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## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1374>

### Reviewer A

The study has been comprehensively written and well done. The final takeaway points are difficult to understand, especially for clinicians. Would recommend to simplify the language and explain it in a more reader friendly manner, if feasible.

This is an important clinical question. The authors have presented a very comprehensive analysis. I would recommend review of the methodology and results by an experienced pathologist and bio-informatics specialist prior to publication to ensure accuracy of the data. If found acceptable, then the data would be useful for clinicians.

Comment 1: The final takeaway points are difficult to understand, especially for clinicians. Would recommend to simplify the language and explain it in a more reader friendly manner, if feasible.

Reply 1: Thanks for your comments, we have simplified the conclusion

Changes in the text: see Page 18mlin, 591-593.

Comment 2: I would recommend review of the methodology and results by an experienced pathologist and bio-informatics specialist prior to publication to ensure accuracy of the data. If found acceptable, then the data would be useful for clinicians.

Reply 2: Thank you for your comments. The bioinformatics methods used in this study have been verified in other published articles and are reliable (PMID: 34957118, PMID: 33097495). Besides, we will further verify the reliability of the model genes at the clinical and cellular levels in the future.

Changes in the text: NA

### Reviewer B

While the proposed study appears to have valuable findings, there are some concerns that should be considered:

1. The study is based on data from the TCGA database, which is a valuable resource but has limitations, including potential heterogeneity in data quality and patient characteristics.
2. The development of the IRGPI model is described, but it's essential to provide details on the statistical methods used for feature selection and model building. Additionally, external validation of the model's performance is crucial to ensure its generalizability.
3. The study should provide clear and transparent details about the specific immune-related genes (IRGs) used in the analysis, the criteria for selecting differentially expressed immune-related genes (DEIRGs), and the weighting scheme for the IRGPI.
4. While the study focuses on molecular and immune characteristics, it's important to discuss

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the clinical relevance of the findings. How could the IRGPI be used in clinical practice? Does it provide insights that could inform patient management or treatment decisions?

5. The study identifies associations between the IRGPI and various biological features, such as mutation rates and immune cell infiltration. However, a deeper biological interpretation of these associations is needed to understand the underlying mechanisms.

6. External validation using independent datasets is critical to confirm the robustness of the IRGPI and its associations with patient outcomes.

7. More references on bioinformatics-based workflow should be added to attract a broader readership i.e., PMID: 36936815, PMID: 35851932.

8. The study suggests that the high-risk group may benefit more from immune checkpoint inhibitor (ICI) therapy based on TIDE score. However, it's essential to validate these findings with real-world clinical data on ICI treatment responses.

9. The study should explicitly discuss its limitations, including those related to data sources, model assumptions, and potential sources of bias.

10. Discussing potential future research directions based on the study's findings can provide context for the significance of the work.

Comment 1: The study is based on data from the TCGA database, which is a valuable resource but has limitations, including potential heterogeneity in data quality and patient characteristics.

Reply 1: Data from the TCGA database do have limitations including potential heterogeneity in data quality and patient characteristics. However, in view of the lack of data set selection from more large-sample databases, the data from the TCGA database is still a reliable choice. In addition, in the application of data samples, we deleted samples that lacked survival time, age, gender and other data

Changes in the text: NA

Comment 2: The development of the IRGPI model is described, but it's essential to provide details on the statistical methods used for feature selection and model building. Additionally, external validation of the model's performance is crucial to ensure its generalizability.

Reply 2: In the development process of the IRGPI model, we have introduced the statistical methods of model construction in detail in the article, and the selection of various thresholds is also clearly marked. However, the criteria for selecting the wgcna module are not clearly explained. WGCNA has determined 4 modules, 3 of which are tumor-related, have p-values less than 0.05. We integrate the genes of these three modules for subsequent research, and  $p < 0.05$  is used as a tumor-related standard, which has been described in the manuscript

Changes in the text: see Page 8, line 262.

Comment 3: The study should provide clear and transparent details about the specific immune-related genes (IRGs) used in the analysis, the criteria for selecting differentially expressed immune-related genes (DEIRGs), and the weighting scheme for the IRGPI.

