Establishment of a prognostic risk prediction model for non-small cell lung cancer patients with brain metastasis

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Background: Non-small cell lung cancer patients who develop brain metastases (BM) have a poor prognosis. This study aimed to construct a clinical prediction model in NSCLC patients with BM for overall survival (OS).

Methods: We retrospectively analyzed 300 NSCLC patients diagnosed with BM at Yunnan Cancer Center. The LASSO-Cox regression was used to construct the prediction model. the bootstrap sampling method was used for internal validation. The performance of our prediction model was compared with recursive partitioning analysis (RPA), graded prognostic assessment (GPA), the Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA), basic score for brain metastases (BSBM) and tumor-lymph node-metastasis (TNM) staging.

Results: We constructed prediction models with 15 predictors. We found that the 1-year, 3-year, and 5-year time-dependent ROC curves had area under the curve (AUC) values of 0.746(0.678-0.814),0.819(0.761-0.877), and 0.865(0.774-0.957), respectively. The bootstrap-corrected AUC values and Brier scores of the prediction model were 0.827 (0.663-0.953) and 0.123(0.066-0.188), respectively. The time-dependent C-index indicated that our model was significantly more discriminatory than RPA, GPA, Lung-molGPA, BSBM and TNM staging. Similarly, the decision curve analysis (DCA) showed that our model had the widest range of thresholds and the highest net benefit. In addition, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analysis showed that the prediction model had better predictive power. Finally, the risk subgroups based on our prognostic model were more effective in differentiating patients' OS.

Conclusion: The clinical prediction model we constructed might be useful for predicting OS in NSCLC patients diagnosed with BM. Its prediction performance is better than RPA, GPA, Lung-molGPA, BSBM and TNM staging.

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Abstract

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Introduction

Lung cancer is one of the more prevalent malignancies worldwide, with non-small cell lung cancer (NSCLC) being the most common type of lung cancer pathology(1). Interestingly, the brain is the most common site of distant metastasis in NSCLC. About 10% of patients have brain metastases (BM) at the time of diagnosis, and another 40%-50% of patients develop BM during the course of their disease(2). The prognosis of NSCLC combined with BM is extremely poor, and the median overall survival (mOS) of untreated patients is only 1-3 months, with a 1-year survival rate of 10%-20%(3). The main treatment modalities for NSCLC BM include radiotherapy, surgery, chemotherapy, molecular targeting, and immunotherapy, among others, which can be divided into either local or systemic treatment. Due to the diverse clinicopathological characteristics of patients, predicting the prognosis of NSCLC patients with brain metastases is important for selecting a more individualized treatment strategy.

The gold standard for evaluating cancer prognosis remains to be the tumor-lymph node-metastasis (TNM) staging system, but it still has limitations. First, it is primarily based on the anatomical progression of the disease correlating with more advanced staging. However, patients with the same anatomical progression may have the same staging, yet their prognostic outcomes may be different. Second, TNM staging does not include the primary tumor size, lymph node metastasis, and distant metastasis as continuous variables, which can create an imprecise staging. Lastly, TNM staging does not account for other variables, such as patient age, gender, and histology, to predict the prognosis of cancer patients(4). Therefore, TNM staging remains to be insufficient in accurately predicting the prognosis of NSCLC patients with BM.

Currently, the most widely used prognostic models for BM are the recursive partitioning analysis (RPA), graded prognostic assessment (GPA), the Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA) and basic score for brain metastases (BSBM) (5-8). RPA focuses on Age, Karnofsky performance score (KPS), control of the primary tumor, and the presence of extracranial metastases. GPA focuses on age, KPS, number of brain metastases, and the presence of extracranial metastases. In addition, Lung-molGPA takes into account the mutation status of NSCLC driver genes, in addition to factors considered in GPA. Lastly, BSBM focuses on KPS, control of the primary tumor, and presence of extracranial metastases. While these models are simple and convenient to use, they have some limitations. For example, RPA and GPA are general models for BMs and are not specific to lung cancer primaries, and BSBM does not take into account brain metastatic lesions. Lung-molGPA is a relatively good

model, being a specific model for lung cancer brain metastases. On the other hand, the evaluation metrics used by these models are subjective or difficult to quantify. Moreover, a few researchers have constructed prognostic prediction models for BM in NSCLC patients. For instance, Li et al. developed a novel prognostic model based on clinical features and inflammation markers to more accurately reflect the prognostic information of BM in NSCLC patients compared with Adjusted Prognostic Analysis (APA), RPA, and GPA(9). Zhang et al. studied the feasibility of using computed tomography imaging radiomics to predict survival of BM in NSCLC patients receiving whole-brain radiotherapy(10).

In addition, these studies have some limitations, such as the non-rigorous nature of the selection method used for choosing the predictors and the poor clinical applicability of the constructed models. Therefore, identifying clinically meaningful and inexpensive prognostic factors available at the time of BM onset would provide more valuable insights. To bridge this knowledge gap, this study aimed to establish a novel prognostic model based on clinicopathological characteristics, serological indicators, and treatment information using LASSO-Cox regression analysis, to more accurately reflect the prognostic information of NSCLC patients diagnosed with BM. Our model may provide a basis for clinicians to formulate reasonable treatment plans.

Materials & Methods

This clinical prediction model was constructed according to the TRIPOD checklist(11).

The ethics of this research is in line with the Declaration of Helsinki. The research was approved by the Ethics Committee of the Third Affiliated Hospital of Kunming Medical University, with the review number of KYLX2022221. Due to the retrospective nature of the study and the inability to reach some patients, the Ethics Committee granted exemption of informed consent for a subset of the patients.

Study population and follow-up

This retrospective study included 300 NSCLC patients who were diagnosed with BM from January 2006 to May 2020 at Yunnan Cancer Hospital, Third Affiliated Hospital of Kunming Medical University. The following inclusion criteria were used in selecting the subjects: (1) pathologically confirmed NSCLC; (2) MRI-confirmed BM; (3) available patient demographic characteristics, clinicopathological features, serological indicators, and treatment information; and (4) no current other types of cancer. The survival time of the patients was determined by reviewing the medical records and telephone inquiries. The overall survival (OS) was defined as the interval from the initial diagnosis to any form of death or the time of the last follow-up visit(12).

Data Collection

Medical records were reviewed to collect baseline clinical data upon the first diagnosis with BM. The general conditions (age, sex, BMI, smoking history, Karnofsky performance score (KPS)), tumor markers (carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratins (CYFRA21), squamous cell carcinoma antigen (SCCA)), serological indicators

(albumin (ALB), lactate dehydrogenase (LDH), alkaline phosphatase (ALP)), serum inflammatory indicators (neutrophil, platelet, lymphocyte, monocytes, platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), systemic immune-inflammation index= platelet×neutrophil/lymphocyte (SII), advance lung cancer inflammation index(ALI)=BMI×alb/NLR), prognostic nutritional index (PNI)=alb+5×lymphocyte, advance distant metastases (number of BM, lung metastasis, intra-thoracic metastasis (malignant pleural effusion, pericardial effusion, or pleural metastasis), liver metastasis, bone metastasis, adrenal metastasis, metastases to other sites), signs and symptoms of brain metastases (intracranial hypertension, focal signs and symptoms, epilepsy, decreased cognitive function), type of pathology, pathological stage (T_stage, N_stage, M_stage/TNM_stage), EGFR gene mutation status, treatment status (surgery for primary lung cancer foci, radiotherapy of primary lung cancer, radiotherapy for BM lesions(whole-brain radiation therapy, stereotactic radiation therapy), surgical treatment of metastatic brain lesions, chemotherapy, EGFR-tyrosine kinase inhibitors (TKIs) treatment), classification information of RPA, GPA, Lung-molGPA and BSBM models were all evaluated. The above predictors were complete and were comprised of objective data. Furthermore, all predictors were assessed independently of each other, without any knowledge of the clinical outcome. All continuity predictors maintained their continuity and were not processed by classification. The categorized predictors were all predetermined before model construction. The sample size of this study satisfied the events per variable (EPV) of > 10(13-15).

