Peer Review File

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Reviewer A

Comment 1: While I think that it is interesting that these factors independent of other well-known predictive indicators such as PD-L1, could separate the patients, I think it is somewhat misleading to think that these have anything to do with ICI. All of these factors are related to how sick the patient is - ie. poor PS, low BMI, high LDH and High ANC, and high ACCI - all suggest a patient who is quite ill and less likely to live long regardless of what treatment we choose rather than specific to immunotherapy. Would these factors still be at play in a cohort of patients that did not receive immunotherapy? I would predict yes. The key question in many of these patients is do we do chemoiO or just IO alone and since the vast majority of patients here had chemoIO it is difficult to make any assumnptions about that decision in this dataset. The premise that we do not understand the role of IO in patients with distant metastasis is also faulty in that nearly all of the trials of IO and chemoIO have been done on patients with advanced lung cancer - the vast majority have had distant metastasis. While it is true that they are not representative of real world patients due to good PS, there is a lot of data on patients with distant metastasis and outcomes with IO therapy.

Reply 1: Thanks for your detailed review and critical suggestions. First, it is well known that PD-L1 expression can predict prognosis among patients without distant organ metastasis prior to immunotherapy. However, in our study, the variable of PD-L1 expression level was excluded from the column chart (P = 0.487). Due to the heterogeneity of PD-L1 expression between metastatic and primary sites, PD-L1 expression may thus have limited use as a prognostic indicator in patients with distant organ metastases.

Secondly, as for the variable BMI included in our prognosis model, low baseline BMI is associated with poor prognosis and higher mortality in these patients, which conflicts with current literature described that high BMI is correlated with poor prognosis and response to chemotherapy. The results of a multicenter study on metastatic NSCLC patients with PD-L1 expression more than 50% also showed that obese patients had significantly higher ORR, PFS and OS than patients with normal weight (PMID: 33077515). More significantly, this result was not observed in patients who received chemotherapy. Actually, the microenvironment in the metastatic foci during obesity may lead to the activation and enhancement of T cells after the use of ICI.

In addition, for example, ACCI, combining age and multiple complications as a composite indicator, has been confirmed for the first time as one of the important variables of prognostic survival model in our study. As mentioned in this paper, age is not a statistically significant factor in multivariate analysis. Age itself is often insufficient to reflect the reserve capacity of organs and the risk-benefit ratio of immunotherapy. ACCI is a comprehensive index after quantifying a variety of complications and weighted age score, which can better reflect the overall functional status of patients. ACCI is mainly used in chemotherapy and surgery, while the evidence of which in immunotherapy is relatively limited

Moreover, unlike previous studies, in our real clinical study, all patients were confirmed

to have distant organ metastasis before immunotherapy. This group of people often has a poor prognosis and is easily excluded from clinical trials, requiring more clinical attention. Large-scale clinical trials such as Keynote001, Keynote024, Checkmate026, and CAMEL have confirmed that immunotherapy can bring significant clinical benefits to patients with advanced NSCLC. The 5-year survival rate of patients with advanced NSCLC has increased from 5% with chemotherapy to 16%-23%. However, only 6.2%-17.5% of patients with asymptomatic or stable lung cancer with distant organ metastasis are included in relevant clinical trials, and most of these patients are often excluded, and direct evidence for ICIs and mNSCLC patients is still scarce.

Thanks again for your valuable advice. We still tend to believe that in the current dataset, these indicators are representative and clinically significant in this population. Of course, more large-scale multicenter clinical are needed to verify the applicability of these indicators and modify the current model. Taking into account the Reviewer C's comments, we have added further relevant content to the Introduction and Discussion sections.

Reviewer B

Comment 1: First of all, my major concern for this study is no external validation sample to provide the accuracy evidence. The title is also unclear, which should indicate the development of a prognosis prediction model.

Reply 1: Thanks for your correction. Indeed, as with other retrospective studies, there are some limitations to our study. Our clinical data were collected from a single center. Although we used the method of computer resampling 500 times to carry out internal verification of the model with considerable efficiency, there was no external verification and it lacked certain persuasiveness. In the future, we will continue to expand the sample size, increase external validation, and further optimize the prognostic model of patients with distant organ metastases receiving immunotherapy. Secondly, for your suggestions on the title, we have also made the following modifications in the article.

