Peer Review File

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Reviewer A

Comment 1: The model development process is not clearly reported. Did the authors first do a univariate analysis and then use the significant variables in the univariate analysis to fit the multivariate cox model? Please clarify this.
a. If the above assumption is correct, why did the authors choose this method?
b. Secondly this method does not include all potential variables as some variables might be significant only when combined with others.
Reply 1: Thank you very much for your comment. Your assumption is correct. A univariate analysis was firstly performed, and the significant variables were then subjected to the multivariate cox analysis. Finally, these identified prognostic factors were used to the construction of our nomogram. We choose this method according to many published studies. In addition, we also conducted a multivariate cox analysis using all the potential variables in this study. However, the result was similar with that in this manuscript. We will further verify this result in future clinical research.
Changes in the text: We have modified our text as advised (see Page 7, line 2-7).

Comment 2: The authors categorized the age variables. What is the motivation for this since this just leads to loss of information?
a. If there is a good motivation for the above point, why not use cutoff points with biological meaning or natural classification.
Reply 2: Thank you for pointing this out. Age was converted into categorical variable because categorical variable could be included into univariate and multivariate cox analyses. The optimal cutoff values for age were determined by the X-tile software, which was considered as a popular method based on the survival time of patients and suitable for our study. The biological meaning or natural classification is also a good method and reported in some studies. But we can only choose one of them.
Changes in the text: We have modified our text as advised (see Page 6, line 17-19).

Comment 3: Radiotherapy and chemotherapy contain No and unknown in the same group. What is the rationale for combining these two groups and not 3 separate groups (No, yes, and unknown).
Reply 3: Thank you for your valuable suggestion. Data of SCLC patients in our study were all obtained from the SEER database. None and unknown of radiotherapy and chemotherapy information in SEER database are merge into one group. We can't change this grouping method, although it looks a little strange.
Changes in the text: We have modified our text as advised (see Page 6, line 15-16).

Comment 4: On page 7 line 28 “Lymph node metastasis was demonstrated to be associated with higher odds of experiencing multiorgan metastases and a worse

prognosis in NSCLC patients".
There is no section in which the above sentence is demonstrated.
Reply 4: Thank you for pointing this out. Yang et al reported that among NSCLC patients with distant organ metastasis, lymph node metastasis was associated with a worse prognosis in terms of longer survival except patients with liver metastasis. We have modified our text. And we cited this article in our manuscript.
Changes in the text: We have modified our text as advised (see Page 10, line 21-22).

Comment 5: Patients were separated into low and high-risk groups based on the median risk score. Please explain how this risk score was derived.
a. Based on the KM-plot, the median survival difference between the low and high-risk groups is about 4 months which is not that different. What is the rationale for using the median risk score value and not the percentile?
b. Why limit to just two groups and not more?
Reply 5: Thank you for your valuable suggestion. The patients were divided into low-risk group and high-risk group according to the median of risk score, which was calculated by the "survival" package in R software. Among all patients, the median follow-up time was only 6 months (1-83 months). And there was a significant difference in survival between the two groups. The median risk score is widely used in clinical research based on SEER database, so we chose this value. In order to use the nomogram conveniently and make our results look easy, patients were separated into just two groups. Study with more groups was also reported in several articles, they were both very useful grouping methods.
Changes in the text: We have modified our text as advised (see Page 7, line 14-16).

Comment 6: Please improve on the figures.
Reply 6: Thank you very much for your comment. We tried our best to improve the resolution of pictures in this manuscript, in order to make them more clearly. I don't know whether it has reached to your standard.
Changes in the text: We have improved the resolution of pictures.

Comment 7: It will be useful to compare the DCA plot (Figure 5) of your model with other study models.
a. Explain the DCA plot with respect to your model endpoint.
Reply 7: Thank you for your valuable suggestion. DCA was performed to evaluate the clinical utility of the nomogram based on net benefits at different threshold probabilities. Compared with similar study models, the increased net benefit of our nomogram was larger, which indicated that the nomogram was a reliable clinical tool for predicting survival. In Figure 5, the dotted line represented the nomogram, and threshold probability above the reference line revealed the net benefit.
Changes in the text: We have modified our text as advised (see Page 12, line 18-20).

