Peer Review File

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Reviewer A

Generic Comment

Comment 1: First, the manuscript is difficult to read and understand for someone that is not familiar with the tools employed by the authors in their work. Several portions of text have been copied and pasted directly from some of the website describing the tools used by the authors.

Reply 1:

Thank you for bringing these concerns to our attention. We recognize the importance of making our manuscript accessible and comprehensible to all readers, including those who may not be familiar with the tools used in our study. In response to the concerns about clarity and originality, we have not only rephrased the descriptions in our words but also added introductory explanations for each tool to facilitate understanding.

Changes in the text:

1. On Page 9, Line 203-205, we have revised the description of Gene Set Enrichment Analysis (GSEA) to

"Gene set enrichment analysis (GSEA) is a special type of computational method used to identify whether a predefined set of genes shows statistically significant differences in expression under different biological states, as determined by analyzing gene expression data.".

2. On Page 9-10, Line 214-227, we have revised Section 2.6 to

"To validate the effectiveness of the PLPI model we proposed, we conducted an analysis of tumor-infiltrating immune cells using three tools: Cell-type Identification By Estimating Relative Subsets Of RNA Transcripts (CIBERSORT) (https://cibersort.stanford.edu/), the single-sample gene set enrichment analysis (ssGSEA), the estimation of stromal and immune cells in malignant tumor tissues using expression data (ESTIMATE). CIBERSORT can determine the proportions of different cell types within a mixed cell population by analyzing gene expression data of the cancer patients [30]. We utilized it to analyze the distribution of 22 immune cell types in the high- and low-risk patient groups from TCGA-LIHC database. The detailed list of 22 cell types is shown in Table S5 of supplementary material. ssGSEA, a bioinformatics method, is used to calculate enrichment scores for gene sets within individual samples and has been employed to assess the infiltration of 28 immune cells in the high- and low-risk patient groups from TCGA-LIHC database [31]. The 28 immune gene sets are shown in Table S6 of supplementary material. ESTIMATE is a tool that estimate the compositions of stromal and immune cells within the tumor microenvironment by analyzing gene expression data from cancer patients [32], which was applied to estimate tumor purity, stromal, immune and estimate scores.".

3. On Page 10, Line 231-237, we have revised the description of pRRophetic package to

“In addition, the pRRophetic package was used to establish the relation between drug response and gene expression data to identify potential therapeutic drugs. Therefore, we used the pRRophetic package to calculate the semi-inhibitory concentration (IC50) values of each patient in the high- and low-risk groups of 29 drugs, which had previously been shown to have promising efficacy in relevant studies [33-35]. In this study, the gene expression and drug sensitivity data from cell lines in Cancer Genome Project (https://www.sanger.ac.uk/group/cancer-genome-project/) and gene expression data from TCGA-LIHC database were used in the drug analysis.”.

Comment 2: Second, the authors do not provide the description of the abbreviation they use, and when an explanation is given is, most of the time, not when the abbreviation was first used. Also, the authors should include a list of abbreviations, which is currently missing.

Reply 2:

Thanks to the reviewer’s careful review and for pointing out the issues with the use of abbreviations in our manuscript. We have ensured that each abbreviation is defined upon its first occurrence in the text. Furthermore, we have compiled a comprehensive list of abbreviations and included it at the end of the manuscript for easy reference.

Changes in the text:

1. On Page 4, Line 81, we changed “HCC” to “Hepatocellular carcinoma (HCC)”.

2. On Page 5, Line 121, we changed “REOs” to “relative expression orderings (REOs)”.

3. On Page 9, Line 215-216, we changed “CIBERSORT” to “Cell-type Identification By Estimating Relative Subsets Of RNA Transcripts (CIBERSORT)”.

4. On Page 9, Line 217-218, we changed “ESTIMATE” to “estimation of stromal and immune cells in malignant tumor tissues using expression data (ESTIMATE)”.

5. On Page 22-23, Line 493-517, we added a list of abbreviations.

Comment 3: Third, many of the tools employed by the authors require as input a list of genes (e.g., GSEA, pRRophetic, etc …), which are not provided by the authors, therefore it is impossible to evaluate whether the data they generate support the conclusion they reach. Table listing these genes should be made available as Online Supplementary material.