Model construction and evaluation

The reduced predictors were selected via a 10-fold cross-validation of LASSO-Cox regression by choosing the λ value corresponding to the minimum standard error. Subsequently, the reduced predictors were included in a multivariate Cox regression analysis, and the risk score for each patient was calculated using the "predict ()" function. Finally, a prognostic model was constructed.

$$\text{Risk score}=h_0(t)\times\exp(\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)$$

The discriminatory ability of the model was determined by evaluating the area under the receiver operating characteristic (ROC) curve (AUC). Furthermore, the calibration curve was plotted and the Brier score was calculated to measure the calibration of the model, and the bootstrap method (resampling of 1,000 times) was used for internal validation. The discrimination and clinical benefit of the novel prognostic models were compared with RPA, GPA, Lung-molGPA, BSBM and TNM staging using time-dependent C-index and decision curve analysis (DCA). The larger the AUC, the better the risk prediction of the model(16). The DCA curve demonstrates the relationship between benefits and risk from different cut points (thresholds) in different models(17). Meanwhile, IDI and NRI were used to assess how well our novel prediction models performed in terms of reclassification performance and discrimination compared to RPA, GPA, Lung-molGPA, BSBM and TNM staging. We combined the screened predictors to develop a nomogram that may be useful for individual survival prediction in NSCLC patients with BM. Finally, we classified patients into low-risk, intermediate-risk, and high-risk groups according to the new prediction model RiskScore, and analyzed the differences in OS among the 3 subgroups

using the Kaplan-Meier method. All statistical analyses were performed using the R software (version 4.2.1), and P values ≤0.05 were considered statistically significant.

Results

Patient characteristics

We recruited 300 NSCLC patients diagnosed with BM who had complete baseline clinical and laboratory data. The clinicopathological characteristics and laboratory results of these patients are summarized in **supplementary files 1**. The mean age of the patients was 55.4 years (range 31-83 years). The group was composed of 185 males and 115 females. In addition, the median follow-up time of the patients was 13.9 months, with a minimum follow-up time of 0.1 months and a maximum follow-up time of 173.83 months. The last follow-up was on June 16, 2021. The overall survival rates of these patients at 1, 3, and 5 years were: 75%, 49%, and 40.3%, respectively.

Construction of the prognostic models

First, we used the LASSO-Cox regression analysis to filter the best predictors and construct the model. Using cross-validation, we selected the λ value corresponding to lambda.min (λ = 0.054), at which λ takes the highest model fit (**Fig. 1**). This corresponds to the predictor that is the most important prognostic factor for OS, which includes 15 predictors: age, KPS, NSE, PLR, lymphocyte, alp, smoking history, intra-thoracic metastasis, metastases to other sites, N_stage, M_stage, surgery for primary lung cancer foci, chemotherapy, EGFR mutation and TKIs treatment. The EPV for each variable was 12.4. Finally, a prediction model for predicting OS was constructed based on the regression coefficients of these 15 predictors. The risk score of the prognostic model was calculated as follows: Risk score = h0(t) exp [(age × 0.0105543) + (kps × -0.0082627) + (nse × 0.0017274) + (PLR × 0.0007071) + (lymphocyte × -0.0174690) + (alp × -0.0001577)+ (smoke × 0.1433414)+ (Intrathoracic_metastasis×0.4382260)+ (Metastases_to_other_sites × 0.0330467)+(N_stage × 0.1062274)+(M_stage × 0.0277756)+(Surgery × -0.2624173)+ (chemothera × -0.0027364)+(TKIs_Therapy × -0.3508606)+ (EGFRmutation × -0.0952148)]. The continuous variables in the formula were based on the original numerical levels, and the codes representing the categorical variables are shown in **supplementary files 1**.

The Cox proportional risk regression analysis was performed for the 15 predictors selected based on the LASSO regression technique **(Fig. 2)**. The time-dependent ROC curves suggested AUC values of 0.746(0.678-0.814),0.819(0.761-0.877) and 0.865(0.774-0.957) for our prediction model at 1, 3, and 5 years, respectively. The Brier was 0.103 (0.072-0.134). The Brier Score combines the performance of discrimination and calibration and is used to evaluate the overall performance of the model, with smaller values indicating better model performance (0 for perfect overall performance and 0.25 for worthless model)(18, 19). Meanwhile, the bootstrap method (resampling of 1,000) for internal validation showed an AUC of 0.811 (0.638-0.950) and Brier of 0.123 (0.066-0.188; based on 5 years), indicating that our model has good discrimination and calibration **(Fig. 3)**.

Evaluation of performance between our novel prognostic model, RPA, GPA, Lung-molGPA, BSBM and TNM staging

We introduced the time-dependent C index to evaluate the accuracy of model prediction. Our model predicted prognosis with higher discrimination than RPA, GPA, Lung-molGPA, BSBM and TNM staging, and we obtained similar results in our bootstrap validation **(Fig. 4)**.

In addition, we introduced DCA curves, which focus on evaluating the clinical benefit of predictive model applications. We observe that the threshold range applicable to the six DCA curves differs. The threshold range for our model is approximately 0.4-0.8, which is relatively the widest among the six DCA curves. Furthermore, within most of the threshold ranges, our model has the highest net profit among the six DCA curves (**Fig. 5**). Therefore, our model is the optimal model.

Finally, we introduced the IDI and NRI metrics. IDI was used to determine how much the new model improved its predictive power compared to the old model, and NRI was used to determine how much the new model improved the proportion of correct reclassifications compared to the old model. The IDI analysis showed that our model improved positively compared to GPA 0.152(0.063~0.287)，RPA 0.209(0.113~0.347), Lung-molGPA 0.106(0.030~0.240), BSBM 0.120(0.044~0.247) and TNM 0.218(0.122~0.354) with IDI＞0. Meanwhile, the NRI analysis showed that our model compared to GPA 0.537(0.172~0.676), RPA 0.474(0.270~0.722), Lung-molGPA 0.525(0.124~0.641), BSBM 0.457(0.149~0.644) and TNM 0.536(0.269~0.711) with NRI > 0, all of which were positive improvements **(Table 1)**. These indicate that the new model has improved the proportion of correct judgments of outcome events compared to the old model.

Constructing a nomogram for predicting OS

A nomogram was constructed to visualize our model. This provides a convenient, personalized tool to predict the probability of 1, 3, and 5-year OS in NSCLC patients with BM. Each predictor corresponds to a score, and the scores of all predictors are summed together to obtain a total score, from which the probability of OS at 1, 3, and 5 years can be obtained (**Fig. 6**).

Risk stratification based on our model

To assess whether our model can correctly assess patient risk, we calculated the risk score of each patient and classified them into three groups based on their risk score: low-risk, intermediate-risk, and high-risk groups. The OS was significantly lower (P<0.001) in the high-risk group (risk score>1.863) compared to the low-risk group (risk score<1.014) and the intermediate-risk group (1.014≤riskscore≤1.863). Patients in the intermediate-risk group also had lower OS than the low-risk group (P<0.001).

Both Lung−molGPA and BSBM, along with our model, are capable of distinguishing the OS of patients. In contrast, risk groupings constructed based on the GPA and RPA models could not fully and effectively differentiate patients' OS. Based on the GPA model, the OS of patients in the "GPA 1.5-2.5" group was not statistically significant compared with that in the "GPA 3" group (P=0.275). Meanwhile, on the RPA model, there was no statistically significant difference between the OS of patients in the "class II" group and the "class III" group (P=0.122).

The dichotomous risk grouping based on TNM staging, although also effective in differentiating patients' OS, was not as detailed as our model, which consisted of three subgroups.

The results indicate that our prognostic model performs well in distinguishing the prognosis of NSCLC patients with BM. (**Fig. 7,** Fig8).

Discussion

In this study, a prediction model based on the LASSO-Cox regression algorithm was developed for predicting OS in NSCLC patients diagnosed with BM. The prediction model contains 15 variables, including age, KPS, NSE, PLR, lymphocyte, alp, smoking history, intra-thoracic metastasis, metastases to other sites, N_stage, M_stage, surgery for primary lung cancer foci, chemotherapy, EGFR mutation and TKIs treatment. The prediction model has good discriminative ability, calibration, and clinical utility. In addition, our model had better performance compared with the conventional brain metastasis models GPA, RPA, Lung-molGPA, BSBM and classical TNM staging. Furthermore, we were able to group the patients based on their risk scores and showed that there were statistically significant differences in the OS of the low, intermediate, and high-risk subgroups as classified by our model.

