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ORIGINAL RESEARCH

Multicenter Development of a Clinical-Molecular Nomogram for Predicting Survival in Lung Cancer Brain Metastasis Patients

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Background: Lung cancer brain metastasis (LCBM) accounts for 40–50% of intracranial malignancies, with emerging evidence of alternative metastatic pathways circumventing the blood-brain barrier. Existing prognostic models lack validation in Asian populations and molecular stratification. This multicenter study aimed to develop a clinical nomogram integrating clinicopathological and molecular determinants for personalized LCBM management.

Methods: Retrospective analysis of 522 surgically treated LCBM patients (2015–2021) from four Chinese institutions was conducted. Patients were randomized 7:3 into training (n=365) and validation (n=157) cohorts. Multivariate Cox regression identified independent prognostic factors, which were incorporated into a nomogram predicting 6-/12-/18-month overall survival (OS). Model performance was assessed via time-dependent ROC curves (AUC), calibration plots, and decision curve analysis (DCA).

Results: The median OS after neurosurgery was 9 months (range: 4–18 months), with 6-, 12-, and 18-month survival rates of 86.2%, 46.7%, and 17.2%, respectively. Independent predictive factors included brain metastasis size ≥5 cm, Leptomeningeal metastasis(LM), EGFR mutation with TKI treatment, and extracranial metastases. The nomogram demonstrated robust discriminative ability and calibration. EGFR-mutant patients receiving postoperative TKIs showed significantly prolonged survival attributable to enhanced blood-brain barrier permeability. Finally, the authors developed a web-based dynamic nomogram for LCBM patients to facilitate clinical implementation.

Conclusion: This study establishes a validated prognostic model integrating tumor burden, EGFR mutation status, and metastatic patterns. It demonstrates that EGFR-guided TKI therapy and bone metastasis surveillance critically influence LCBM outcomes. The nomogram provides a quantifiable framework for risk-adapted therapeutic decisions, advancing precision oncology in neuro-oncology practice.

Keywords: nomogram, overall survival, lung cancer brain metastases, cranial metastases, surgery

Introduction

Lung cancer (LC), as the leading cause of global cancer morbidity and mortality, poses a significant public health threat in China with approximately 1.06 million new cases annually and a mortality rate of 28.5 per 100,000.[1,2] Approximately 40–50% of LC patients develop brain metastases during disease progression, with its incidence surpassing gliomas to become the most prevalent type of intracranial malignancy.[3,4] The mechanisms underlying lung cancer brain metastasis (LCBM) formation include the classical hematogenous dissemination route (intracranial vascular invasion by cancer cells) and novel metastatic patterns revealed through breakthrough research: tumor cells may migrate along the perivascular spaces of vertebral vessels,[5,6] penetrating the leptomeninges via cranial emissary veins to infiltrate brain

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parenchyma. This pathway completely circumvents blood-brain barrier(BBB) defense mechanisms.[7] Notably, the bone metastatic pattern, as a newly identified LCBM pathway, demonstrates insufficient clinical translatability evidence thus far.

In recent years, innovations in targeted/immunotherapy have significantly extended median survival in advanced LC. Evidence-based medicine findings demonstrate that LCBM prognosis is strongly associated with driver gene status.[8] While patients with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) exhibit 27–35% prolonged survival compared to wild-type counterparts, their risk of brain metastasis increases 2–3-fold.[9–11] However, the underlying pathophysiological mechanisms of this paradoxical association between genotype and metastatic risk remain incompletely elucidated.

Additionally, the quantitative associations between features such as brain metastasis volume (>3cm), Leptomeningeal metastasis(LM), neurological dysfunction, and extracranial multi-organ metastases with survival outcomes still require validation through large-scale studies. While existing prognostic models based on Recursive Partitioning Analysis (RPA) classification and Graded Prognostic Assessment (GPA) scores provide clinical references,[12,13] their generalizability within Asian populations with LCBM has not yet been sufficiently validated.

This study, utilizing multi-center clinical data from socioeconomically diverse regions including Fujian, Jiangxi, and Guangxi, systematically investigated prognostic variables in postoperative LCBM patients, with particular focus on elucidating the mechanistic impacts of EGFR mutation status, bone metastatic patterns, and clinicopathological characteristics. By developing a clinicopathological nomogram model with clinically significant predictive efficacy, it provides robust evidence-based evidence to inform precision medicine practices and stratified clinical trial management.