Reply 3:

We thank the reviewer for their insightful comments regarding the necessity of providing the lists of genes used as input for the computational tools mentioned in our study. The availability of these gene lists is crucial for the validation of our results.

It should be noted that the gene sets employed in our analyses were directly downloaded from the official websites at the respective analysis tools to ensure standardization and reproducibility of our analyses. We have provided the URLs to these genes set in the revised manuscript at the points where the tools (e.g., GSEA, pRRophetic, etc …) are mentioned, so that the readers can easily access and download the gene sets used in our study.

Changes in the text:

1. On Page 9, Line 207-210, we changed the description of GSEA to

"Specifically, based on the Hallmarks gene set "h.all.v7.0.symbols.gmt" and the gene set "c2.cp.kegg.v7.5.1.symbols.gmt" from the MSigDB database, GSEA was carried out through GSEA software [27, 28] and clusterProfiler package (Version 4.8.2) [29]. The gene sets could be downloaded on the website (https://www.gsea-msigdb.org.).".

2. On Page 9, Line 220-222, we changed the description of CIBERSORT to

"We utilized it to analyze the distribution of 22 immune cell types in the high- and low-risk patient groups from TCGA-LIHC database. The detailed list of 22 cell types is shown in Table S5 of supplementary material.".

3. On Page 9, Line 222-225, we changed the description of ssGSEA to

"ssGSEA, a bioinformatics method, is used to calculate enrichment scores for gene sets within individual samples and has been employed to assess the infiltration of 28 immune cells in the high- and low-risk patient groups from TCGA-LIHC database [31]. The 28 immune gene sets are shown in Table S6 of supplementary material.".

4. On Page 10, Line 235-237, we changed the description of pRRophetic package to

"In this study, the gene expression and drug sensitivity data from cell lines in Cancer Genome Project (https://www.sanger.ac.uk/group/cancer-genome-project/) and gene expression data from TCGA-LIHC database were used in the drug analysis.".

Comment 4: Forth, most of the information included in the material and method section are nearly impossible to read. I understand that this is a technical study, but if the aim of the authors is to connect with physicians treating HCC patients the authors need to deeply change this section.

Reply 4:

Thank you for your valuable suggestions about the readability of the material and method section of our manuscript. In order to improve the readability of our manuscript, we have thoroughly revised the material and method section with the following improvement:

1. We have added a flowchart of the data collection for differentially expressed pyroptosis-related lncRNAs (DEPR-lncRNAs) to visually represent the sources and collection of the data, which will help readers better understand.

2. We have rephrased the introductions of tools used in our study in our own words to facilitate readability for readers who are not familiar with these tools.

3. We have included additional references to existing literature and reviews that provide more detailed explanations of the tools and methods.

Changes in the text:

1. On Page 10, Line 252-253, we have added a flowchart of the data collection for DEPR-lncRNAs.

2. On Page 9-10, Line 202-237, we have rephrased the description of tools.

3. On Page 9, Line 209, we have added additional references to the description of GSEA software.

Specific Comment

Comment 1: Page 2, line 54, the authors stated that "could offer a fresh viewpoint for better clinical judgment". While the "better clinical judgment" is an important skill that must be learned by physicians during their study and training. I do not see how the work presented by the authors can help the physicians in this process. Furthermore, the "better clinical judgment" is only reported here, so please remove.

Reply 1:

We are very thankful to the reviewer for the valuable advice. We appreciate the opportunity to clarify our intent with the phrase "could offer a fresh viewpoint for better clinical judgment". Our goal in this statement was to suggest that the results from our study could serve as a theoretical reference for physicians and contribute to their understanding of hepatocellular carcinoma (HCC), which may in turn assist them in their clinical decision-making process.

However, we agree with the reviewer's concern that our statement may not have been sufficiently substantiated within the context of our manuscript. Following the reviewer's advice, we have removed the phrase "better clinical judgment" and revised the sentence in the revised manuscript to reflect the contributions of our study more accurately.

Changes in the text:

On Page 2, Line 53-54, we changed the sentence to

"The novel PLPI not only greatly predicted the prognosis of patients with HCC but could also offer novel ideas and approaches for the therapeutic management of HCC.".