Comment 8: Explain what we see on the calibration plot (Figure 4). What do the dot and bar represent?
a. Why use just 3 groups when the sample size is large.
b. Patients with high survival probability are not captured in your model?
Reply 8: Thank you for pointing this out. In essence, a calibration curve is a scatterplot of actual and predicted incidences. The predicted probability is divided into buckets, and the average value of the predicted probability of all samples in each bucket is obtained as the abscissa. Find the probability of positive examples in each bucket as the ordinate. Connecting these points becomes the calibration curve. The closer the calibration curve is to the diagonal, the more accurate the model prediction is. In Figure 4, the calibration plots presented good agreement between predicted and actual CSS, suggesting that the nomogram was reliable for predicting survival. We used just 3 groups in this study because the results look simple and clear. There is no obvious difference in the results between 3 groups and more groups. The prognosis for SCLC patients with BM is very poor, and the median survival time in our data was only 6 months. Therefore, we constructed the prognostic nomogram to predict 6-month, 9-month and 12-month CSS. But in clinical work, we can adjust the prediction time of patients individually.
Changes in the text: We have modified our text as advised (see Page 7, line 10-12).

Other comments
Comment 9: The model looks to be doing better in the validation cohort than in the training cohort. Any comments on this?
Reply 9: Thank you for pointing this out. The data of patients were analyzed again in our revised manuscript. The C-index of novel nomogram was 0.683 (95% CI 0.667–0.699) in the training cohort, and 0.659 (95% CI 0.634–0.684) in the validation cohort. The AUC values of 6-month, 9-month and 12-month CSS were 0.723, 0.742 and 0.737 in the training cohort, while 0.715, 0.737 and 0.739 in the validation cohort. The results showed good discriminative ability and predictive accuracy in both training cohort and validation cohort. There was no significant difference between them.
Changes in the text: We have modified our text as advised (see Page 9, line 10-13).

Comment 10: The manuscript will benefit from motivation for the model choice and why translate the model to a nomogram.
Reply 10: Thank you very much for your comment. The nomogram is a statistical prediction tool that incorporates the contribution of each factor and precisely estimate the probability of clinical events for the individual. Nomogram is user-friendly, superior to clinician judgment in estimating disease course, and has been widely used to predict the prognosis of various tumors. Therefore, we choose the nomogram to exhibit our prediction model.
Changes in the text: We have modified our text as advised (see Page 5, line 8-10).

Comment 11: N1 patients have poorer survival than N0 patients. Any thoughts

on this difference?
Reply 11: Thank you very much for your comment. The detailed score of N0 was higher than N1 in our nomogram. The average survival time of N0 patients was 8.35 months and the average survival time of N1 patients was 8.37 months. But there was no significant difference between them. This outcome might be due to the reason that N1 patients received higher rates of radiotherapy and chemotherapy than N0 patients.
Changes in the text: We have modified our text as advised (see Page11, line 2-4).

Reviewer B
Comment 1: Introduction: There is much room for improvement, and the authors should focus on the purpose and importance of this study. Descriptions that are not relevant to the core of this study should be removed, for example, P3 L6-9 "Due to the lack of specific clinical symptoms and rapid tumor growth, early detection of SCLC is challenging [4]. The majority of SCLC patients are diagnosed with lymph node metastasis or distant metastasis and lost opportunity of surgical treatment", this statement conveys an underlying message to the reader that this study will construct a model to assist/predict the early diagnosis/detection of SCLC.
Reply 1: Thank you for your valuable suggestion. This study aimed to establish a novel nomogram for predicting the cancer-specific survival in SCLC patients with BM. These descriptions and relevant literature of early diagnosis in the introduction section was removed in the revised manuscript. In addition, relevant content about prognostic factors and model was added.
Changes in the text: We have modified our text as advised (see Page 4, line 12-17).