Materials and Methods

Patient Selection

This retrospective analysis examined 1158 LCBM surgical cases from January 2015 to January 2021, ultimately enrolling 522 eligible patients (Figure 1). The cohort comprised cases from four institutions: The First Affiliated Hospital of Xiamen University (128), Ganzhou People's Hospital (261), Guilin Medical University Affiliated Hospital (90), and Guangxi Second People's Hospital (43). Participants were randomized 7:3 into training (n=365) and validation (n=157) cohorts. Conducted per *China's Clinical Practice Guideline for Lung Cancer Brain Metastases*,[14] the study followed surgical recommendations throughout, with operative indications including: 1) Single lesion in anatomically resectable locations (eg, non-eloquent cortex); 2) Significant mass effect (perilesional edema >30 mL) or obstructive hydrocephalus; 3) Acute intracranial pressure decompensation (tumor hemorrhage, impending herniation); 4) Diagnostic histopathological confirmation. All data underwent consensus review by neurosurgical, radiological, and pathological specialists.

This study conducted a systematic review of 1158 surgically managed LCBM cases from healthcare institutions across four provinces between January 2015 and January 2021, ultimately enrolling 522 rigorously screened surgical patients meeting inclusion criteria (Figure 1). The cohort comprised four regional medical centers: The First Affiliated Hospital of Xiamen University (n=128), Ganzhou People's Hospital (n=261), Guilin Medical University Affiliated Hospital (90), and Guangxi Second People's Hospital (43), with cases randomly allocated in a 7:3 ratio to model training (n=365) and internal validation cohorts (n=157). The protocol strictly adhered to *the Chinese Clinical Practice Guideline for Brain Metastases of Lung Cancer*,[14] with surgical indications for LCBM defined as: ① Solitary lesion with anatomically favorable location for gross total resection (eg, non-eloquent cortical areas); ② Significant mass effect (peritumoral edema volume >30mL) or obstructive hydrocephalus; ③ Acute intracranial pressure decompensation (tumor apoplexy/pre-herniation status); ④ Surgical intervention for histopathological diagnostic confirmation.

Inclusion Criteria

(1) Histopathologically confirmed pulmonary-origin brain metastases;
(2) PET-CT/contrast-enhanced MRI verified lung as the sole primary lesion;
(3) Postoperative systemic chemotherapy ≥3 weeks and complete follow-up records

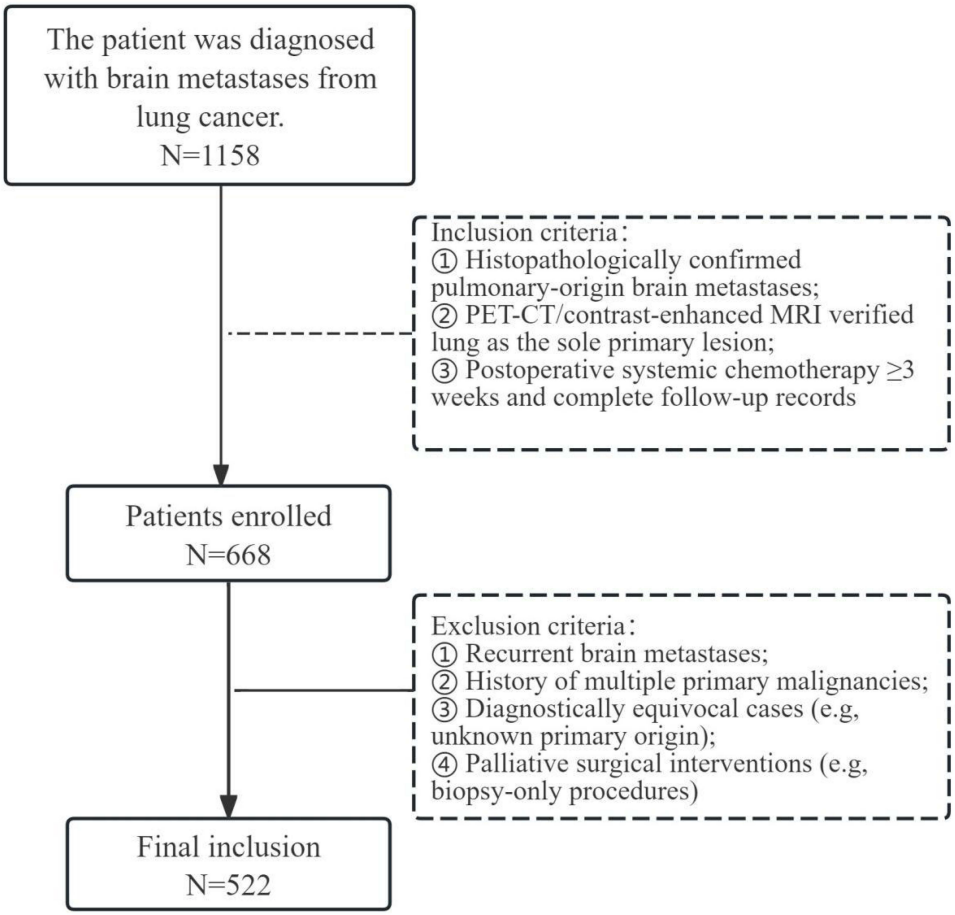

Figure 1 Flow chart for patient selection.