Previous studies have identified that age, surgical treatment of the primary tumor, KPS, extracerebral metastasis, targeted therapy, NSE level, ALP level, and PLR are factors influencing the prognosis of NSCLC patients with BM(20-26). In our model, we identified five individual prognostic factors: NSE, PLR, ALP, intra-thoracic metastasis, and targeted therapy, none of which had been considered in previously published clinical prediction models for NSCLC with BM. Jacot, et al. demonstrated that high serum NSE levels are associated with a worse prognosis in NSCLC patients with BM and that elevated NSE may be related to the extent of tumor-induced dmage to the normal brain tissue(25). PLR is an index of inflammation, and a study by Anna Cho et al. noted that for every 10 increase in PLR, there was a 1.3% increase in the risk of death in patients with BM from NSCLC(26). These findings may be explained by the association of inflammation with cancer progression, where an increase in platelets leads to the production of inflammatory cytokines and chemokines, resulting in tumor progression(27). In addition, lymphocytes are known to be essential for antitumor immunity. Thus, a decrease in lymphocytes indicates an impaired cell-mediated immune response and compromised antitumor immunity(28). Jacot et al. also found that patients with BM from NSCLC with elevated ALP levels had shorter surviva(25). Furthermore, tyrosine kinase inhibitors (TKIs) targeting driver mutations in NSCLC, such as EGFR-TKIs and ALK-TKIs, greatly improve the prognosis of NSCLC patients with BM who have corresponding gene mutations(29, 30). Based on the above evidence, the predictors incorporated in our model are valid and plausible. The controversial point is that the study by Hirashima et al. found that intra-thoracic metastasis is a significant favorable prognostic factor for NSCLC patients with distant metastases(31). However, our study came to the opposite conclusion that intra-thoracic metastasis is a risky prognostic factor in NSCLC patients with BM. Further studies are warranted to further confirm these findings and resolve existing conflicts.

Only a few studies have constructed predictive models for the prognostic risk of patients with BM from NSCLC, and these studies have some limitations. For example, the clinical prediction models constructed by Wang et al. were based on univariate analysis to screen predictors(10, 32,

33) . The PROBAST guidelines state that when constructing clinical prediction models based on univariate analysis to screen predictors, bias can occur when univariate analysis prompts the removal of some variables from the model because some predictors only become significant when adjusted for other factors in the analysis at the same time(15). In contrast, our model is based on LASSO regression to filter predictors, which is an effective predictor reduction algorithm that actively selects from a large number of variables with possible multicollinearity to obtain a more relevant and interpretable set of predictors, and it is effective in avoiding model overfitting(4, 34). In addition, when the predictive model constructed by Zhang et al. is to be used in a real healthcare setting, the predictor in the model, which is based on the CT imaging histology score (Rad-score), is not available promptly because the predictor is not a routine item on the patient's examination at the time of hospitalization, which greatly reduces the clinical applicability of the predictive model(10). In contrast, our model ultimately incorporates readily available predictors, which facilitates the application of the model in the clinic. A similar study by Li et al. also established a nomogram combining patient clinicopathological factors and serological inflammatory markers (PLR, NLR, SII, PNI, ALI) to predict survival in patients with BM from NSCLC(9). Our study not only included these indices, but also added a series of lung cancer-related tumor markers, such as CEA, NSE, CYFRA21 and SCCA which have a potential impact on the prognosis of NSCLC patients with BM.

Overall, based on the results of our LASSO-Cox regression analysis, our prediction model has a good fit for predicting OS in NSCLC patients with BM. Calibration plots showed good calibration of our model, and time-dependent C-index analysis also indicated that our model showed good prognostic accuracy in predicting OS in NSCLC patients with BM compared with RPA, GPA, Lung-molGPA, BSBM and TNM staging. Also, the DCA shows that our model has the highest overall net benefit. Furthermore, the IDI and NRI results showed that our model had an improvement in predictive power and reclassification ratio compared to RPA, GPA, Lung-molGPA, BSBM and TNM staging. In addition, the prediction model can successfully classify NSCLC patients with BM into low, intermediate, and high-risk subgroups, with high-risk patients having the worst survival outcomes. In conclusion, we demonstrated that our clinical prediction model has the advantages of low cost, strong applicability, simple operation, accessibility, high applicability and accuracy, which can help predict the prognosis and contribute to the treatment decision of NSCLC patients with BM.

There are still some limitations of our study. First, our study was retrospective and, therefore, could not exclude all potential biases. Second, our data were obtained from a single hospital and the sample size was not large. Future multicenter, large-scale studies are needed to validate our findings. Finally, easy and accessible predictors were included in our model, which facilitates the application of the model in the clinic; however, it is undeniable that the specificity of the prognostic model can be improved if NSCLC-related immunohistochemical markers or other relevant genetic mutations, such as PD-L1, CTLA-4, ALK rearrangement, and ROS1 rearrangement, are included(35).

Conclusions

The clinical prediction model we constructed might be useful for predicting OS in NSCLC patients diagnosed with BM. Its prediction performance is better than RPA, GPA, Lung-molGPA, BSBM and TNM staging.

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ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors. LUNG CANCER. 2019;130:76-83.doi:10.1016/j.lungcan.2019.02.009.
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Table 1(on next page)

Table1 IDI and NRI were used to evaluate the improvement in predictive power and proportion of correct reclassifications of our model compared to the older models for RPA, GPA, Lung-molGPA, BSBM and TNM staging.

IDI and NRI were used to evaluate the improvement in predictive power and proportion of correct reclassifications of our model compared to the older models for RPA, GPA, Lung-molGPA, BSBM and TNM staging.

Table1 IDI and NRI were used to evaluate the improvement in predictive power and proportion of correct reclassifications of our model compared to the older models for RPA, GPA, Lung-molGPA, BSBM and TNM staging.

	IDI*(95% CI)	P value	NRI*(95% CI)	P value
our model vs GPA	0.152(0.063~0.287)	0.002	0.537(0.172~0.676)	0.002
our model vs RPA	0.209(0.113~0.347)	＜0.001	0.474(0.270~0.722)	0.002
our model vs Lung_molGPA	0.106(0.030~0.240)	0.014	0.525(0.124~0.641)	0.01
our model vs BSBM	0.120(0.044~0.247)	0.002	0.457(0.149~0.644)	0.004
our model vs TNM	0.218(0.122~0.354)	＜0.001	0.536(0.269~0.711)	＜0.001

IDI, Integrated Discrimination Improvement; NRI, Net Reclassification Index.

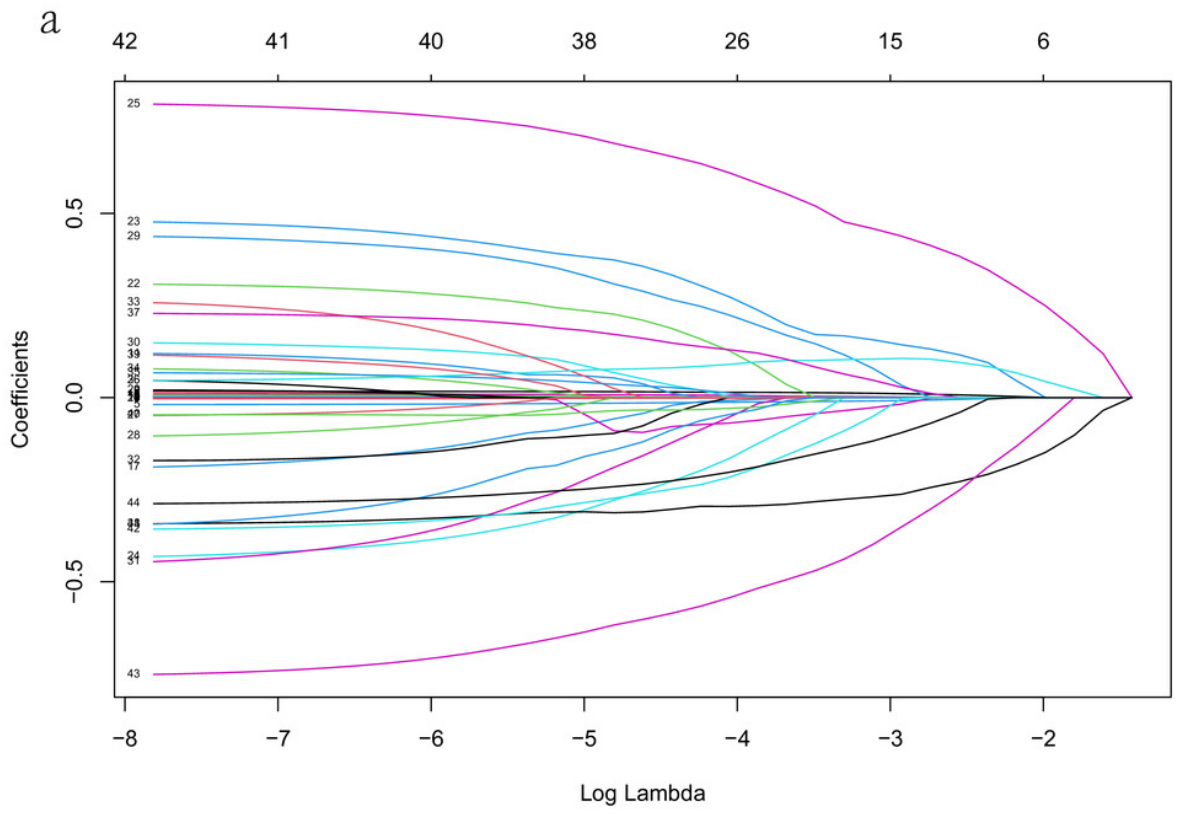
*Positive value represents better accuracy, negative velue represents worse accuracy

1

Figure 1

The LASSO regression algorithm was used for screening the predictors.