Reply 3: Immune-related genes (IRGs) were obtained from the InnateDB database (<https://www.innatedb.ca/>) and the immunology database and analysis portal (ImmPort; <https://www.immport.org/home>) (accessed July 31, 2021). We did not do any special screening, we just integrated and utilized the immune-related genes from the two databases. The

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"Duplicate genes were removed" in the manuscript may cause misunderstanding, and we have deleted it (see Page 5, line 148). To select differentially expressed immune-related genes (DEIRGs), we used the limma package to evaluate in TCGA lung adenocarcinoma samples with a cutoff criteria  $|\log_2 \text{ fold-change}| > 1$  and false discovery rate (FDR)  $< 0.05$ . The differentially expressed genes were screened out, and then intersect with the above IRGs, the intersection genes are DEIRGs.

Changes in the text: see Page 5, line 152.

Comment 4: While the study focuses on molecular and immune characteristics, it's important to discuss the clinical relevance of the findings. How could the IRGPI be used in clinical practice? Does it provide insights that could inform patient management or treatment decisions?

Reply 4: Clinicians can detect the expression of 13 model genes in patients, then use our formula to calculate the patient's IRGPI, initially assess the patient's prognosis, and then combine it with the patient's clinical information to use our nomogram to better predict the 1-, 3-, and 5-year survival of patients. In addition, patients classified into high-risk groups may be more inclined to be given certain immunotherapy.

Changes in the text: NA

Comment 5: The study identifies associations between the IRGPI and various biological features, such as mutation rates and immune cell infiltration. However, a deeper biological interpretation of these associations is needed to understand the underlying mechanisms.

Reply 5: Thank you for your suggestion. Indeed, the association between IRGPI and various biological features requires a deeper biological interpretation and a lot of work. We will gradually improve it in subsequent research.

Changes in the text: NA

Comment 6: External validation using independent datasets is critical to confirm the robustness of the IRGPI and its associations with patient outcomes.

Reply 6: Thank you for your comment. To further validate the reliability of the IRGPI risk score, an independent cohort of 442 LUAD samples, GSE72094, was obtained from the Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>), along with transcriptomic data and clinical outcomes as an independent dataset for external validation in the manuscript, and the results confirm the generalizability of IRGPI in different datasets. see Page 5, line 140-143.

Changes in the text: NA

Comment 7: More references on bioinformatics-based workflow should be added to attract a broader readership i.e., PMID: 36936815, PMID: 35851932.

Reply 7: Thanks for your suggestions, we have added the latest published references on bioinformatics-based workflow in the Discussion section and compared the models they built with ours. (PMID: 37197492, PMID: 37745054), see Page 17, line 571.

Changes in the text: see Page 17, line 571.

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Comment 8: The study suggests that the high-risk group may benefit more from immune checkpoint inhibitor (ICI) therapy based on TIDE score. However, it's essential to validate these findings with real-world clinical data on ICI treatment responses.

Reply 8: Thank you for your comment, real-world clinical data on ICI treatment response is a focus of our future clinical studies

Changes in the text: NA

Comment 9: The study should explicitly discuss its limitations, including those related to data sources, model assumptions, and potential sources of bias.

Reply 9: Thanks for your suggestion, we have changed the discussion of limitations based on your suggestion

Changes in the text: see Page 17-18, line 574-576.

Comment 10: Discussing potential future research directions based on the study's findings can provide context for the significance of the work.

Reply 10: Thanks for your suggestions, we have added potential future research directions to the discussion.

Changes in the text: see Page 18, line 584-587.

### **Reviewer C**

The authors attempted to explore a prognostic marker for LUAD based on immune-related genes (IRGs), which could predict a patient's outcome and the benefit of ICI treatment. They also used the GSE72094 cohort to verify the results, which showed that the results are consistent with those of The Cancer Genome Atlas (TCGA). Finally, the molecular and tumor microenvironment (TME) characterization of IRGPI was verified and its prognostic predictive ability in patients with immunotherapy was validated, and contrasted with other immunotherapy biomarkers, angiogenesis-related genes (ARGs), tumor immune dysfunction and exclusion (TIDE), and tumor inflammation signature (TIS). Albeit, I consider these findings to provide new insight into cancer-related fields, I still have some suggestions.

