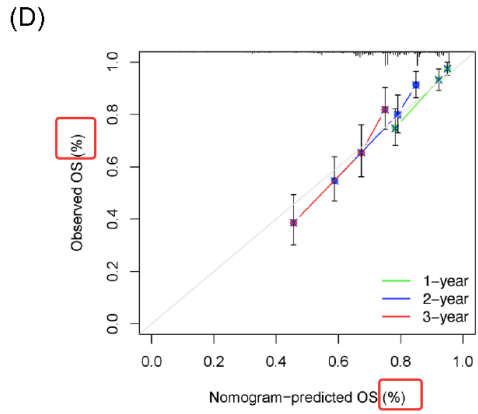
8. Spellings need to be checked throughout the manuscript.

We do agree with the reviewer's comment and have corrected the spelling errors in the article carefully.

Reviewer C

1. Fig 3D
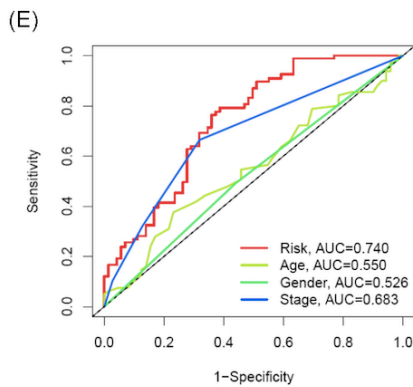"%" should be deleted since the data is 0-1.0.

(D)

We edited the figure.

2. Figure 3E

It seems that the legend for Figure 3E differs from the content of Figure 3E. Please check and revise.

642   Calibration curve to verify nomogram prediction accuracy. (E) ROC curves showing

643   OS of LUAD cases showing diverse clinical features at 1, 2, and 3 years. ***,

(E)

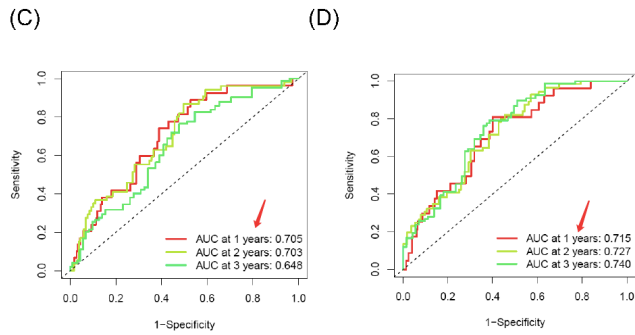Thanks for the good suggestion. We had edited the figure legend.

3. Figure 5A

Did the below content (red box) has P value? Please check and confirm.
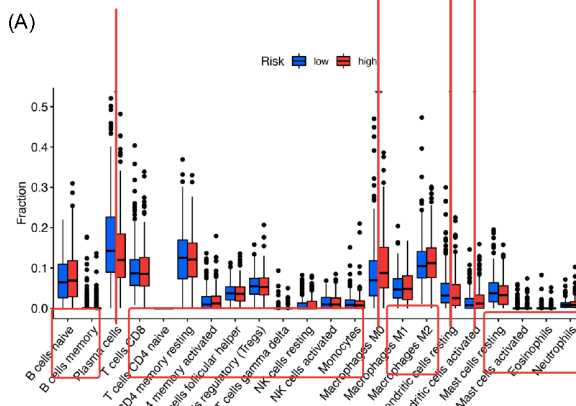
(A)

4. Figure S2C-S2D

Please revise "1 years" to "1 year".

(C)   (D)

5. Figure 2E
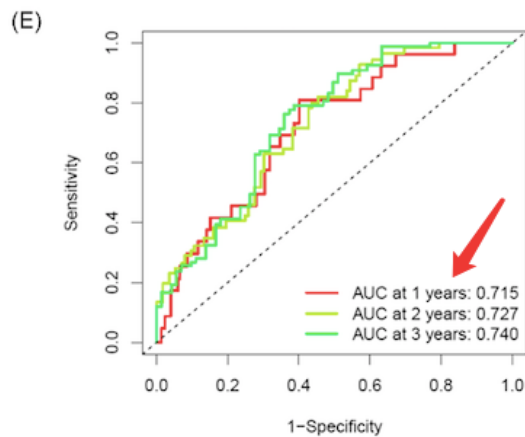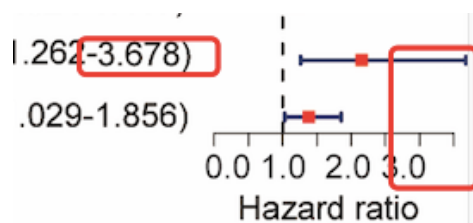
Please revise "1 years" to "1 year".

(E)
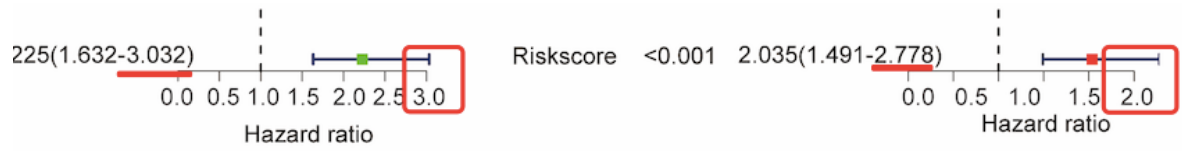
6. Figure 2C and Figure 3A, B

Please extend the length of the X-axis and also indicate the number.
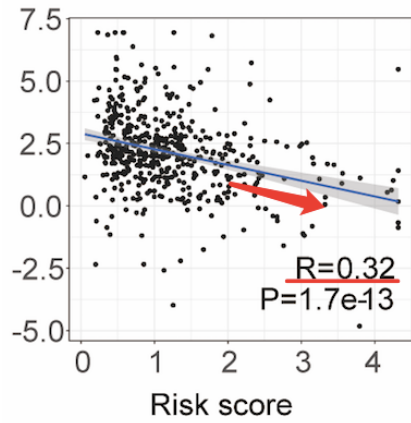
Thank you for the good suggestion. We have reversed Figure 2 and Figure 3.

7. Figure S3

The line in the graph is down and R should be negative, please check and revise.

Thank you for the good suggestion. We have reversed Figure S3.