Exclusion Criteria

(1) Recurrent brain metastases;
(2) History of multiple primary malignancies;
(3) Diagnostically equivocal cases (eg, unknown primary origin);
(4) Palliative surgical interventions (eg, biopsy-only procedures)

Ethical Statement

This study received approval from the Institutional Review Board of The First Affiliated Hospital of Xiamen University (XMYY-2022KY076). In accordance with national regulations for retrospective observational studies using fully anonymized data, the requirement for informed consent was formally waived. All procedures strictly adhered to the ethical principles of the Declaration of Helsinki.

Data Collection and Variables Definitions

Collected patient data included: gender, age, presenting symptoms, histological subtype, skull invasion, LM, tumor number, tumor size (The maximum diameter of the tumor on CT or MRI scans), extracranial metastases, EGFR mutation status, survival data, and cause of death.

Overall survival (OS) was defined as the duration from craniotomy diagnosis to death or last follow-up, with the final follow-up date being December 31, 2024.

Survival Data Analysis, Nomogram Construction and Evaluation

All data were organized and analyzed using Microsoft Excel (version 2016), SPSS (version 25.0), and R (version 4.4). All patients were randomly divided into training and validation sets at a 7:3 ratio and classified using R software. We then used the training set to identify independent prognostic factors associated with OS and construct a prognostic nomogram, while the validation set was used to verify the nomogram's performance. Details are as follows:

(1) Screening of influencing factors: Using overall survival (OS) of brain metastasis patients as the dependent variable, potential predictors with statistical significance (P<0.10) were first screened via univariate Cox regression analysis, incorporating clinically observed features with potential prognostic value to form an initial variable pool. Risk variables identified by univariate Cox regression (P<0.1) were further analyzed using multivariate Cox regression to determine independent prognostic factors associated with OS in LCBM patients.

(2) Nomogram development: A visual predictive tool was constructed based on the final Cox model parameters. Through linear transformation, the regression coefficients of each independent prognostic variable were mapped to a 0–100-point scoring scale. The total score for individual patients was obtained by summing the corresponding points for each variable. This total score could then be converted into predicted probabilities of 6-month, 12-month, and 18-month survival, enabling individualized prognostic assessment.

(3) Model validation system: Model performance was evaluated using a multidimensional approach:

① Discriminative ability: Time-dependent receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC), assessing sensitivity and specificity for 6-, 12-, and 18-month survival predictions.

② Calibration: Bootstrap resampling (1000 repetitions) was used to generate calibration curves, evaluating the agreement between predicted survival rates and actual Kaplan-Meier estimates.

③ Clinical utility: Decision curve analysis (DCA) quantified the model's net benefit across different threshold probabilities.

④ Internal validation: Bootstrap resampling was applied to calculate the corrected mean AUC and its 95% confidence interval, assessing the degree of model overfitting.

Results

Patient Characteristics

According to our inclusion criteria, a total of 522 patients were enrolled, including 372 males (71.26%) and 150 females (28.74%). The median age at BM surgery was 61 years (range: 31–81 years). Histopathological subtypes included: adenocarcinoma (42.91%), squamous cell carcinoma (22.8%), large cell carcinoma (19.92%), and small cell carcinoma (14.37%). In addition to brain tissue involvement, 72 cases (13.79%) presented with skull invasion and 84 cases (16.09%) had LM. Detailed demographic and clinicopathological characteristics are summarized in Table 1 below.

Survival Analysis

Kaplan-Meier Survival Curves and Associated Parameters

At final follow-up, 16 of the 522 enrolled patients remained alive, with a median overall survival (OS) of 9 months (range: 4–18 months). The survival rates at 6, 12, 18, 24, and 36 months were 86.20%, 46.74%, 17.24%, 9.96%, and 4.21%, respectively (Figure 2A). Significant prognostic factors included tumor size, multiplicity, and anatomical location (Figure 2B–E); histopathological characteristics, intracranial hemorrhage, and clinical manifestations (Figure 2F–I); and extracranial metastasis status with postoperative therapeutic strategies (Figure 2J–N).