1, Most figures are highly professional; however, the authors should guide the readers to the meaning of the images appropriately; otherwise, it will likely cause misunderstandings. Therefore, I suggest the author consider revising these figure legends again.

2, The author established an immune-related gene prognostic index (IRGPI) for lung adenocarcinoma (LUAD) based on immune-related genes (IRGs). Since the authors gave a general answer on gene and protein expression, is there any evidence of different roles in cancer phenotypes of these genes? Please perform pertinent bioinformatic analyses and provide examples of studies investigating miRNA alteration or DNA methylation (<https://biit.cs.ut.ee/methsurv/>)(PMID: 29264942, 34834441, 33437202).

3, The author may need to use other statistical analyses, such as ANOVA to calculate the P-value for three or more groups of data, and please update the "Statistical Analysis" of the Method during further revision (PMID: 37274638, 34329194, 34400890).

4, Since Connectivity Map (CMap) can be used to discover the mechanism of action of small

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molecules, functionally annotate genetic variants of disease genes, and inform clinical trials. It would be fascinating if these data could be correlated with other clinical databases. Therefore, I suggest the authors can validate their data via CMap, and discuss these methodologies and literature in the manuscript (PMID: 17008526, 29195078, 32064155).

5, There are few typo issues for the authors to pay attention to; please also unify the writing of scientific terms. “Italic, capital”? Please double-check superscripts and subscripts for the whole manuscript.

6, Most references are out of date, the author needs to discuss the recent paper as well as the analysis methods in this manuscript. Meanwhile, the introduction part needs to be rewritten and present the purpose of the investigation and cite pertinent literature.

7, The font is too small for some of the current figures.

Comment 1: Most figures are highly professional; however, the authors should guide the readers to the meaning of the images appropriately; otherwise, it will likely cause misunderstandings. Therefore, I suggest the author consider revising these figure legends again.

Reply 1: Thanks for your suggestion, we have modified the annotations for Figure 1A-B

Changes in the text: see Page 30, line 933-934

Comment 2: The author established an immune-related gene prognostic index (IRGPI) for lung adenocarcinoma (LUAD) based on immune-related genes (IRGs). Since the authors gave a general answer on gene and protein expression, is there any evidence of different roles in cancer phenotypes of these genes? Please perform pertinent bioinformatic analyses and provide examples of studies investigating miRNA alteration or DNA methylation (<https://biit.cs.ut.ee/methsurv/>)(PMID: 29264942, 34834441, 33437202).

Reply 2: Thank you for your comments. In the discussion we have described the general answers to model gene and protein expression. Most of these results are based on experimental studies, so we thought to perform relevant bioinformatics analysis and provide information to investigate miRNA changes or Examples of studies on DNA methylation are not necessary.

Changes in the text: see Page 13-15, line 432-485.

Comment 3: The author may need to use other statistical analyses, such as ANOVA to calculate the P-value for three or more groups of data, and please update the “Statistical Analysis” of the Method during further revision (PMID: 37274638, 34329194, 34400890).

Reply 3: Thank you for your opinion. At present, no obvious errors have been found in the statistical methods we used (PMID: 34796177), and other statistical methods are not considered for the time being.

Changes in the text: NA

Comment 4: Since Connectivity Map (CMap) can be used to discover the mechanism of action of small molecules, functionally annotate genetic variants of disease genes, and inform clinical trials. It would be fascinating if these data could be correlated with other clinical databases. Therefore, I suggest the authors can validate their data via CMap, and discuss these methodologies and literature in the manuscript (PMID: 17008526, 29195078, 32064155).