Comment 2: Add P-values to the "Survival Analysis" section as well.
Reply 2: Thank you very much for your comment. The P-values have been added into the "Survival Analysis" section in our revised manuscript.
Changes in the text: We have modified our text as advised (see Page 10, line 2-4).

Comment 3: Although this study implemented a reasonable validation methodology and included a large number of patients. However, as a clinically oriented article, it does not give the reader more useful information relative to previous studies that the risk factors screened for in the study have been widely identified and reported. Moreover, considering the arrival of the immunotherapy era, the authors used a publicly available database of patients who did not use immunotherapy. Therefore, the value for future clinical guidance is limited.
Reply 3: Thank you for pointing this out. This is the first study to identify independent prognostic factors for CSS in SCLC patients with BM and construct a prognostic nomogram based on SEER database with a large number of patients. Some important variables that may influence survival could not be obtained from the SEER database, including immunotherapy. This is a great pity and the limitations of our study has been discussed in the "Discussion" section. However,

based on this current predictive model, we will develop novel nomogram using data from our own hospital in the next research. Then more clinical useful factors will be included.
Changes in the text: We have modified our text as advised (see Page 13, line 1-4).

Comment 4: In addition, there are potential risks given to clinical practice based on the nomogram results, such as the prognosis of patients who underwent surgery in the nomogram is much better than those who did not. This conclusion is partially in conflict with the actual clinical practice and should be developed based on the actual patient situation. The conclusion reached by the authors is only reported from a pure modeling perspective. Further subgroup analysis, etc., should be performed to obtain more convincing conclusions.
Reply 4: Thank you for your valuable suggestion. The nomogram is a statistical prediction tool that incorporates the contribution of each factor and precisely estimate the probability of clinical events for the individual. The average survival time of patients who underwent surgery was 8.34 months and the average survival time of who did not undergo surgery was 8.45 months. In our nomogram, surgery was a positive prognostic factor for SCLC patients with BM, which was also demonstrated in previous studies. However, only 33 (1.3%) of all 2462 patients received surgery, which might influence the statistical result and lead to selection bias. The predictive model was developed with the SEER database and were not verified by external data, which would be performed in our next research.
Changes in the text: We have modified our text as advised (see Page 13, line 1-4).

Comment 5: Some analysis and explanation should be given as to why radiotherapy did not show a prognostic benefit in the study. I know this is difficult due to the inherent information limitations of public databases.
Reply 5: Thank you for your valuable suggestion. In order to verify the result, the patients were re-grouped and the data of patients were re-analyzed in our revised manuscript. Age, N stage, surgery, radiation, chemotherapy, bone metastasis, liver metastasis and lung metastasis were identified as independent prognostic factors. In addition, the novel nomogram was developed. Radiotherapy also showed a prognostic benefit in the predictive model, which was reported by previous studies.
Changes in the text: We have modified our text as advised (see Page 8, line 20-21).

Reviewer C
Comment 1: First of all, I recommend English correction for this article. There are vague sentences with unclear meanings. One should check appropriate use of capital letters, parentheses, units, symbols, and punctuation marks before submitting an article. Furthermore, please check the tables and figures if they are in the right format for this journal. The font size is too small in the nomograms and survival curves. A meticulous inspection will improve the quality of this article.
Reply 1: Thank you for your valuable comment. About the English writing of the

manuscript, we ask for native English speaker to revise the paper before it was submitted to the magazine and this time. The error has been corrected in the revised manuscript. I don't know whether it has reached to your standard. On the other hand, the figures were re-constructed. We tried our best to improve the resolution of figures in this manuscript, in order to make them more clearly.
Changes in the text: We have improved the English writing of the manuscript and the resolution of figures.