Univariate and Multivariate Cox Regression Analyses

All patients were included in univariate and multivariate analyses to identify survival predictors. Univariate analysis revealed significantly worse prognosis for patients with LM (HR=2.93, 95% CI: 2.19–3.91, P<0.001) and intratumoral hemorrhage (HR=1.48, 95% CI: 1.03–2.14, P=0.034). Additionally, brain metastasis area >5 cm (HR=2.14, 95% CI: 1.42–3.24, P<0.001), tumor number >3 (HR=0.78, 95% CI: 0.50–1.21, P=0.27), concurrent neurological signs and intracranial hypertension symptoms (HR=2, 95% CI: 1.45–2.74, P<0.001), Small cell lung cancer (SCLC) (HR=2.5, 95%

Table 1 Baseline Demographic and Clinicopathological Characteristics of OS-Related Variables in Lung Cancer with Brain Metastases

Variables	Total	Training Set	Validation Set
	522 (100.00%)	366 (70.11%)	156 (29.89%)
Survival state			
Survival	16 (3.07%)	13 (3.55%)	3 (1.92%)
Death	506 (96.93%)	353 (96.45%)	153 (98.08%)
Gender			
Male	372 (71.26%)	258 (70.49%)	114 (73.08%)
Female	150 (28.74%)	108 (29.51%)	42 (26.92%)
Cranial metastases			
No	450 (86.21%)	317 (86.61%)	133 (85.26%)
Yes	72 (13.79%)	49 (13.39%)	23 (14.74%)
Meningeal metastases			
No	438 (83.91%)	318 (86.89%)	120 (76.92%)
Yes	84 (16.09%)	48 (13.11%)	36 (23.08%)
Stage of lung cancer when first diagnosed			
Stage 1	44 (8.43%)	32 (8.74%)	12 (7.69%)
Stage 2	176 (33.72%)	115 (31.42%)	61 (39.1%)
Stage 3	160 (30.65%)	119 (32.51%)	41 (26.28%)
Stage 4	142 (27.2%)	100 (27.32%)	42 (26.92%)
Brain Metastases Size			
≤3cm	50 (9.58%)	33 (9.02%)	17 (10.9%)
3–5cm	322 (61.69%)	223 (60.93%)	99 (63.46%)
>5cm	150 (28.74%)	110 (30.05%)	40 (25.64%)
Number of brain metastases			
1	353 (67.62%)	242 (66.12%)	111 (71.15%)
2	131 (25.1%)	98 (26.78%)	33 (21.15%)
≥3	38 (7.28%)	26 (7.1%)	12 (7.69%)
Clinical manifestation			
Asymptomatic	93 (17.62%)	69 (18.85%)	24 (15.38%)
Intracranial hypertension	111 (21.26%)	84 (22.95%)	27 (17.31%)
Neurological symptoms	165 (31.61%)	107 (29.23%)	58 (37.18%)
Both of them	153 (29.31%)	106 (28.96%)	47 (30.13%)
Ki-67 index			
<5%	10 (1.92%)	7 (1.91%)	3 (1.92%)
≥5%	512 (98.08%)	359 (98.09%)	153 (98.08%)
BMI			
≤18.5	32 (6.13%)	24 (6.56%)	8 (5.13%)
18.5–24.9	481 (92.15%)	336 (91.8%)	145 (92.95%)
>25	9 (1.72%)	6 (1.64%)	3 (1.92%)

(*Continued*)

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Table 1 (Continued).

Variables	Total	Training Set	Validation Set
	522 (100.00%)	366 (70.11%)	156 (29.89%)
Pathological types			
Adenocarcinoma	224 (42.91%)	156 (42.62%)	68 (43.59%)
Squamous Carcinoma	119 (22.8%)	89 (24.32%)	30 (19.23%)
Large Cell Carcinoma	104 (19.92%)	68 (18.58%)	36 (23.08%)
Small Cell Carcinoma	75 (14.37%)	53 (14.48%)	22 (14.1%)
Grade of pathology			
Low differentiation	292 (55.94%)	211 (57.65%)	81 (51.92%)
Moderately differentiated	145 (27.78%)	98 (26.78%)	47 (30.13%)
Highly differentiated	85 (16.28%)	57 (15.57%)	28 (17.95%)
Extracranial bone metastases			
No	169 (32.38%)	109 (29.78%)	60 (38.46%)
Yes	353 (67.62%)	257 (70.22%)	96 (61.54%)
Liver metastases			
No	316 (60.54%)	233 (6.66%)	83 (53.21%)
Yes	206 (39.45%)	133 (36.34%)	73 (46.79%)
Intrapulmonary metastases			
No	392 (75.1%)	286 (78.14%)	106 (67.95%)
Yes	130 (24.9%)	80 (21.86%)	50 (32.05%)
Lymphatic metastases			
No	257 (49.23%)	191 (52.19%)	66 (42.31%)
Yes	265 (50.77%)	175 (47.81%)	90 (57.69%)
Adrenal metastases			
No	431 (82.76%)	304 (83.06%)	127 (81.41%)
Yes	91 (17.43%)	62 (16.94%)	29 (18.59%)
Treatment of primary lung cancer before brain metastases			
No treatment	74 (14.18%)	52 (14.21%)	22 (14.1%)
One scheme	64 (12.26%)	47 (12.84%)	17 (10.9%)
Two scheme	264 (50.57%)	185 (50.55%)	79 (50.64%)
Three scheme or more	120 (22.99%)	82 (22.4%)	38 (24.36%)
Intratumoral hemorrhage			
No	475 (91.0%)	337 (92.08%)	138 (88.46%)
Yes	47 (9.0%)	29 (7.92%)	18 (11.54%)
Postoperative treatment of brain metastases			
Less than two scheme	416 (79.69%)	289 (78.96%)	127 (81.41%)
Three or more scheme	106 (20.31%)	77 (21.04%)	29 (18.59%)
Age	61 (56, 66)	62 (57, 66)	61 (56, 65)
Time between brain metastases and lung cancer	9 (4, 18)	9 (4, 18)	9 (4, 18.25)