Figure 1. The LASSO regression algorithm was used for screening the predictors. (a) Path diagram of regression coefficients. Each curve represents the trajectory of each independent variable coefficient with log(ë). (b) Cross-validation curves of the LASSO regression analysis. The left dashed line is lambda.min, which is the smallest deviation of ë, while the right dashed line is lambda.1se, which is one standard error to the right of the smallest ë.


a
42
41
40
38
26
15
6
Coefficients
0.5
0.0
−0.5
−8
−7
−6
−5
−4
−3
−2
Log Lambda

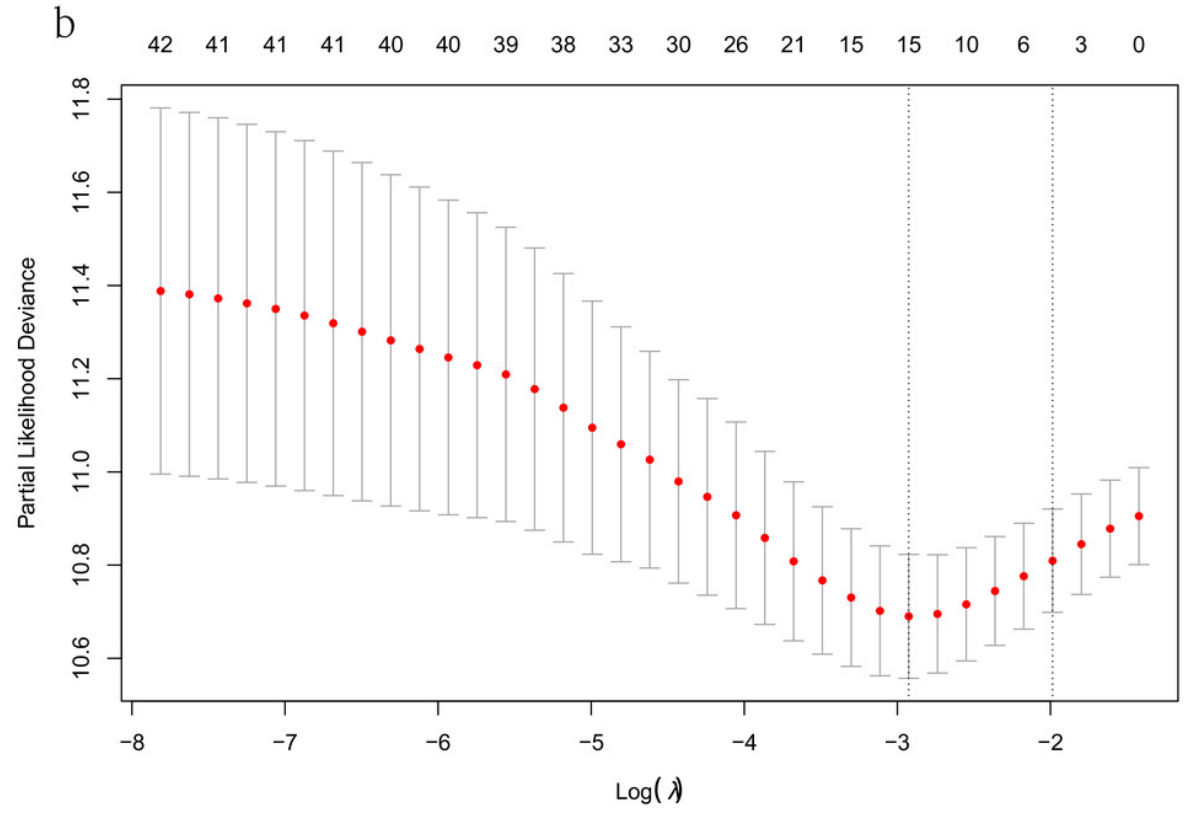

b
42 41 41 41 40 40 39 38 33 30 26 21 15 15 10 6 3 0
Partial Likelihood Deviance
11.8
11.6
11.4
11.2
11.0
10.8
10.6
−8
−7
−6
−5
−4
−3
−2
Log(λ)

Figure 2

The hazard ratios and 95% confidence intervals for the 15 predictors.

Figure 2. The hazard ratios and 95% confidence intervals for the 15 predictors.

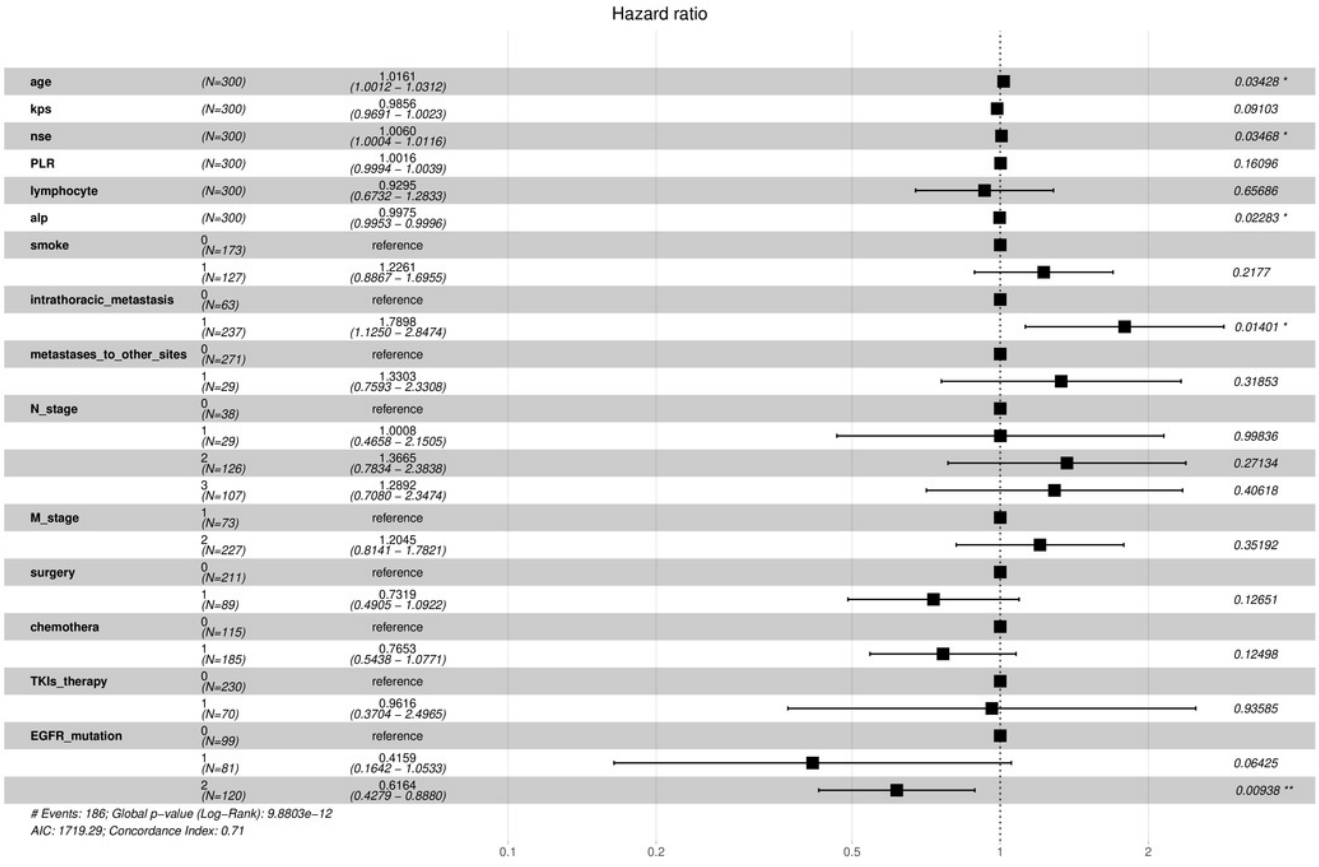
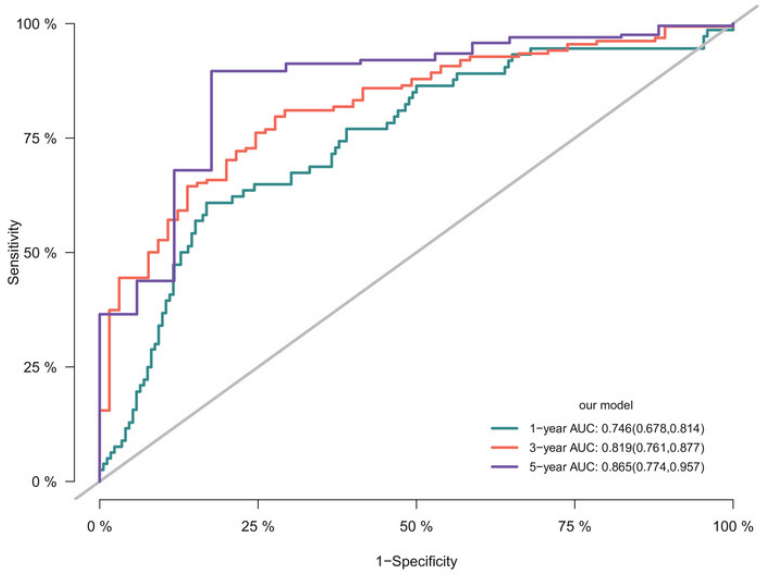