Comment 2: Page 4, line 83, the authors stated that "overall survival (OS) rate of HCC patients is still strongly unsatisfactory with a postoperative 5-year recurrence rate of approximately 70% owing to tumor heterogeneity". This is true only for advanced HCC.

The missing biomarker are for early detection, and I still do not understand how their finding can help in identifying these biomarkers. Please include it in the explain.

Reply 2:

Thank you for your insightful comment. We realize that the statement "overall survival (OS) rate of HCC patients is still strongly unsatisfactory with a postoperative 5-year recurrence rate of approximately 70% owing to tumor heterogeneity" may have been misleading and did not clearly differentiate between stage of HCC. The 70% postoperative 5-year recurrence rate is particularly associated with advanced HCC, and we have made the necessary corrections to specify this in our revised manuscript.

In response to your query on how our findings may help in identifying the biomarkers for early detection, we would like to explain that our research on the novel PLPI provide insight from the molecular mechanism and pathways that are active in HCC, by which the researchers can identify specific molecules or gene expressions that are altered in the early stages of HCC. To elucidate this point clearly in our manuscript, we revised the sentence in our revised manuscript.

Changes in the text:

1. On Page 4, Line 83-85, we revised the sentence to accurately reflect that this high recurrence rate is characteristic of advanced HCC:

"Although liver transplantation and surgical resection are the backbones of curative therapies for HCC, the overall survival (OS) rate of patients with advanced HCC is still strongly unsatisfactory, with a postoperative 5-year recurrence rate of approximately 70% primarily due to tumor heterogeneity [2, 3].".

2. On Page 4, Line 86-88, we have revised the sentence as:

"Therefore, the urgent identification of reliable biomarkers and the establishment of a molecular prognostic signature for HCC are imperative. These advancements are not only important for aiding in the early detection of HCC but also critical for substantially improving the prognosis of patients through earlier diagnosis and precisely targeted therapeutic intervention.".

Comment 3: Page 4, line 98, the line "As a newly programmed cell death triggered by inflammatory bodies" does not make any sense to me. Authors should simply explain what is triggering pyroptosis and why it leads to inflammatory cell death. The general principle is to keep to the basic.

Reply 3:

Thank you for your feedback on our description of pyroptosis. To provide a clearer and more fundamental explanation of pyroptosis, we have revised this sentence in our revised manuscript.

Changes in the text:

On Page 4, Line 100-104, we have replaced the original sentence with the follow:

"Pyroptosis is a form of programmed cell death characterized by its inflammatory nature, typically initiated by the activation of caspase-1 or caspase-11 within

inflammasomes in response to inflammatory signals. This process leads to the activation of Gasdermin D and the disruption of the cell membrane, which facilitates the release of cellular contents and the generation of an inflammatory response, culminating in inflammatory cell death [8, 9].".

Comment 4: In general, the introduction is way too long and does not really highlight way this study was done and how to interpret the presented findings.
Reply 4:
Thank you for your suggestion regarding the length and focus of our introduction. We have taken your comments in consideration and would like to explain the reason and necessity for our approach to the introduction.

Our introduction firstly demonstrated that despite available treatment such as liver transplantation and resection, the long-term survival rates of patients remain unsatisfactory due to tumor heterogeneity. This background is crucial for establishing the urgency of our research.

Furthermore, we highlight the important role of long non-coding RNA (lncRNAs) and pyroptosis in cancer therapy, as well as their potential as biomarkers for the prognosis and treatment of HCC. This provides the scientific basis for our research and reveals our motivation for investigating these biomarkers.

We also discuss the limitations of current gene expression-based prognostic models, which have led us to develop a new pyroptosis-related lncRNA prognostic index (PLPI). The PLPI aims to offer a more reliable tool for predicting the prognosis of HCC patients.

In crafting our introduction, we have made effort to ensure that the content of our manuscript is concise and focused. At the same time, we have ensured that the introduction still clearly conveys the core themes and objectives of our study.