Changes in the text: We have modified our text as advised (page 1, line 2-3).

Comment 2: Second, the abstract is inadequate. The background did not describe the clinical needs for such prediction model and what the current knowledge gap is. The methods need to describe the inclusion of subjects, the assessment of baseline potential predictors, follow up procedures, and measurements of prognosis outcomes. The results need to briefly report the clinical characteristics of the study sample and the overall survival and progression in the whole sample. The conclusion is overstated since the authors did not test its external validity.

Reply 2: Thanks for your valuable suggestions. We are very sorry that we have deleted some specific content due to the limitation of the number of words required by the journal. As suggested by the reviewer, we have revised the abstract based on the comments one by one.

Changes in the text: We have modified our text as advised (page2, line 42-56).

Comment 3: Third, the introduction of the main text is poor. The authors need to review what has been known on the prognosis prediction models in NSCLC, as well as their predictors, and explain why it is important to predict prognosis in patients with distant organ metastasis

receiving ICIs. The authors also need to have comments on the limitations of prior studies including their limited accuracy.

Reply 3: Thanks for your valuable suggestions, we have revised the introduction to enrich relevant contents based on the comments one by one.

Changes in the text: We have modified our text as advised (page3-4, line 100-117).

Comment 4: Fourth, the methodology of the main text needs to describe the clinical research design, sample size estimation, and follow up procedures. In statistics, please consider to calculate sensitivity and specificity of the model and indicate their acceptable levels since the focus is not the overall accuracy. What we need to know from the model is the probability of death or survival within five years, for example. Please ensure $P<0.05$ is two-sided.

Reply 4: Thanks for your detailed review. We apologized for not specifying these procedures in the methods. As suggested by the reviewer, we have added relevant description based on the comments one by one.

Changes in the text: We have modified our text as advised (page5, line 158-160; page6, line 190-191).

Comment 5: Finally, please consider to review and cite several related papers: 1. Tian Y, He Y, Li X, Liu X. Novel nomograms to predict lymph node metastasis and distant metastasis in resected patients with early-stage non-small cell lung cancer. Ann Palliat Med 2021;10(3):2548-2566. doi: 10.21037/apm-20-1756. 2. Deng K, Li S, Zhang J, Ye X, Yao K, Li Y, Xiao J. Prognostic value of thoracic tumor staging and volume parameters in non-small cell lung cancer patients with synchronous solitary bone metastasis. J Thorac Dis 2022;14(4):1130-1138. doi: 10.21037/jtd-22-113. 3. Chen Y, Zhang Q, Lv Y, Li N, Xu G, Ruan T. Prognostic factors of survival in patients with non-small cell lung cancer: a competing risk model using the SEER database. Transl Cancer Res 2022;11(11):3974-3985. doi: 10.21037/tcr-21-2114. 4. Kim J, Jang TW, Choi CM, Kim MH, Lee SY, Park CK, Chang YS, Lee KY, Kim SJ, Yang SH, Ryu JS, Lee JE, Lee SY, Park CK, Lee SH, Jang SH, Yoon SH. Real-world analysis of first-line afatinib in patients with EGFR-mutant non-small cell lung cancer and brain metastasis: survival and prognostic factors. Transl Lung Cancer Res 2023;12(6):1197-1209. doi: 10.21037/tlcr-22-832.

Reply 5: Thank you for your detailed review. The above references will be cited at the appropriate places in the paper.

Changes in the text: We have modified our text as advised (page27, line 659-664; page28, line 695-697).

Reviewer C

Comment 1: What are the biggest advantages and disadvantages of the prognostic model in this study? It is recommended to add relevant contents.

Reply 1: Thanks for your comments, we have added the description about pros and cons of prognostic models in the discussion section.

Changes in the text: We have modified our text as advised (page10, line 310-321).

Comment 2: Some fonts need to be enlarged, as shown in Figures 3, 5 and 7.
Reply 2: Thank you for your detailed review. We have checked all the figures one by one and made modification to reviewer's advice in the revised manuscript.
Changes in the text: We have modified our text as advised (page17,19,20).