Figure 3

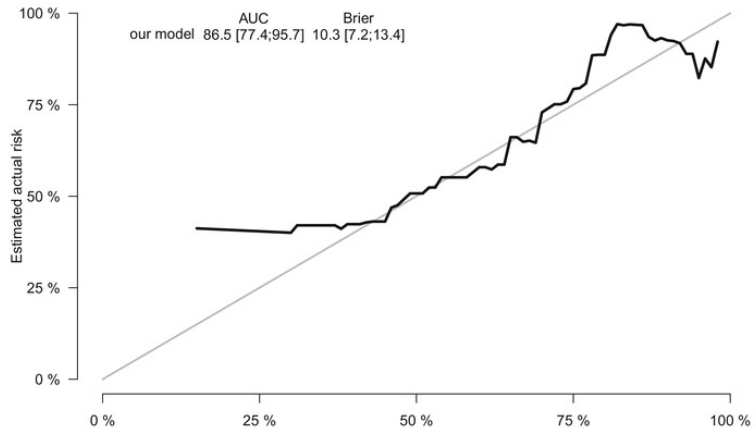
The ROC, calibration curves, and Brier scores for the prediction model and internal validation.

Figure 3.(a) The figure shows the time-dependent ROC curves, with AUC values and 95% confidence intervals, of the prediction model for 1, 3, and 5 years; (b) Figure shows calibration curves, with AUC values, Brier scores, and 95% confidence intervals, based on 5 years. The solid gray line represents a perfect prediction of an ideal model, while the solid black line indicates the performance of the constructed model. (c) The internal validation using the bootstrap method (resampling of 1,000).

a


100 %
75 %
50 %
25 %
0 %
Sensitivity
0 %
25 %
50 %
75 %
100 %
1−Specificity
our model
1−year AUC: 0.746(0.678,0.814)
3−year AUC: 0.819(0.761,0.877)
5−year AUC: 0.865(0.774,0.957)

b


AUC Brier
our model 86.5 [77.4;95.7] 10.3 [7.2;13.4]
100 %
75 %
50 %
25 %
0 %
Estimated actual risk
0 %
25 %
50 %
75 %
100 %

c

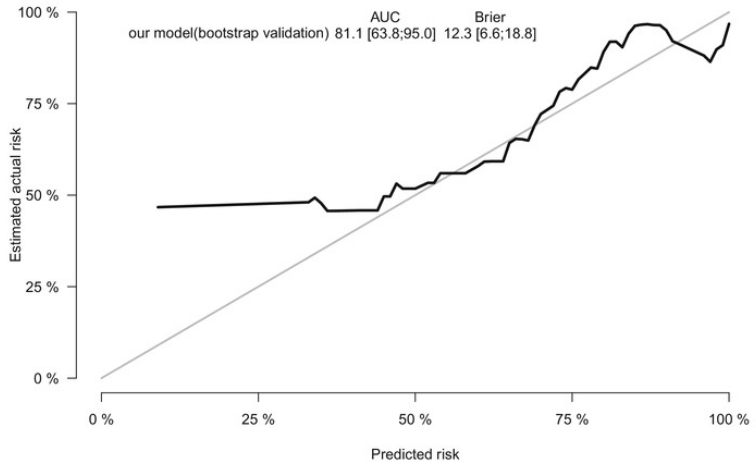
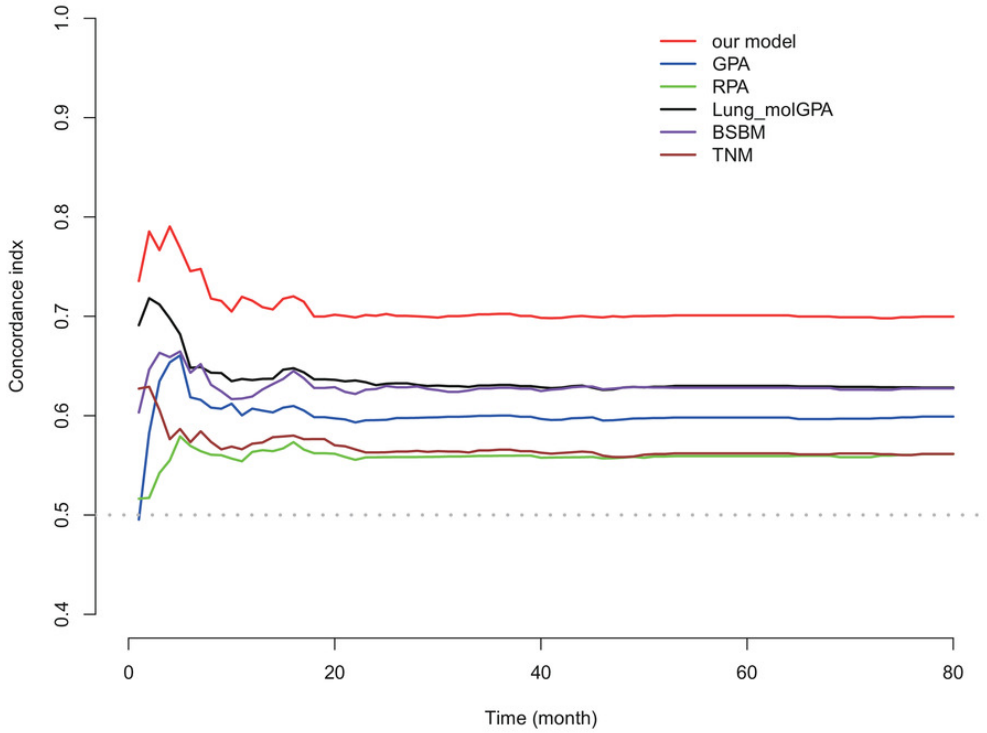

AUC Brier
our model(bootstrap validation) 81.1 [63.8;95.0] 12.3 [6.6;18.8]
100 %
75 %
50 %
25 %
0 %
Estimated actual risk
0 %
25 %
50 %
75 %
100 %
Predicted risk

Figure 4

Comparison of the time-dependent C-index of the six models.