Comment 5: Page 10, line 229, in the result section the authors stated that "10877 lncRNAs and 54561 mRNAs shared in TCGA-LIHC and NODE databases were obtained". As these two databases contain the sequencing information from a large number of donors, it would be meaningful to state the number of patients/control included from each database and how were the two databases intersected. Anything in the section 3.1 is nearly impossible to understand. If your aim is to be read, then you should simplify the text and highlight the outcome/message. Furthermore, the list of DE lncRNA and mRNA are missing.
Reply 5:
Thank you very much for your comment to highlight the need for improving the quality of our work.

According to your suggestions regarding the number of patients and controls included from the TCGA-LIHC and NODE databases, we have now provided this information

in Section 2.1 Data Collection (Page 6, Line 139-141).

Regarding the intersection of the two databases, we initially converted gene names into gene symbols using annotation files (hg38.99) from the gene expression profiles. Subsequently, we matched the gene symbols in both databases to figure out which genes they had in common. To provide readers with a clearer understanding of the gene intersection between the two databases, we have included a data flow diagram of the data collection for DEPR-lncRNAs in the supplementary material Figure.1.

In addition, we have revised Section 3.1 with the aim of simplifying the text and highlighting the outcomes and messages. For the convenience of the readers, we have included the list of differentially expressed lncRNAs (DElncRNAs) and differentially expressed mRNAs (DEmRNAs) in the supplementary materials Table S2 and Table S3, respectively.

Changes in the text:
1. On Page 6, Line 139-141, we state the number of patients/control included from each database.

2. On Page 10, Line 246-253, we have revised Section 3.1 to
"Initially, we obtained 10,877 lncRNAs and 54,561 mRNAs shared in TCGA-LIHC and NODE databases according to the same gene symbol. We performed the Wilcoxon rank sum test and identified 764 differentially expressed lncRNAs (DElncRNAs) and 5,642 differentially expressed mRNAs (DEmRNAs) ($|\log_2(foldchange)|>1$, $FDR<0.05$). The volcano plot of the DElncRNAs is displayed in Fig. 2a. Next, we intersected the 5,642 DEmRNAs and 155 pyroptosis-related mRNAs based on the same gene symbol, resulting in 110 DEPR-mRNAs. Finally, we identified 407 DEPR-lncRNAs from the co-expression network between 110 DEPR-mRNAs and 764 DElncRNAs ($|R^2|>0.4$, $p<0.001$). Additionally, a data flow diagram of the data collection for DEPR-lncRNAs is shown in the supplementary material Figure.1.".

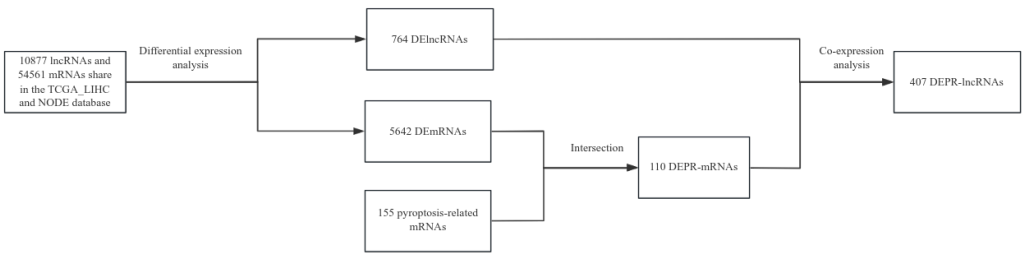


Figure. 1 The data flow diagram of the data collection for DEPR-lncRNAs.

Comment 6: Page 10, line 241, where are the list including the 595 DEPR-lncRNA?
Reply 6:
Thanks to the reviewer's suggestion. The list of 595 DEPR-lncRNA has been added to the supplementary material in Table S4.
Changes in the text:
We have made the necessary revisions to our text Table S4 of the supplementary material in our revised manuscript to ensure that both the reviewers and readers can easily access this information.

Comment 7: Page 11, line 259, the authors stated "leaving a total of 346 HCC patients" from which database? Also at line 264 the authors should mention based on which parameters the 346 HCC patients were segregated into high- and low-risk groups. Furthermore, the "calculation formula of the RS" (line 263) is meaningless to me and it might be more appropriate in a supplementary material and method section.
Reply 7:
We are grateful for the reviewer's suggestion, which have help us improve our manuscript.