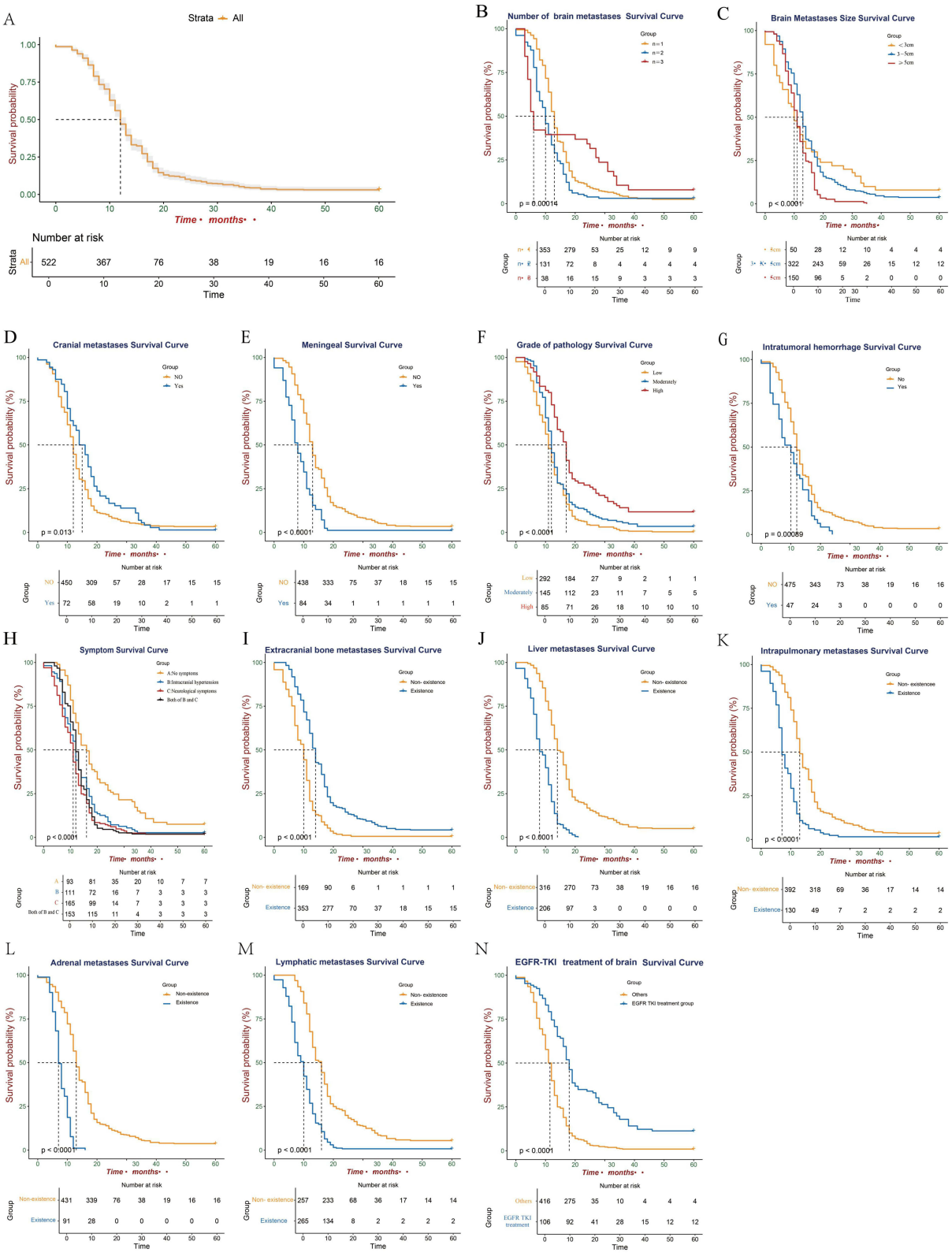

Figure 2 Analysis of overall survival-related risk variables in patients with cranial metastases from lung cancer using Kaplan-Meier survival curves. (**A**) Overall survival curve; (**B**) Tumor size; (**C**) Number of tumors; (**D**) Meningeal metastases; (**E**) Craniofacial metastases; (**F**) Type of pathology; (**G**) Intratumoral hemorrhage; (**H**) Clinical presentation; (**I**) Extracranial bone metastases; (**J**) Contralateral lung metastases; (**K**) Lymphatic metastases; (**L**) Hepatic metastases; (**M**) Adrenal metastases; (**N**) EGFR-TKI treatment of brainSurvival Curve.