Comment 3: What are the characteristics and evaluation criteria of immunotherapy? What are the effects of immunotherapy on tumor metastasis? It is recommended to add relevant content.
Reply 3: Thanks for your valuable comments. As described in the Methods, evaluation criteria for the efficacy of immunotherapy were established based on the RECIST, version 1.1. As for the immunotherapy on tumor metastasis, taking into account the Comment 4, we have incorporated additional relevant content in the discussion section.
Changes in the text: We have modified our text as advised (page9, line 274-301).

Comment 4: How to understand the tumor immune microenvironment of NSCLC? How to better understand the interaction between the immune system and distant organ metastasis? It is recommended to add relevant content.
Reply 4: Thanks for your critical suggestions. As suggested by the reviewer, we have added relevant content in the discussion section.
Changes in the text: We have modified our text as advised (page9, line 274-301).

Comment 5: This study is a retrospective analysis, which is likely to cause some deviations in the results. It needs to be further confirmed by multi-center clinical trials.
Reply 5: Thank you for your correction. As a retrospective clinical study, this study does have some limitations that most retrospective studies have. In future studies, we will continue to expand the sample size, increase external validation, reduce bias, and further optimize the prognostic model of patients with distant organ metastases undergoing immunotherapy.

Comment 6: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Prognostic models for immunotherapy: emerging factors for an evolving treatment landscape, Transl Lung Cancer Res, PMID: 33569288". It is recommended to quote this article.
Reply 6: Thank you for your detailed review. we have revised the introduction to enrich relevant contents based on the reviewer B's comments one by one. Moreover, the above references will be cited at the appropriate places in the paper.
Changes in the text: We have modified our text as advised (page3-4, line 100-117; page28, line 665-666).

Comment 7: What are the predictors of efficacy of immunotherapy? It is recommended that relevant information be added to the discussion.
Reply 7: Thank you for your correction. In the discussion section, we have added an explanation of the relevant prognostic indicators of immunotherapy in response to your suggestion.
Changes in the text: We have modified our text as advised (page 9, line 274-278).

Comment 8: How to identify and validate a prognostic signature for the prediction of both disease-free survival and overall survival of NSCLC patients by integrating multiple datasets? It is recommended to add relevant content.

Reply 8: Thanks for your critical suggestion. We are sorry that our analysis is based on a single database established from a single center. Of course, in the discussion section, we have cited the relevant literature of model prognostic analysis using the SEER database.

Changes in the text: We have modified our text as advised(page 10, line 308-310).

Reviewer D

1. The citations of Refs 6, 7, 8, 28, 29, 36, 38, 48 are missing. Please check and revise.

Reply 4: Thank you for your positive feedback, I have made corresponding modifications in the original text.

2. There are 57 references in your list, while 58 references were cited in your main text. Please check and revise.

Reply 5: Thank you for your positive feedback, I have made corresponding modifications in the original text.

3. Ref.23 and Ref.32 are the same.

Ref.20 and Ref. 34 are the same.

Ref.6 and Ref. 29 are the same.

Ref.11 and Ref. 14 are the same.

Please check and revise.

Reply 6: Thank you for your positive feedback. I have reinserted the literature in the full text of the manuscript and corrected the literature that needs to be modified. In order to avoid unnecessary mistakes caused by changing the style of the literature, I did not change the style of the literature to TLCR, so I need to ask you to modify it in the editing process. I would like to express my sincere thanks again.

4. The information of Ref. 58 in the main text differed from the information in the reference list. Please revise.

Takada et al.(58) found that among patients with advanced NSCLC treated with nivolumab, PFS and OS decreased significantly more in those with LDH >222 U/L than in those with LDH ≤222 U/L.

824 57. Takada K, Takamori S, Matsubara T, et al. Clinical significance of preoperative inflammatory markers
825 in non-small cell lung cancer patients: A multicenter retrospective study[J]. PLoS One, 2020, 15(11):
826 e241580.
827

Reply 7: Thank you for your positive feedback, I have made corresponding modifications in the original text. At present, there are 58 literatures in total.