The 346 HCC patients were derived from the TCGA-LIHC database. This information has been updated on Page 11, Line 275 of our revised manuscript.

Regarding "based on which parameters 346 HCC patients were segregated into high- and low-risk groups", the stratification was based on the median risk score (RS), calculated using the RS formula mentioned in our manuscript (on Page 12, Line 279). Patients with an RS above the median value were categorized into the high-risk group, whereas those with and RS below the median were assigned to the low-risk group.

Although the calculation formula for the RS has already been provided in the methods section, the reason for presenting the formula again in this section is not only for the convenience of the reader but also to highlighting our results, particularly those lncRNAs that have been identified in our study.

Changes in the text:
On Page 11, Line 275, we have changed our text to
"leaving a total of 346 HCC patients from TCGA-LIHC database.".

Comment 8: Page 14, line 294, which list of gene was used to perform the GSEA?
Reply 8:
Thanks to the reviewer for pointing this out. There are two gene sets that we used when performing GSEA, including h.all.v7.0.symbols.gmt (Page 9, Line 208) and c2.cp.kegg.v7.5.1.symbols.gmt (Page 9, Line 208). These two gene sets are also available download on the website (https://www.gsea-msigdb.org.).
Changes in the text:

On Page 9, Line 207-209, We have changed our text to
"Specifically, based on the Hallmarks gene set "h.all.v7.0.symbols.gmt" and the gene set "c2.cp.kegg.v7.5.1.symbols.gmt" from the MSigDB database, GSEA was carried out through GSEA software [27, 28] and clusterProfiler package (Version 4.8.2) [29]."

Comment 9: Page 15, line 307, again, the authors do not provide the list of genes that were used to run CIBERSORT analyses. Is this the same as the GSEA?
Reply 9:
Thanks to the reviewer for pointing this out. The list of genes used for CIBERSORT analysis is different from GSEA. CIBERSORT analysis uses 22 immune cell types as the list of genes (Page 9, Line 220-221), which is also added to Table S5 of supplementary material.
Changes in the text:
We have added Table S5 of the supplementary material in the revised manuscript.

Comment 10: Page 15, line 315, the author stated "However, the high-risk group showed higher tumor purity compared to the low-risk group". What does it mean "higher tumor purity" in this context? A minimal of explanation is required, unless a potential reader is not familiar with the tools, he/she will not understand and stop reading your work.
Reply 10:
Thanks to the reviewer for this valuable insight. We fully agree with that we should give a minimal of explanation of higher tumor purity. Actually, tumor purity is defined as the proportion of tumor cells compared to normal cells. Through applying ESTIMATE algorithm, we can obtain the tumor purity of high- and low-risk groups, where the high-risk group showed higher tumor purity compared to the low-risk group in Fig. 5d (Page 16, Line 334).
Changes in the text:
On Page 15, Line 331-333, we have changed our text to
"However, the high-risk group showed higher tumor purity compared to the low-risk group (Fig. 5d), where tumor purity represents the proportion of tumor cells compared to normal cells.".

Comment 11: Page 16, line 326, the author selected/analyzed, based on certain parameter 335 patients. From which database are these patients? Also, I could not follow which subset of genes was used to perform the personalized drug susceptibility analyses.
Reply 11:
Thanks to the reviewer's valuable comments.

The 335 patients for our study were selected from TCGA-LIHC database. This selection was made after patients with incomplete mutation data were excluded to ensure the reliability of our analysis.

Regarding the personalized drug susceptibility analyses, the data in Cancer Genome Project and the gene expression profile from TCGA-LIHC database were used to perform the personalized drug susceptibility analyses, which were extracted from RNA-seq data (Page 6, Line 142-143). To explore differences in therapeutic effects of chemotherapeutic drugs in patients between the high- and low-risk patients and validate the effectiveness of PLPI, we used the pRRophetic package to perform drug analyses.

Changes in the text:
1. On Page 16, Line 343-345, we have changed our text to
"We compared the somatic mutations of 335 patients with complete mutation data from the TCGA-LIHC database who were divided into high- and low-risk groups based on the median RS of the training set.".