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CI: 1.83–3.42, P<0.001), and poorly differentiated adenocarcinoma (HR=0.46, 95% CI: 0.33–0.64, P<0.001) were significantly associated with shorter BMOS. Other variables, including extracranial metastases (bone, liver, lung, lymph nodes, adrenal glands, etc), initial LC diagnosis stage, and whether patients received active treatment after craniotomy, also showed significant correlations with survival (Table 2).

Table 2 Univariate and Multivariate Cox Regression Analysis of OS-Related Variables in Lung Cancer Patients with Craniocerebral Metastases

Variables	Number of Patients	Univariate Cox Regression Analysis		Multivariate Cox Regression Analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Gender					
Male	260 (71.0%)	Reference			
Female	106 (29.0%)	0.94 (0.74–1.19)	0.604		
Brain Metastases Size					
≤3cm	33 (9.0%)	Reference		Reference	
3–5cm	223 (60.9%)	1.20 (0.82–1.77)	0.349	1.12 (0.72–1.72)	0.620
>5cm	110 (30.1%)	2.14 (1.42–3.24)	<0.001	1.73 (1.11–2.71)	0.016
Number of brain metastases					
1	251 (68.6%)	Reference		Reference	
2	92 (25.1%)	1.49 (1.17–1.91)	0.001	1.28 (0.98–1.67)	0.076
≥3	23 (6.3%)	0.78 (0.50–1.21)	0.270	1.37 (0.83–2.26)	0.219
Clinical manifestation					
Asymptomatic	71 (19.4%)	Reference		Reference	
Intracranial hypertension	72 (19.7%)	1.89 (1.34–2.65)	<0.001	1.30 (0.88–1.90)	0.185
Neurological symptoms	114 (31.1%)	2.28 (1.67–3.12)	<0.001	1.35 (0.95–1.91)	0.090
Both of them	109 (29.8%)	2.00 (1.45–2.74)	<0.001	1.65 (1.17–2.34)	0.005
Ki-67 index					
<5%	6 (1.6%)	Reference			
≥5%	360 (98.4%)	0.96 (0.43–2.15)	0.917		
BMI					
≤18.5	22 (6.0%)	Reference			
18.5–24.9	339 (92.6%)	0.78 (0.51–1.21)	0.270		
>25	5 (1.4%)	1.04 (0.39–2.75)	0.942		
Pathological types					
Adenocarcinoma	157 (42.9%)	Reference		Reference	
Squamous Carcinoma	83 (22.7%)	1.19 (0.91–1.56)	0.214	1.10 (0.83–1.47)	0.507
Large Cell Carcinoma	70 (19.1%)	1.33 (0.99–1.77)	0.055	1.09 (0.80–1.48)	0.587
Small cell lung cancer (SCLC)	56 (15.3%)	2.50 (1.83–3.42)	<0.001	1.85 (1.31–2.61)	0.001
Grade of pathology					
Low differentiation	204 (55.7%)	Reference		Reference	
Moderately differentiated	109 (29.8%)	0.77 (0.61–0.98)	0.031	0.95 (0.73–1.22)	0.672
Highly differentiated	53 (14.5%)	0.46 (0.33–0.64)	<0.001	0.54 (0.38–0.77)	0.001

(*Continued*)

Table 2 (Continued).