Reply 4: Thank you for your suggestion. We are also very interested in Connectivity Map (CMap). Through understanding of relevant research, we plan to conduct online analysis from Connectivity Map (CMap, <https://portals.broadinstitute.org/cmap/>) (PMID: 33717423). Unfortunately, due to the update of the online platform, data of less than 10 genes can no longer be analyzed. Therefore, we used the SPIED3 (<http://212.48.67.52/cgi-bin/HGNC-SPIED3.cgi>) online analysis tool to conduct a preliminary study on the IRGPI model gene (PMID: 35368048) (Table 1). We identified a total of 20 drugs: Prestwick-1084, (+)-isoproterenol, deferoxamine, ergot, fluthiazide, galantamine, piperidine, fluocinolone, flunisolide, LM- 1685, vidarabine, novobiocin, calcium leucovorin, arecoline, thapsigargin, chlorhexidine, lincomycin, ondansetron, guanaben, methoxamine. Given that this online analysis platform is rarely used in published studies, we made a considered decision not to use this data in the manuscript. However, we will conduct relevant research based on this result in the future to verify its accuracy.

(Table 1) (The table is based on the IRGPI model gene and is created by the SPIED3 (<http://212.48.67.52/cgi-bin/HGNC-SPIED3.cgi>) online analysis tool.)

COMPOUND	skew	log(p)
<a href="#">Prestwick-1084</a>	1.00	-5.12(6)
<a href="#">(+)-isoprenaline</a>	1.00	-4.18(3)
<a href="#">deferoxamine</a>	0.71	-5.68(7)
<a href="#">lysergol</a>	1.00	-3.81(3)
<a href="#">bendroflumethiazide</a>	1.00	-3.58(4)
<a href="#">galantamine</a>	1.00	-3.40(3)
<a href="#">pempidine</a>	0.60	-5.14(5)
<a href="#">fluocinonide</a>	0.67	-4.41(6)
<a href="#">flunisolide</a>	0.67	-3.94(6)
<a href="#">LM-1685</a>	0.50	-3.88(4)
<a href="#">vidarabine</a>	0.50	-3.58(4)
<a href="#">novobiocin</a>	-0.50	-3.91(4)
<a href="#">calcium folinate</a>	-0.67	-3.98(6)
<a href="#">arecoline</a>	-0.60	-4.62(5)
<a href="#">thapsigargin</a>	-1.00	-3.01(5)
<a href="#">chlorhexidine</a>	-1.00	-3.16(3)
<a href="#">lincomycin</a>	-1.00	-3.49(3)
<a href="#">ondansetron</a>	-1.00	-3.56(3)
<a href="#">guanabenz</a>	-0.67	-5.81(6)
<a href="#">methoxamine</a>	-1.00	-4.10(3)

Changes in the text: NA

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Comment 5: There are few typo issues for the authors to pay attention to; please also unify the writing of scientific terms. "Italic, capital"? Please double-check superscripts and subscripts for the whole manuscript.

Reply 5: Thank you for your comments. We have carefully checked the "italics, capitals" in the manuscript, and we have not found errors. For example, page 11, line 357-362, capitals represent proteins, and we use the expression level of the gene for verification, so it is in italics. If there are still errors that we have overlooked, can you please point them out clearly? Thank you!

Changes in the text: NA

Comment 6: Most references are out of date, the author needs to discuss the recent paper as well as the analysis methods in this manuscript. Meanwhile, the introduction part needs to be rewritten and present the purpose of the investigation and cite pertinent literature.

Reply 6: Thank you for your comments. We have updated some of the references in the introduction and modified the part about the purpose of the investigation in the introduction.

Changes in the text: see Page 4, line 110-114.

Comment 7: The font is too small for some of the current figures.

Reply 7: Thank you for your reminder, we have increased the font size in Figure 1.

Changes in the text: Figure 1.

#### **Reviewer D**

The study "Development and Validation of an Immune-Related Gene Prognostic Index for Lung Adenocarcinoma" presents a comprehensive and well-structured investigation into establishing an Immune-Related Gene Prognostic Index (IRGPI) for lung adenocarcinoma (LUAD) based on immune-related genes (IRGs).

Addressing limitations of the study, such as potential biases or constraints in the dataset, and proposing future directions for research based on the findings would add depth to the discussion and provide a more complete view of the study's scope and potential avenues for further exploration.