2. On Page 10, Line 235-237, we have changed our text to
"In this study, the gene expression and drug sensitivity data from cell lines in Cancer Genome Project (https://www.sanger.ac.uk/group/cancer-genome-project/) and gene expression data from TCGA-LIHC database were used in the drug analysis.".

Comment 12: The discussion is too long, and based on what the authors have shown/included in their submitted work, I am not sure that the data support their conclusion. In the introduction/discussion/conclusion the authors stated multiple times that they have identified "10 pyroptosis-related lncRNA pairs" that could be used as novel prognostic model. However, I could not find these lncRNAs listed anywhere is their work.
Reply 12:
Thank you for your valuable feedback. We understand your concerns regarding the connection between the discussion and the data supporting our conclusions. In our manuscript, the discussion section is indeed constructed and discussed based on the experimental results presented in the results section. We have carefully reviewed our data and the corresponding details within the discussion to make sure how our conclusions are substantiated by the findings in our study.

Regarding the identification of the "10 pyroptosis-related lncRNA pairs", we realize that the omission of a clear and accessible list of these lncRNAs within our manuscript may have caused confusion. To rectify this, we have now included a table listing these lncRNA pairs in Table S7 of the supplementary material.

Changes in the text:
On Page 11, Line 266-267, we have changed our text to
"Finally, we identified 10 DEPR-lncRNA pairs by the above multiple algorithms for constructing the PLPI, which is shown in Table S7 of supplementary material.".

Reviewer B

Comment 1: Please provide the full name of "AUC" in the abstract and "TCGA-LIHC" "NODE" "mRNAs" "RNA-seq" "C-index" "HR" "CI" "FDR" "NES" "mTOR" "PPAR" in the main text. Please also check through your article to make sure **all** the abbreviated terms have been defined when they **FIRST** appear in the Abstract and the main text.

Reply 1: Thank you for your valuable feedback. We have provided the full name of "AUC" in the abstract, and "TCGA-LIHC" "NODE" "mRNAs" "RNA-seq" "C-index" "HR" "CI" "FDR" "NES" "mTOR" "PPAR" in the main text. We have also ensured that all the abbreviated terms are defined when they first appear in the abstract and the main text.

Comment 2: Please provide the full name of "lncRNA" in the highlight box.

Reply 2: According to your suggestion, the full name of "lncRNA" has been provided in the highlight box as "long non-coding RNA".

Comment 3: Figures and Table

Reply 3: Thank you for your suggestions regarding the Figures and Table. We appreciate your assistance in enhancing the presentation of our work. We have carefully reviewed your recommendations and have made the appropriate modifications. All the revised Figures and Table have been uploaded as supplementary materials. The specific comments and our responses are as follows:

Comment 3 (1): Do not insert Figures/Table in the main text. Please remove them from the main text.

Reply 3 (1): We have removed the Figures and Table from the main text.

Comment 3 (2): Please provide an **editable** version of Figure 1 as a stand-alone **WORD/PPT** file, so that the editor can slightly and properly adjust the lines and structures, and text during the editing.

Reply 3 (2): We have prepared an editable version of Figure 1 in PowerPoint format. The file has been uploaded as supplementary material to the revised manuscript.

Comment 3 (3): All abbreviations in figures/table and legends should be explained. "RNA-seq" "TCGA-LIHC" "NODE" "lncRNAs" "mRNAs" "REOs" "PLPI" in Figure 1, and "HR" "CI" in Table 1 for example. Please check all abbreviations and provide the full names in the corresponding figure legend/table foot.

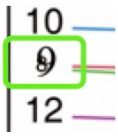
Reply 3 (3): We have carefully reviewed all the Figures and Tables in the manuscript, to ensure that all the abbreviations are provided the full names in the corresponding figure legend or table foot.

Comment 3 (4): Please use **uppercase letters A, B, C**,… to number and cite the subparts of a

figure, such as Figure 2A. Please check through and revise.

Reply 3 (4): We have reviewed our manuscript and revised the labeling of all figure subparts. Each subpart is now numbered with uppercase letters as suggested.

Comment 3 (5): The numbers are not clear enough in Figure 2.



Reply 3 (5): We have taken steps to enhance the legibility of the numerical data in Figure 2, to ensure that all numbers are clear and easily readable.