Variables	Number of Patients	Univariate Cox Regression Analysis		Multivariate Cox Regression Analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Cranial metastases					
No	317 (86.6%)	Reference		Reference	
Yes	49 (13.4%)	0.74 (0.54–1.00)	0.049	0.51 (0.34–0.77)	0.001
Leptomeningeal metastasis					
No	306 (83.6%)	Reference		Reference	
Yes	60 (16.4%)	2.93 (2.19–3.91)	<0.001	2.35 (1.64–3.36)	<0.001
Stage of lung cancer when first diagnosed					
Stage 1	27 (7.4%)	Reference		Reference	
Stage 2	128 (35.0%)	1.14 (0.74–1.76)	0.539	1.40 (0.88–2.23,)	0.161
Stage 3	115 (31.4%)	1.44 (0.93–2.23)	0.102	1.62 (1.01–2.61)	0.046
Stage 4	96 (26.2%)	1.47 (0.95–2.30)	0.086	1.70 (1.04–2.76)	0.034
Extracranial bone metastases					
No	111 (30.3%)	Reference		Reference	
Yes	255 (69.7%)	0.41 (0.32–0.52)	<0.001	1.29 (0.86–1.96)	0.221*
Liver metastases					
No	222 (60.7%)	Reference		Reference	
Yes	144 (39.3%)	3.27 (2.60–4.12)	<0.001	1.46 (0.99–2.15)	0.054*
Intrapulmonary metastases					
No	279 (76.2%)	Reference		Reference	
Yes	87 (23.8%)	2.78 (2.17–3.57)	<0.001	1.70 (1.17–2.48)	0.006
Lymphatic metastases					
No	181 (49.5%)	Reference		Reference	
Yes	185 (50.5%)	3.20 (2.54–4.03)	<0.001	1.83 (1.24–2.71)	0.002
Adrenal metastases					
No	304 (83.1%)	Reference		Reference	
Yes	62 (16.9%)	5.54 (4.03–7.61)	<0.001	1.70 (1.08–2.68)	0.023
Treatment of lung cancer after diagnosis					
No treatment	54 (14.8%)	Reference			
One scheme	38 (10.4%)	1.01 (0.66–1.54)	0.960		
Two scheme	185 (50.5%)	1.22 (0.89–1.67)	0.211		
Three scheme or more	89 (24.3%)	1.00 (0.71–1.42)	0.978		
Intratumoral hemorrhage					
No	334 (91.3%)	Reference		Reference	
Yes	32 (8.7%)	1.48 (1.03–2.14)	0.034	1.19 (0.81–1.76)	0.373
Postoperative treatment of brain					
Less than two scheme	296 (80.9%)	Reference		Reference	
Three or more scheme	70 (19.1%)	0.33 (0.24–0.44)	<0.001	0.41 (0.29–0.56)	<0.001
Age (Mean ± SD)	61.3 ± 7.3	1.00 (0.98–1.02)	0.970		

Notes: *$P > 0.05$; It was retained due to its significant clinical value and contribution to the model.

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Further multivariate Cox regression analysis demonstrated that brain metastasis size ≥5 cm, multiple brain metastases, presence of neurological clinical manifestations, preoperative intratumoral hemorrhage, poorly differentiated SCLC, skull metastasis, LM, stage IV LC at initial diagnosis, extracranial metastases (bone, liver, contralateral lung, lymph node, adrenal gland), and EGFR-positive status with TKI treatment were all independent prognostic factors for LCBM patients (Table 2).

Nomogram Development and Validation

The 15 independent prognostic predictors identified from the multivariate Cox regression analysis were integrated to construct a predictive nomogram for quantitatively assessing 6-month, 12-month, and 18-month OS risk in LCBM patients (Figure 3). By assigning weighted scores to each variable and calculating the total points, the nomogram estimated individual mortality probabilities for LCBM patients. All patients were then randomly divided into training