The study demonstrates a robust methodology and provides valuable insights into the prognostic potential of the IRGPI in LUAD. The findings have significant clinical implications and contribute to our understanding of the role of immune-related genes in LUAD prognosis and treatment. Addressing the suggested improvements would further enhance the clarity and impact of the research.

Comment 1: Addressing limitations of the study, such as potential biases or constraints in the dataset, and proposing future directions for research based on the findings would add depth to the discussion and provide a more complete view of the study's scope and potential avenues for further exploration.

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Reply 1: Thank you for your comments. Regarding this issue, we have added future research directions at the end of the discussion.

Changes in the text: we will clinically measure the expression of 13 model genes in patients with lung adenocarcinoma to predict patient prognosis, and verify the predictive ability of the prognostic model in practice through long-term follow-up. (see Page 18, line 584-587).

### **Reviewer E**

In this manuscript, Liu et. al. have explored the prognostic significance of immune gene signature in lung cancer. This is an interesting manuscript, however, there are several areas that need improvement:

1. The authors need to provide more details on the data analysis part. What was the raw data used for initial analysis? For example, FPKM data, as processed counts are not a useful metric for comparison across samples. These, along with TPM, RPKM, and FPKM, can lead to spurious results.
2. The lack of clinical validation using internal cohorts:- (Authors need to use clinical samples and validate the prognostic or higher/lower expression in samples. They can use a variety of techniques, most prominently real-time PCR or protein detection). Refer : Wu, Pu, Jinyuan Shi, Wei Sun, and Hao Zhang. "Identification and validation of a pyroptosis-related prognostic signature for thyroid cancer." *Cancer cell international* 21, no. 1 (2021): 1-16.
3. Although the authors have presented results, they need to validate the accuracy of their model using independent datasets. Validation should be conducted using separate datasets.
4. The authors should compare their model's predictive power to other recently published models. This comparison should provide an overview of the model's precision and performance in comparison to other models (the authors can add a new table for this comparison).
5. Absence of hazard ratios in Kaplan Meier curves: - The hazard ratio of each individual gene or gene signature, along with the 95% confidence interval, is required to illustrate the statistical importance of genes/signature.

Comment 1: The authors need to provide more details on the data analysis part. What was the raw data used for initial analysis? For example, FPKM data, as processed counts are not a useful metric for comparison across samples. These, along with TPM, RPKM, and FPKM, can lead to spurious results.

Reply 1: Thanks for the reminder that FPKM data tend to perform poorly as treatment counts for cross-sample comparisons. However, the scientific community does not seem to have reached a consensus on which RNA-seq quantitative method should be used for cross-sample comparisons due to the lack of experimental data generated from different types of replicates for further validation. Many recent peer-reviewed articles as well as publicly available databases still use TPM or RPKM/FPKM for summary data analysis, cross-sample comparisons, and differential expression analysis (PMID: 33747902, PMID: 37025600, PMID: 32913098, PMID: 32355273). This study uses standardized FPKM data for correlation analysis (PMID: 34796177).



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Changes in the text: see Page 5, line 139.

Comment 2: The lack of clinical validation using internal cohorts:- (Authors need to use clinical samples and validate the prognostic or higher/lower expression in samples. They can use a variety of techniques, most prominently real-time PCR or protein detection). Refer : Wu, Pu, Jinyuan Shi, Wei Sun, and Hao Zhang. "Identification and validation of a pyroptosis-related prognostic signature for thyroid cancer." *Cancer cell international* 21, no. 1 (2021): 1-16.

Reply 2: Thanks for your comment. The lack of clinical validation is indeed a shortcoming of our research. We will improve this part in future research.

Changes in the text: NA.

Comment 3: Although the authors have presented results, they need to validate the accuracy of their model using independent datasets. Validation should be conducted using separate datasets.

Reply 3: To further verify the reliability of the IRGPI risk score, we obtained an independent cohort of 442 LUAD simple samples GSE72094 from the Gene Expression Omnibus (GEO) database, and the results demonstrated that the IRGPI risk score is equally reliable in different samples. see Page 9, line 303

Changes in the text: NA

Comment 4: The authors should compare their model's predictive power to other recently published models. This comparison should provide an overview of the model's precision and performance in comparison to other models (the authors can add a new table for this comparison).