Figure 4. Comparison of the time-dependent C-index of the four models. (A) Comparison of our models with RPA, GPA, Lung-molGPA, BSBM and TNM staging based on the time-dependent C-indices. (B) Internal validation using the bootstrap method.

a


Time−dependent C−index
our model
GPA
RPA
Lung_molGPA
BSBM
TNM
Concordance indx
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
20
40
60
80
Time (month)

b

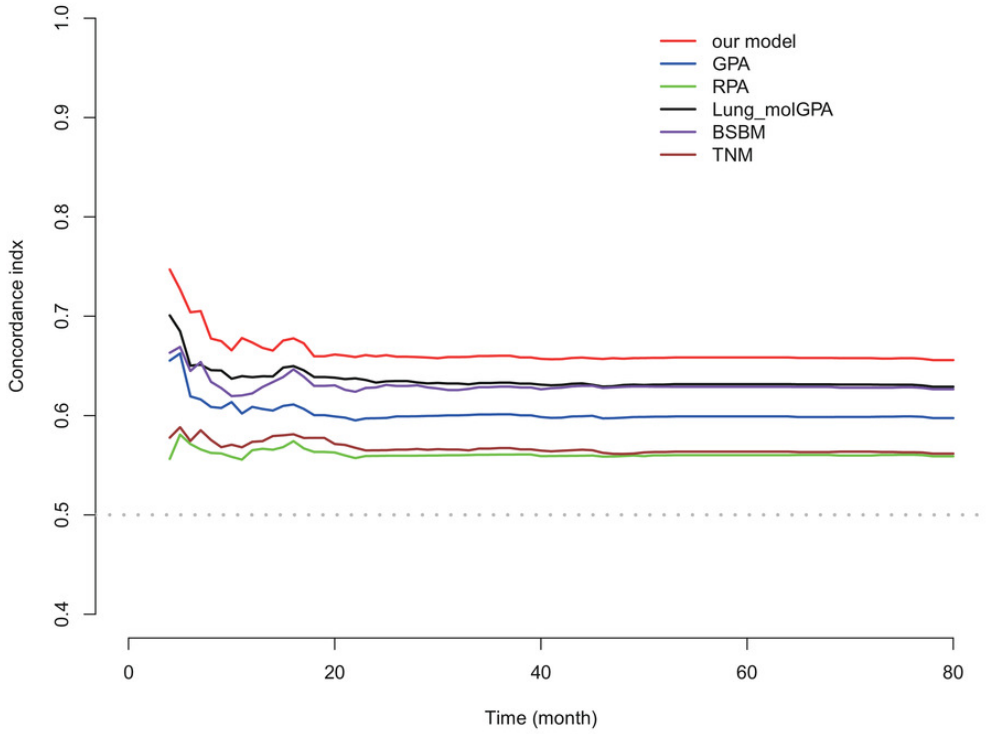

Time−dependent C−index(Bootcv B=1000)
our model
GPA
RPA
Lung_molGPA
BSBM
TNM
Concordance indx
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
20
40
60
80
Time (month)

Figure 5

The DCA curves of the six models.

Figure 5. The DCA curves of the six models. The decision curves show that the threshold probabilities of our models range from 0.4-0.8, which is the widest threshold range of all models. Among most of the threshold ranges, our constructed model has the highest net benefit overall DCA curves compared to the curves for all treatment ("ALL" curve), no treatment ("None" curve), and the other three models.

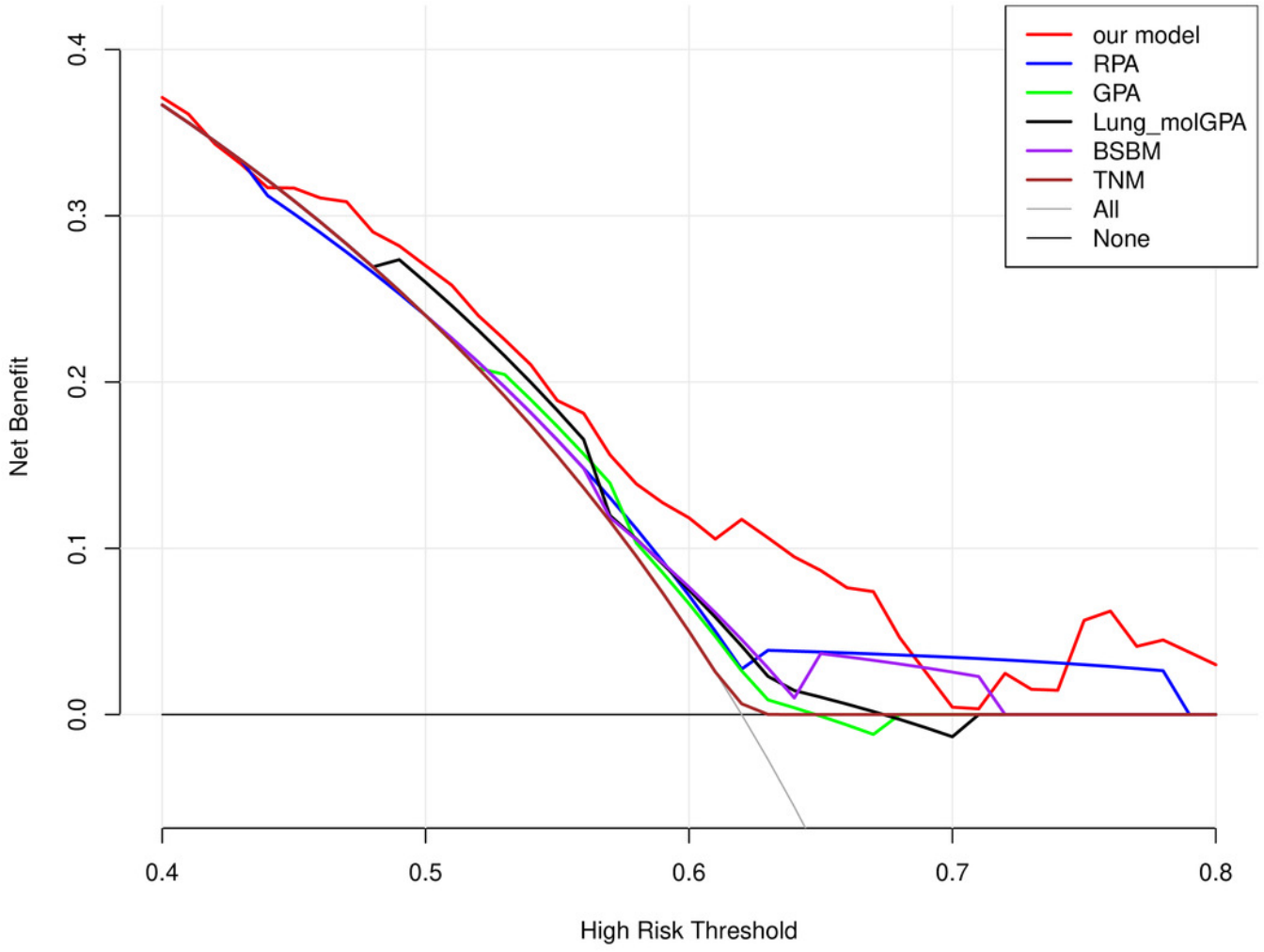


Figure 6

Constructed nomogram for predicting 1, 3, and 5-year OS in NSCLC patients diagnosed with BM based on 15 predictors.

Figure 6. Constructed nomogram for predicting 1, 3, and 5-year OS in NSCLC patients diagnosed with BM based on 15 predictors. The nomogram is used by summing the points for each prognostic factor. The total score on the bottom scale corresponds to the patient's probability of survival at 1, 3, and 5 years.