Comment 3 (6): Figures should be cited **consecutively** in the text and numbered in the order in which they are discussed. Therefore, Figure 3c should be cited before Figure 3d, 3e, unless Figure 3 is cited as a whole before. Figure 4b should be cited before Figure 4c. Please check through and revise.

Reply 3 (6): We have thoroughly reviewed the manuscript and adjusted the citations to ensure that they are mentioned in a consecutive order, in accordance with their discussion in the main text.

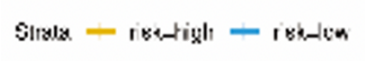
Comment 3 (7): Please add unit for **Time** in Figure 3a-3c.

Reply 3 (7): We have already added the appropriate units for Time in Figure 3A-3C.

Comment 3 (8): Please revise “p” to “P” in Figure 3a-3c and Figure 7.

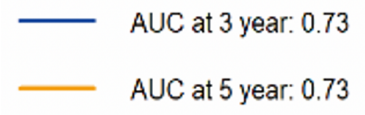
Reply 3 (8): Figure 3A-3C and Figure 7 have been carefully reviewed, and we already corrected the notation for the p-value from “p” to “P”.

Comment 3 (9): Please provide Figure 3, 7 in higher resolutions. Some words are not clear enough.



Reply 3 (9): We have generated new versions of Figure 3 and Figure 7 at a higher resolution, which ensures that all words and details within the Figures are clear and easily legible.

Comment 3 (10): Please revise “3/5/4 year” to “3 years” “5 years” “4 years” in Figure 3d-3f.



Reply 3 (10): We have already revised “3/5/4 year” to “3 years”, “5 years”, and “4 years” in Figure 3D-3F.

Comment 3 (11): Please recheck the P value in the following sentence.

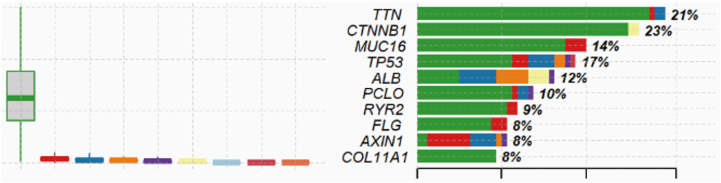
differences in 18 types of immune cells (Fig. 5b). Additionally, ESTIMATE analysis revealed that the stromal score, immune score and estimate score were higher in the low-risk group than those in the high-risk group (Fig. 5c, $p < 0.05$). However, the high-risk group showed higher tumor purity

Reply 3 (11): We have rechecked the P value in our manuscript and corrected the notation for the p-value from "p < 0.05 " to " P < 0.001, P < 0.01, P < 0.001".

Comment 3 (12): Please add description for the x-axes in Figure 6.

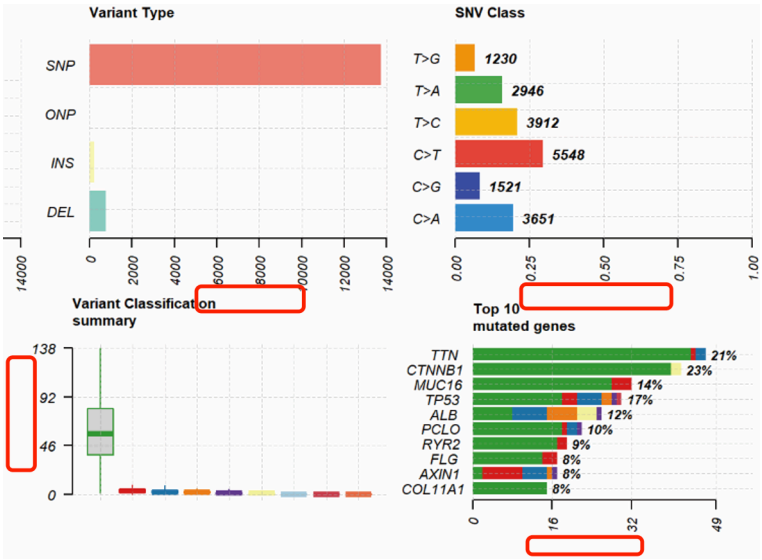
Reply 3 (12): We have already added detailed descriptions for the x-axes in Figure 6.