Reply 4: Thanks for your comments, we have added a discussion comparing accuracy and performance with other models (PMID: 37197492, PMID: 37745054), see Page 17, line 571

Changes in the text: The model we constructed has certain advantages. By comparing with other recently released models, our model has higher reliability and stronger pertinence. ROC analysis shows that the predictive value of our prognostic model is better than other models, and for the predictive ability of 1-year, 3-year, and 5-year survival times, our calibration curve showed high accuracy between actual incidence and predicted incidence better than other models (PMID: 37197492, PMID: 37745054). And the deep combination of this model with immunity has significant advantages in predicting the efficacy of immunotherapy.

Comment 5: Absence of hazard ratios in Kaplan Meier curves: - The hazard ratio of each individual gene or gene signature, along with the 95% confidence interval, is required to illustrate the statistical importance of genes/signature.

Reply 5: Thanks for your comments, we have shown the hazard ratios for the model genes along with 95% confidence intervals in Figure 3A.

Changes in the text: NA

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## **Reviewer F**

Liu et al. explore a prognostic marker for LUAD based on immune-related genes (IRGs), which

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could predict a patient's outcome and the benefit of ICI treatment. An immune-related gene prognostic index (IRGPI) of LUAD was established by exploiting weighted gene co-expression network analysis (WGCNA) using transcriptomic data and clinical outcomes. Univariate and multivariate Cox regression analysis were utilized to recognize differentially expressed immune-related genes (DEIRGs) associated with survival, and then to build IRGPI, a quantitative score that distinguishes between low and high risk of prognosis. The following comments in this regard are below:

1) There are a lot of papers published in this field but the authors did not discuss it here, need to discuss and write your contribution and the novelty of this work.

Reply: Thanks for your suggestion, we've added it to the Discussion section.

Changes in the text: page 17-18, line 566-587.

2) The authors need to mention the steps of pre-processing (i.e., normalization, log transformation) and batch-correction corresponding to the RNA-seq data both in methods and results section. The authors can have a look at these papers for more clarity: <https://www.sciencedirect.com/science/article/pii/S277304412300013X>, <https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.881246/full>.

Reply: Thanks for the reminder, we have mentioned the pre-processing corresponding to RNA-seq data in the methods section.

Changes in the text: page 5, line 139.

3) The authors need to mention the values of scale-free topology and beta based on which the dendrogram was constructed. Also, please mention, why the 0.3 cutoff was used for merging? From figure 1C, it doesn't seem that the scale-free topology meets the network, and how come the authors have chosen beta here? Why the grey module was not discarded for further analysis as it contains unassigned genes?

Reply: Thank you for your reminder. The threshold of 0.3 was what we originally planned to set for the gene correlation network diagram within the module. It is not the soft threshold of WGCNA. We have modified it in the text. In addition, we did not use the grey module, and we only used the blue, brown, and turquoise modules in subsequent research (see page 8, line 259)

Changes in the text: page 6, line 176-177.

4) What was the need to use GSEA? Please explain. Please mention the cutoff used for significant terms/pathways screened.

Reply: We used GSEA to understand the enrichment pathways of different groups, and will conduct follow-up targeted research in the future. Furthermore, our description of the subjects of the GSEA analysis was not very accurate, so we revised the manuscript.

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Changes in the text: page 6, line 179 and page 6-7, line 197-205.

5) It would be really interesting to note the RFS pattern along with OS. I insist the authors to draw ROC plot showing AUC of the prognostic model.

Reply: Dear reviewer, thank you for your suggestion, but we have already conducted a ROC analysis on the IRGPI score prediction OS. See Figure 9 for details.

Changes in the text: NA

6) The quality of all figures are poor and their resolution needs to be improved thoroughly.

Reply: We've sent higher resolution images to editors.

Changes in the text: NA

7) Please mention the list of abbreviations separately.

Reply: We have supplemented the list of abbreviations at the end of the manuscript

Changes in the text: page 34-35, line 1018-1067.