5. The authors mentioned “studies...”, while only one reference was cited. Change “Studies” to “A study” or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.

Clinical studies on bone metastasis are extremely limited, but the combination of bone-targeted therapy and immunotherapy seems to have a synergistic effect(30), potentially partially restoring tumor immunogenicity and the bone immune microenvironment. However, these results need to be confirmed in larger-scale prospective clinical trials.

Different from previous studies(31), all patients in our study were confirmed to have distant organ metastases before immunotherapy.

Previous studies suggest complications in lung cancer patients follow similar pathogenic factors and signal transduction mechanisms, exerting synergistic effects and leading to the deterioration of the basic status of patients and decline in treatment efficacy(44).

We also conducted a comprehensive assessment of the peripheral blood parameters and found elevated baseline ANC correlated significantly with poor OS (P=0.02), which is in accordance with previous studies on the treatment of melanoma with ipilimumab(49).

Reply 8: Thank you for your positive feedback, I have made corresponding modifications in the original text.

6. ALL abbreviations used in each table/figure or table/figure description should be defined in a footnote below the corresponding table/figure.

For example,

9.1 PD-L1 and TPS in Table 1 should be explain.

657 PD-L1, ; TPS, ; ACCI, age-adjusted Charlson comorbidity index; ANC, absolute

6.2 ALL abbreviations in Table S1 should be explain.

Reply 9: Thank you for your positive feedback, I have made corresponding modifications in the original text.

7. Table S1

Please check whether the items have unit and supplement.

Age, n (%)

≤ 70

> 70

BMI, n (%)

≤ 23.77

> 23.77

Reply 10: Thank you for your positive feedback, I have made corresponding modifications in the original text.

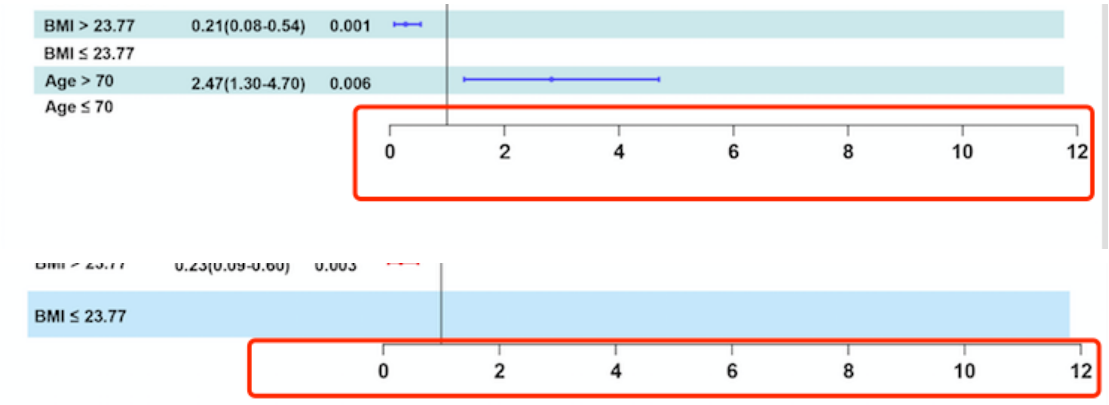
8. Figure 1

It is suggest to change the legend to “A Flow chart of the study”. Please revise.

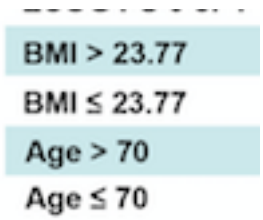
Reply 11: Thank you for your positive feedback, I have made corresponding modifications in the original text.

9. Figure 3

12.1 Please provide the descriptions of the x-axis.



12.2 Please provide the unit for the below items



Reply 12: Thank you for your positive feedback, I have made corresponding modifications in the original text.

10. Figure 5

ECOG.PS or ECOG PS? Which one is correct? Please check and unify.

Reply 14: Thank you for your positive feedback, "ECOG PS " is correct and I have made corresponding modifications in the original text.

11. Figure 7A

Please provide the descriptions for the blue part, the grey part, and the purple part.

Reply 15: Thank you for your positive feedback, I have made corresponding modifications in the original text.