Comment 3 (13): Please add labels to indicate the meaning of colorful bars in Figure 6.



Reply 3 (13): We have added a legend to the Figure 6 to clearly indicate the meaning of each color used in the bars.

Comment 3 (14): Please add the description of each x/y-axis in Figure 6.

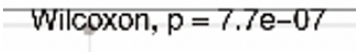


Reply 3 (14): We have already added the description of each x/y-axis in Figure 6 in our revised manuscript.

Comment 3 (15): Please indicate the meaning of "T" "C" "G" "A" in Figure 6 legend.

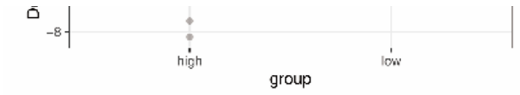
Reply 3 (15): We have updated the legend of Figure 6 to include the meaning of the letters "T", "C", "G" and "A". They represent the nucleotide bases Thymine, Cytosine, Guanine, and Adenine, respectively.

Comment 3 (16): The words/data in Figure 7 are not clear enough. Please check and revise.



Reply 3 (16): We have made the necessary adjustments to enhance the readability of the words and data presented in Figure 7.

Comment 3 (17): Please check the lines in Figure 7.



Reply 3 (17): We have carefully reviewed Figure 7 and regenerated the figures to ensure that all lines are clear.

Comment 3 (18): Please use editable text format to indicate all P values in your whole manuscript, not the image format.

drug sensitivity, is vital in determining appropriate drug options for patients. The results displayed that Erlotinib ($p < 0.0001$) and Lapatinib ($p = 0.045$) showed a lower IC50 in the low-risk group compared to the high-risk group (Fig. 7a, b), indicating that they may be effective options for this patient population. In addition, AKT inhibitor VIII ($p = 0.023$), Cytarabine ($p = 0.0097$), Docetaxel ($p < 0.0001$), Etoposide ($p < 0.0001$), Gemcitabine ($p < 0.0001$), Imatinib ($p = 0.0048$), Methotrexate ($p < 0.0001$), Paclitaxel ($p < 0.0001$), Sorafenib ($p = 0.043$), Vorinostat ($p < 0.0001$), Tipifarnib ($p < 0.0001$), and Vinblastine ($p < 0.0001$) showed lower IC50 in the patients in the high-risk group compared to the low-risk group (Fig. 7 c-n).

Reply 3 (18): We have revised our manuscript accordingly and replaced any instance where P values were previously presented in image format with editable text.

Comment 3 (19): Please indicate the meaning of "**a**" in Table 1.

Reply 3 (19): The meaning of "a" represents the variable derived from the risk score model proposed in our study. To facilitate the reader's understanding, we have added a footnote to Table 1 to clarify the meaning of "a" in our revised manuscript.

Comment 3 (20): Please add unit for **Age** in Table 1.

Reply 3 (20): We have added the unit for Age in Table 1, which is "years".

Comment 4: Supplementary

- The citation of Table S2-S4 is missing in the text.
- Please revise the name of the supplementary figure 1 to Figure S1.
- Please provide an **editable** version of Figure S1, so that the editor can slightly and properly adjust the lines and structures, and text during the editing.

- **All abbreviations** in the supplementary figure/tables and legends should be explained. “DEPR-lncRNAs” “mRNAs” “TCGA-LIHC” “NODE” “DElncRNAs” “DEmRNAs” “DERP-mRNAs” in Figure S1, and “DElncRNAs” in Table S2 for example. Please check all abbreviations and provide the full names in the corresponding figure legend/table foot.

Reply 4: Thank you for your detailed comments regarding the supplementary materials. We have revised our manuscript according to your suggestions as follow:

We have reviewed the manuscript and added the missing citations for Table S2-S4 to the main text, which ensure that all supplementary tables are properly referenced.

The name of the supplementary figure 1 has been revised to Figure S1 as request.

An editable version of Figure S1 has been provided to facilitate any necessary adjustments by the editor during the editing process.

We have thoroughly checked all the abbreviations used in the supplementary figure/tables and legends. The full name of all the abbreviations have been provided in the corresponding figure legend or table footnotes.