8) Limitations, novelty, strength, and future study prospects must be mentioned in the Discussion section.

Reply: Thanks for your suggestions, we have added the limitations, novelty, strength, and future study prospects of the IRPGI score prognosis model in the Discussion section.

Changes in the text: page 17-18, line 566-587.

9) Use italics throughout the manuscript for any gene names.

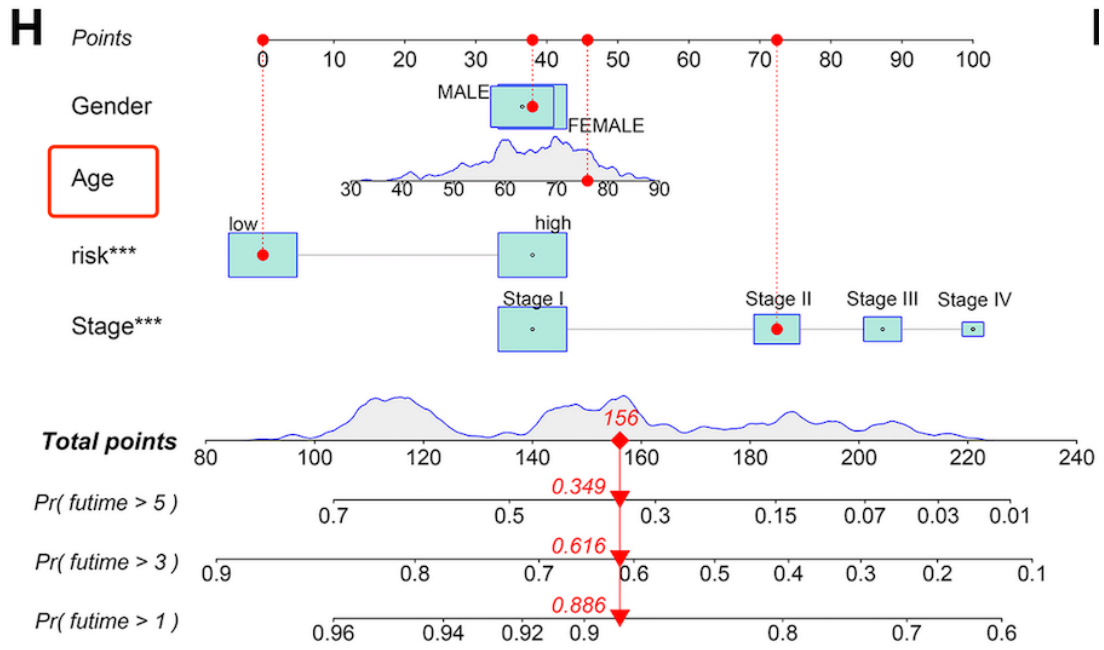
Reply: Thank you for your comments. We have carefully checked the "italics" in the manuscript, and we have not found errors. For example, page 11, line 357-362, capitals represent proteins, and we use the expression level of the gene for verification, so it is in italics. If there are still errors that we have overlooked, can you please point them out clearly? Thank you!