Comment 2: As the authors mentioned in the introduction, cigarette smoking is a very important clinical factor to which more than 90% of patients with SCLC are attributable. But the authors also mentioned in the discussion that important variables such as smoking status could not be obtained from SEER database. Can cigarette smoking be excluded when investigating on SCLC survival? Please explain.
Reply 2: Thank you for pointing this out. One of the limitations in our study is that some important variables that may influence survival could not be obtained from the SEER database, including smoking status. However, based on this current predictive model, we will develop novel nomogram using data from our own hospital in the next research. These clinical useful factors will be included. Cigarette smoking should not be focus of this current study and was removed in the introduction section of revised manuscript.
Changes in the text: We have modified our text as advised (see Page 13, line 1-4).

Comment 3: Isn't the nomogram point for surgery are too high compared to other prognostic factors in stage IV SCLC? As the authors mentioned in the discussion, undergoing primary lung surgery might show its importance in oligometastatic NSCLC setting, but might not in all metastatic cases, while the extent and the total number of metastases is not assessed in this study with SCLC patient cohort. Furthermore, in advanced stage SCLC, the role of radiotherapy might be more important than surgery, but radiotherapy was not a significant prognostic factor in this study. Please explain.
How was the surgery to symptomatic or large brain metastases assessed in this study? Can it be distinguished from primary lung surgery in SEER data?
Reply 3: Thank you for your valuable suggestion. The average survival time of patients who underwent surgery was 8.34 months and the average survival time of who did not undergo surgery was 8.45 months. In our nomogram, surgery was a positive prognostic factor for SCLC patients with BM, which was also demonstrated in several previous studies. However, only 33 (1.3%) of all 2462 patients received surgery, which might influence the statistical result and lead to selection bias. The predictive model was developed with the SEER database and was not verified by external data. We would like to verify the result with more patients in our next research.

Radiotherapy (77.1%) and chemotherapy (78.9%) were important therapeutic method for SCLC patients with BM. The patients were then re-grouped

and the data of patients were re-analyzed in our revised manuscript. Age, N stage, surgery, radiation, chemotherapy, bone metastasis, liver metastasis and lung metastasis were identified as independent prognostic factors. In addition, the novel nomogram was developed. Radiotherapy also showed a prognostic benefit in the predictive model, which was consisted with previous studies.

We can only get information about whether a patient has undergone surgery or not from the SEER database, and the exact surgical procedure was not known. This is a great pity and a limitation of our study.

Changes in the text: We have modified our text as advised (see Page 11, line 5-20).

Comment 4: The authors mentioned that the chemotherapy was identified as a positive prognostic factor for SCLC patients with BM, but radiotherapy was not. What part of human body were the targets for radiotherapy in this patient cohort? As the authors mentioned in the discussion, controlling primary tumor is related to better survival, and radiotherapy to primary SCLC lesion might result in a similar conclusion since SCLC is radiosensitive. We have to distinguish among primary lung lesion radiotherapy, intracranial radiotherapy, and other palliative radiotherapy such as radiotherapy to painful bone metastasis, since they will show different prognosis among them. Please explain.

Reply 4: Thank you for pointing this out. This observation might be contrary to our traditional understanding. The patients were re-grouped and the data of patients were re-analyzed. Finally, chemotherapy and radiotherapy were both positive prognostic factors for SCLC patients with BM. However, due to the limitations of the data in this study, we could not obtain specific treatment information of the patients, such as chemotherapy drugs, chemotherapy cycle, and radiotherapy area. We were unable to analyze the effect of treatment on prognosis in-depth, which is an unavoidable limitation of this study.

Changes in the text: We have modified our text as advised (see Page 8, line 20-21).

Comment 5: The authors included the SCLC patients with BM diagnosed between 2010 and 2015 from the SEER database. Were all the patients in this cohort present with synchronous brain metastasis? Metachronous brain metastasis and synchronous brain metastasis might show different prognosis, and in the case of metachronous brain metastasis, prophylactic cranial irradiation might have been done before the brain metastasis occurs. This may influence the results. Please explain.