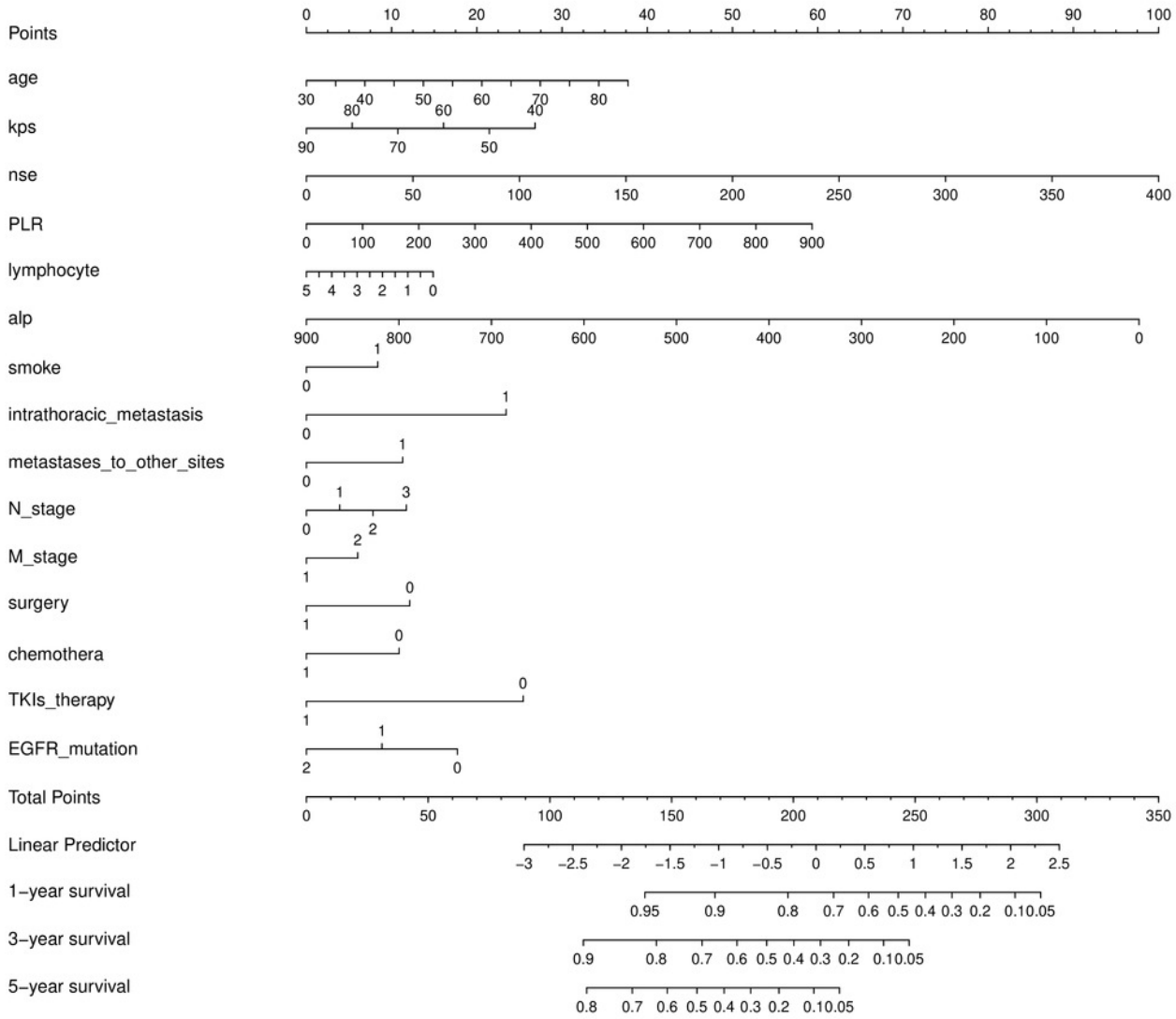
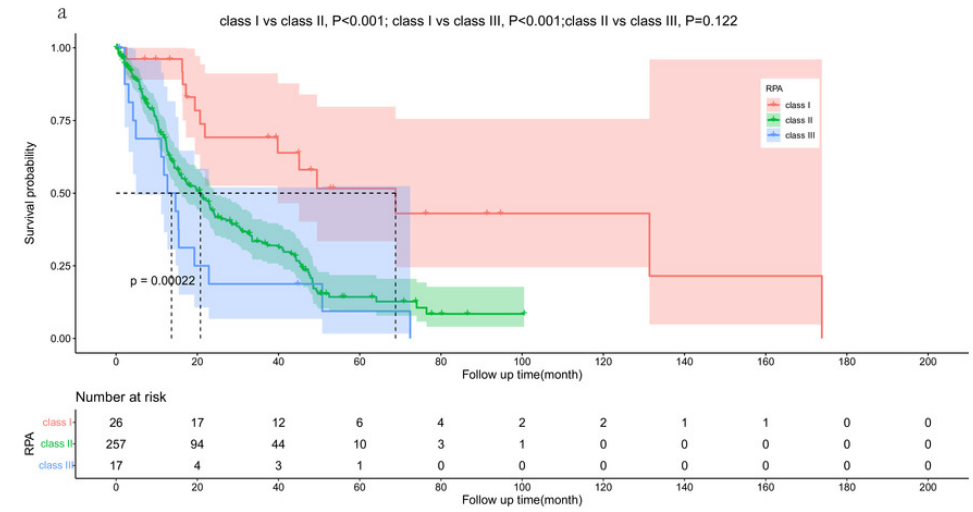
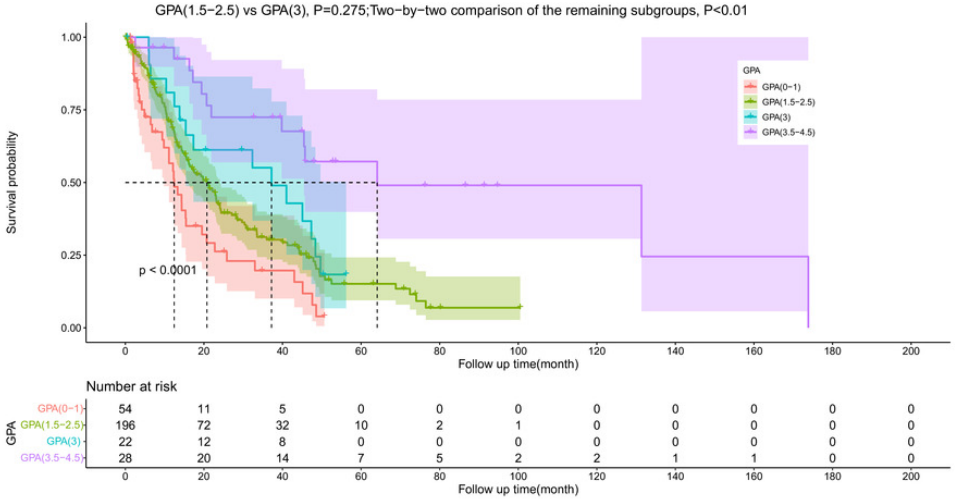

Points
0 10 20 30 40 50 60 70 80 90 100
age
30 40 50 60 70 80
kps
80 60 40
90 70 50
nse
0 50 100 150 200 250 300 350 400
PLR
0 100 200 300 400 500 600 700 800 900
lymphocyte
5 4 3 2 1 0
alp
900 800 700 600 500 400 300 200 100 0
smoke
1
0
intrathoracic_metastasis
1
0
metastases_to_other_sites
1
0
N_stage
1 3
0 2
M_stage
2
1
surgery
0
1
chemothera
0
1
TKIs_therapy
0
1
EGFR_mutation
1
2 0
Total Points
0 50 100 150 200 250 300 350
Linear Predictor
−3 −2.5 −2 −1.5 −1 −0.5 0 0.5 1 1.5 2 2.5
1−year survival
0.95 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05
3−year survival
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05
5−year survival
0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05

Figure 7

Kaplan-Meier survival curve analysis for different models.

Figure 7. Kaplan-Meier survival curve analysis for different models. Kaplan-Meier plots are shown for RPA(a), GPA(b), Lung-molGPA(c), BSBM(d), our model(e) and TNM staging(f).


a
class I vs class II, P<0.001; class I vs class III, P<0.001;class II vs class III, P=0.122
Survival probability
p = 0.00022
RPA
class I
class II
class III
Follow up time(month)
Number at risk
class I 26 17 12 6 4 2 2 1 1 0 0
class II 257 94 44 10 3 1 0 0 0 0 0
class III 17 4 3 1 0 0 0 0 0 0 0


b
GPA(1.5−2.5) vs GPA(3), P=0.275;Two−by−two comparison of the remaining subgroups, P<0.01
Survival probability
p < 0.0001
GPA
GPA(0−1)
GPA(1.5−2.5)
GPA(3)
GPA(3.5−4.5)
Follow up time(month)
Number at risk
GPA(0−1) 54 11 5 0 0 0 0 0 0 0 0
GPA(1.5−2.5) 196 72 32 10 2 1 0 0 0 0 0
GPA(3) 22 12 8 0 0 0 0 0 0 0 0
GPA(3.5−4.5) 28 20 14 7 5 2 2 1 1 0 0