Changes in the text: NA

## **Reviewer G**

### 1. Figure 3H

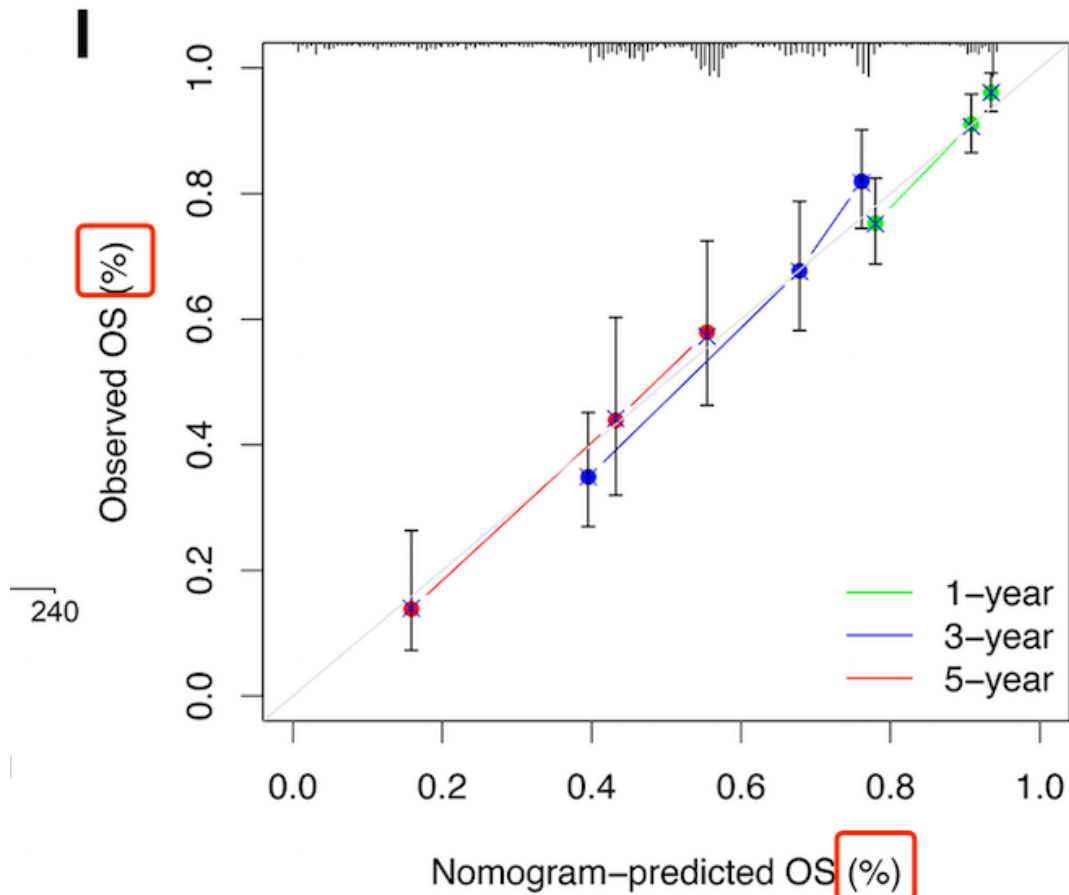
Please provide the unit for "age".



Reply: OK, thanks.

2. Figure 3I

It seems that the “%” should be deleted. Please check and revise.



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Reply: You are right, we have deleted %.

3. Figure 5

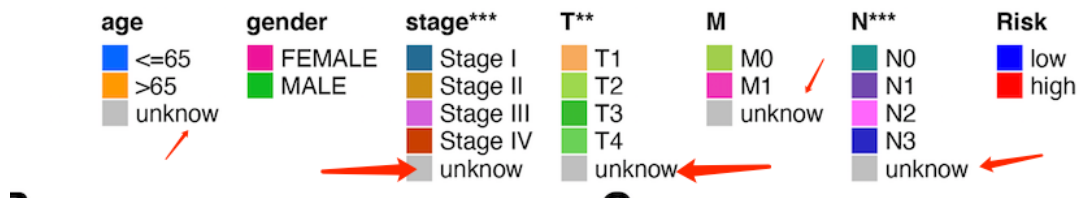
Should (C-F) be (C-P)? Please check and revise.

1107 **Figure 5** Immune features of 2 IRGPI subgroups. (A) The proportions of the 22  
1108 immune cells in 2 IRGPI groups. (B) Immune-associated functions in 2 IRGPI groups.  
1109 (C-F) Association between immune function and survival of aDCs, B cells, CD8<sup>+</sup>T

Reply: Sorry, this was our mistake, we have fixed it.

4. Figure 8A

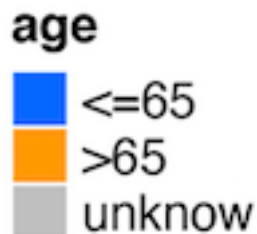
Please revise the pointed typo.



Reply: Thank you for your reminder.

5. Figure 8A

Please provide the unit for “age”.



Reply: OK, thanks.

6. Table S1

Please provide the unit for “age”.

Reply: OK, thanks.