

1 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

Thank the editor for the suggestion. We selected "ACCEPT" and revised the manuscript.

2.Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

There are many missing spaces throughout the manuscript before the parentheses or between the period and the beginning of the sentence.

After checking the version of Microsoft Word, we corrected missing spaces throughout the manuscript before the parentheses or between the period and the beginning of the sentence.

3. There is also no separation between headings and titles.

We have modified the presentation of the titles according to the Guideline.

4. The word "delinquency" does not seem appropriate.

We have revised the sentences and marked them in red in the article.

Patients in the high-risk group had significantly later clinical stages and higher levels of delinquency.

Patients in the high-risk group underwent much more distant metastases and had significantly later clinical stages.

5. Several author citations are given in the text as sole signers of articles without naming collaborators with a simple et al. You should correct this too.

Thank you for your attention, and we have corrected the citation format.

6. Finally, there are interesting articles on Tregs in rejection and/or NK cells in cancer immunosurveillance that you could cite, if it seemed appropriate to the author. These items would be:

[1] San Segundo D et al. High proportion of pretransplantation activated regulatory T cells (CD4+CD25^{high}CD62L+CD45RO⁺) predicts acute rejection in kidney transplantation: results of a multicenter study. *Transplantation*. 2014;98(11):1213-8. doi: 10.1097/TP.0000000000000202

[2] Guillamón CF. Activating KIRs on Educated NK Cells Support Downregulation of CD226 and Inefficient Tumor Immunosurveillance. *Cancer Immunol Res*. 2019;7(8):1307-1317. doi: 10.1158/2326-6066.CIR-18-0847

Thanks to the reviewers' comments, we have read the two articles recommended by the reviewer, and the two articles educated us. We have added some content to the "Discussion" of the manuscript, which is highlighted in red.

It has been proposed as candidates of bio-markers because of their capability to control alloimmune responses^[10].

Meanwhile, NK cells play a central role in cancer immune surveillance through expression up to different activating inhibitory killer-cell immunoglobulin-like

receptors^[16].

7.How has the methodology been validated, and what are its limitations?

In this study, we analyzed publicly available datasets from two databases (<https://portal.gdc.cancer.gov/> and <https://www.ncbi.nlm.nih.gov/geo/>), both with authoritative data, to predict the diagnosis and prognosis of the disease by bioinformatic analysis. The main limitation is that bladder cancer has multiple subtypes, and our model only analyzes bladder cancer in general and not specific subtypes, which is what we will do next.

8.Discussion: How does the prognostic model related to Tregs and NK cells infiltration in bladder cancer compare to other existing models for predicting patient outcomes in bladder cancer? What future directions are recommended for improving and refining this model?

The design of this study was to find mutation genes ensembles of disease to obtain common information about the disease. In this study, as many genes associated with bladder cancer as possible were included, and based on this, the association of the genes of Tregs and NK cells with bladder cancer was further explored among them. We discovered some common information about the disease from a holistic perspective, then we focus on the details of a particular mechanism to find more representative genes. However, this approach will also miss some details of individual expression of the subtypes of the disease.

The current genetic analysis of bladder cancer has been studied more frequently, and some of the models are designed to explore the association between genes and disease symptoms by extraction of differentially expressed genes; the other models are designed to consider the difference in subtypes of the disease. Screening for genes that are characteristic of a disease allows in-depth analysis of the genes associated with the characteristic, but also misses some details of the study in the pursuit of "precision".

In our follow-up study, we will consider expanding the study to several subtypes of bladder cancer to see if there are differences, and also to explore other immune-related mechanisms related to prognosis.

9.LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

This manuscript has been proofread for language by Sadrack Marcelin, a native English speaker. If the editors still feel that the manuscript should also be submitted to a professional retouching agency for retouching, we can do so.

10.ABBREVIATIONS

We have revised the manuscript for this.

11.Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

We have revised the manuscript for this.

12. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

We have corrected all figure formats and submitted editable versions via PPT "82368-Figures.pptx".

13. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

The figures of this manuscript are original, and the copyright information "Copyright ©The Author(s) 2023" has been added to the bottom right-hand side of the picture in PowerPoint (PPT).

15. We have added article highlights with reference to the requirements.

16. __COPYRIGHT LICENSE AGREEMENT AND CONFLICT-OF-INTEREST DISCLOSURE FORM

All authors accepted and signed the Copyright License Agreement (CLA), ICMJE Potential Conflict of Interest Disclosure Form and the corresponding author downloaded the signed CLA and re-saved it as a "PDF" (82368-Copyright License Agreement) and uploaded it to the "Copyright License Agreement" file destination.