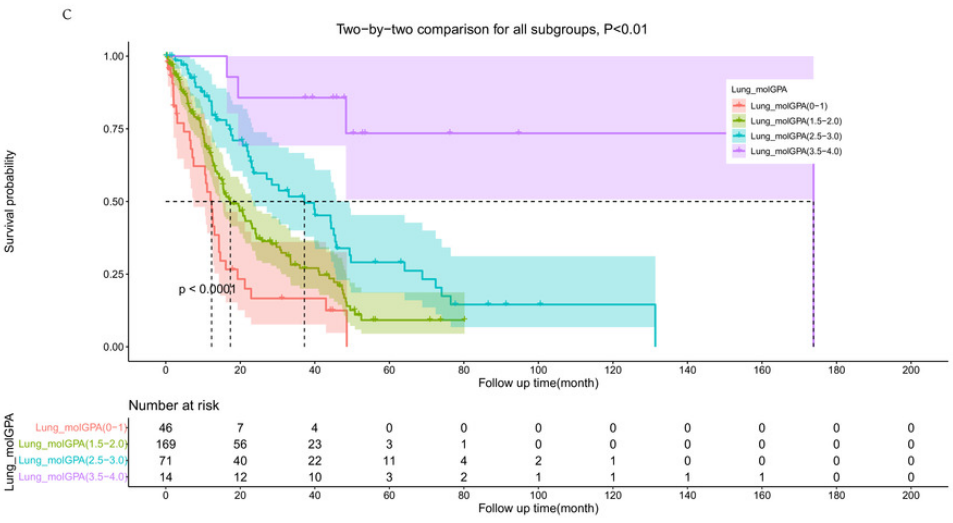
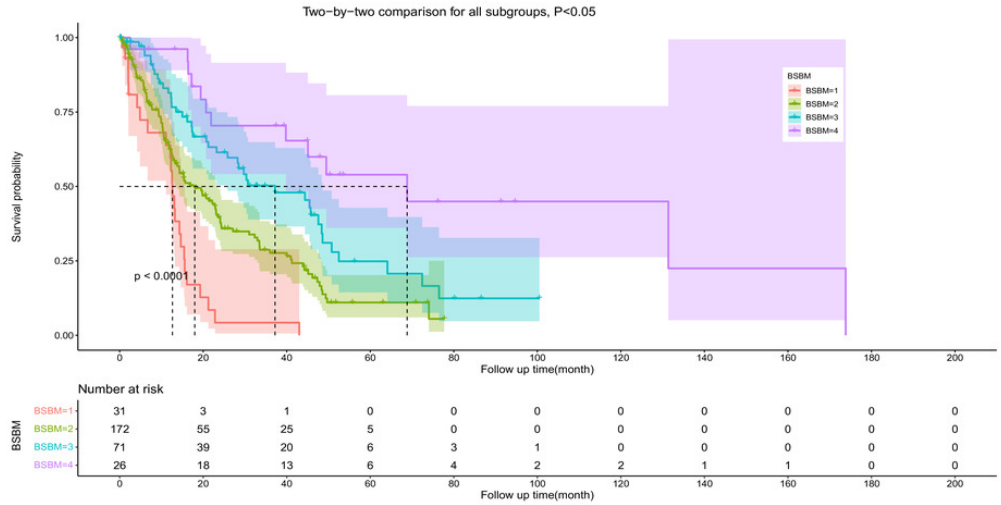

c
Two−by−two comparison for all subgroups, P<0.01
Survival probability
p < 0.0001
Lung_molGPA
Lung_molGPA(0−1)
Lung_molGPA(1.5−2.0)
Lung_molGPA(2.5−3.0)
Lung_molGPA(3.5−4.0)
Follow up time(month)
Number at risk
Lung_molGPA(0−1) 46 7 4 0 0 0 0 0 0 0 0
Lung_molGPA(1.5−2.0) 169 56 23 3 1 0 0 0 0 0 0
Lung_molGPA(2.5−3.0) 71 40 22 11 4 2 1 0 0 0 0
Lung_molGPA(3.5−4.0) 14 12 10 3 2 1 1 1 1 0 0

Figure 8

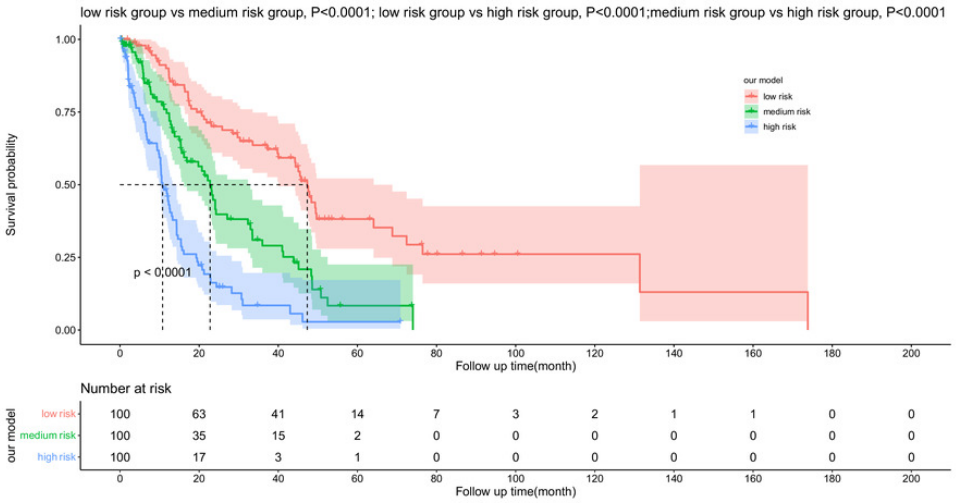
Kaplan-Meier survival curve analysis for different models.

Figure 8. Kaplan-Meier survival curve analysis for different models. Kaplan-Meier plots are shown for RPA(a), GPA(b), Lung-molGPA(c), BSBM(d), our model(e) and TNM staging(f).

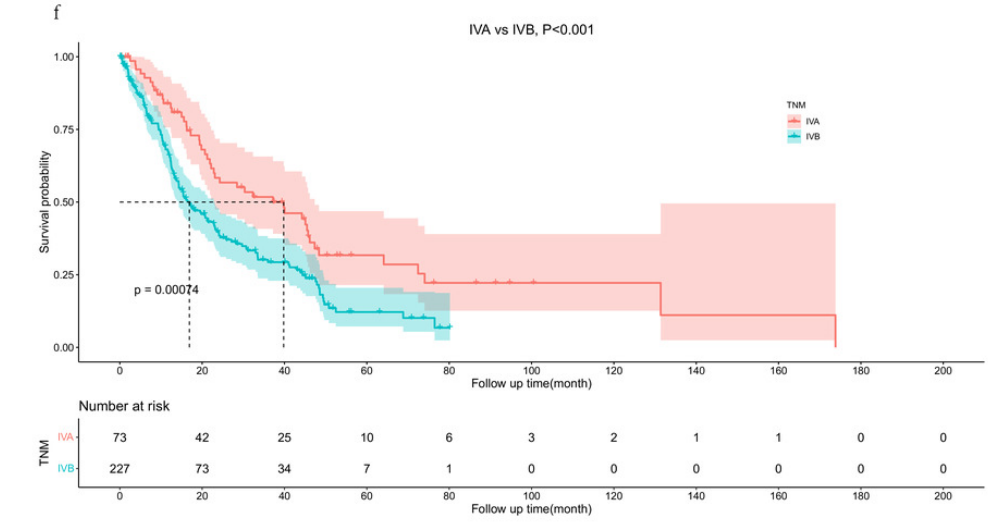
d


Two−by−two comparison for all subgroups, P<0.05
Survival probability
p < 0.0001
BSBM
BSBM=1
BSBM=2
BSBM=3
BSBM=4
Follow up time(month)
Number at risk
BSBM=1 31 3 1 0 0 0 0 0 0 0 0
BSBM=2 172 55 25 5 0 0 0 0 0 0 0
BSBM=3 71 39 20 6 3 1 0 0 0 0 0
BSBM=4 26 18 13 6 4 2 2 1 1 0 0

e


low risk group vs medium risk group, P<0.0001; low risk group vs high risk group, P<0.0001;medium risk group vs high risk group, P<0.0001
Survival probability
p < 0.0001
our model
low risk
medium risk
high risk
Follow up time(month)
Number at risk
low risk 100 63 41 14 7 3 2 1 1 0 0
medium risk 100 35 15 2 0 0 0 0 0 0 0
high risk 100 17 3 1 0 0 0 0 0 0 0

f


IVA vs IVB, P<0.001
Survival probability
p = 0.00074
TNM
IVA
IVB
Follow up time(month)
Number at risk
IVA 73 42 25 10 6 3 2 1 1 0 0
IVB 227 73 34 7 1 0 0 0 0 0 0