Reply 5: Thank you for pointing this out. The patients from the SEER database in this study presented with synchronous brain metastasis at initial small cell lung cancer diagnosis. This has been described in the patients and methods section of the revised manuscript.

Changes in the text: We have modified our text as advised (see Page 6, line 1-2).

Comment 6: Although the number of intracranial metastases might influence CSS in SCLC patients, the number of BM were not assessed in this article. It would

have been better if it were included in the analysis.
Reply 6: Thank you for your valuable comment. The number of intracranial metastases was an important factor. However, due to the limitations of the data in this study, we could not obtain specific number of intracranial metastases. If there is an opportunity and we'd like to explore the influence of number of intracranial metastases on CSS in SCLC patients in the next research.
Changes in the text: We have modified our text as advised (see Page 13, line 1-4).

Comment 7: In SCLC patients with BM, the prognostic factors are well known and clarified in many studies. What is the clinical impact of this study? Do we even need a nomogram in this situation? We don't have many choices to treat SCLC patients with BM, and we already know chemotherapy, surgery, and radiotherapy play important role in treating these patients. Not also treatment modalities, but also nodal metastasis and distant metastasis, of course, have important effects in patients' prognosis. Please explain.
Reply 7: Thank you for your valuable suggestion. This is the first study to identify independent prognostic factors for CSS in SCLC patients with BM and construct a prognostic nomogram based on SEER database with a large number of patients. The nomogram is a statistical prediction tool that incorporates the contribution of each factor and precisely estimate the probability of clinical events for the individual. The nomogram is user-friendly, superior to clinician judgment in estimating disease course, and has been widely used to predict the prognosis of various tumors. Although we don't have many choices to treat SCLC patients with BM and the prognosis is very poor. Accurate estimation of each patient's prognosis can benefit both the patient and the physician in all aspects of decision-making. This is the aim of our study.
Changes in the text: We have modified our text as advised (see Page 5, line 8-10).

Comment 8: The authors predicted 6-month, 9-month, 12-month CSS with nomograms. What is the clinical meaning, significance or implications of each survival duration? Those values do not seem to change through time, and there is no discussion on this aspect. Please explain.
Reply 8: Thank you for pointing this out. Among all patients in our study, the median survival time was 6 months, and 80% of them had the survival time of less than 12 months. Therefore, we selected 6-month, 9-month and 12-month CSS as the point-in-time of the prognostic nomogram, which could meet the needs of most patients.
Changes in the text: We have modified our text as advised (see Page 7, line 5-7).

Comment 9: In figure 1, who are the patients eligible for prognostic nomogram? Please explain.
Also, the number of patients excluded (n=1348) in addition to eligible SCLS patients with BM for prognostic nomogram (n=2462) did not match the total number of patients.

Reply 9: Thank you for pointing this out. The eligible patients for prognostic nomogram were as follows: patients were initially diagnosed with SCLC with BM; patients with complete survival data and clinicopathological information. The content could be found in patients and methods section of our revised manuscript. We feel very sorry for our mistake, the number of excluded patients was 1322. This has been corrected in revised figure 1.
Changes in the text: We have modified our text as advised (see Page 6, line 1-6).

Comment 10: There are no explanation for the nomogram building process.
Please describe the process in detail in patients and methods section.
Reply 10: Thank you for your valuable comment. The patients that we finally included were randomly divided into training cohort (70%) and validation cohort (30%). A univariate Cox regression analysis was firstly performed in the training cohort, and the significant variables were then subjected to a multivariate Cox regression analysis to identify independent prognostic factors. These identified factors were finally applied to construct the prognostic nomogram to predict 6-month, 9-month and 12-month CSS. Nomogram was constructed using the R software version 4.0.3. These were added into patients and methods section of our revised manuscript.
Changes in the text: We have modified our text as advised (see Page 7, line 2-7).