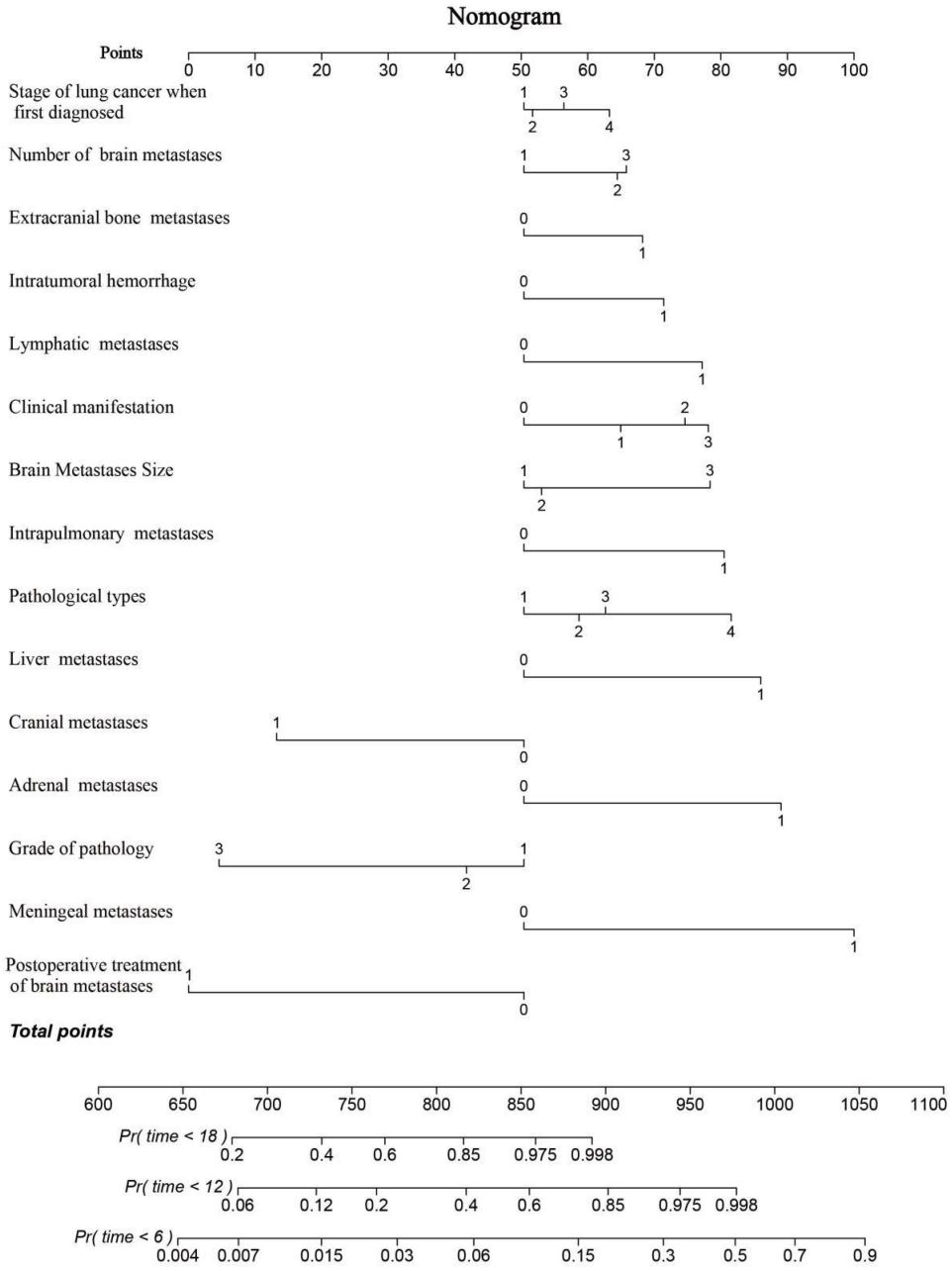

Figure 3 The prognostic nomogram predicts the 6, 12, and 18 months probability of OS in patients with LCBM.

(Figure 4A) and validation cohorts (Figure 4B) at a 7:3 ratio. Calibration curves at 6, 12, and 18 months demonstrated close agreement between predicted and observed mortality probabilities in both cohorts, confirming the nomogram's high predictive accuracy.

In the training cohort, the AUC values for the ROC curves were 0.919 (6-month), 0.872 (12-month), and 0.927 (18-month, Figure 5A), while in the validation cohort the corresponding values were 0.900, 0.851, and 0.873 (Figure 5B), indicating robust discriminative ability of the nomogram. Furthermore, decision curve analysis confirmed that the nomogram serves as an effective clinical tool for evaluating mortality risk in LCBM patients, demonstrating significant clinical utility (Figure 6A and B).

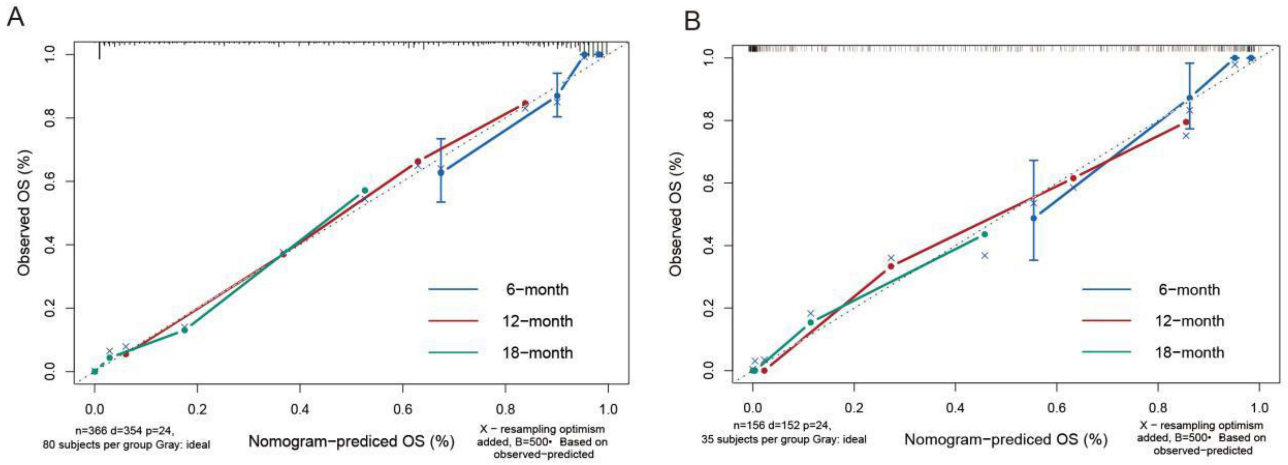

Figure 4 Calibration curves for 6, 12 and 18 months prediction in training set (**A**) and validation set (**B**).

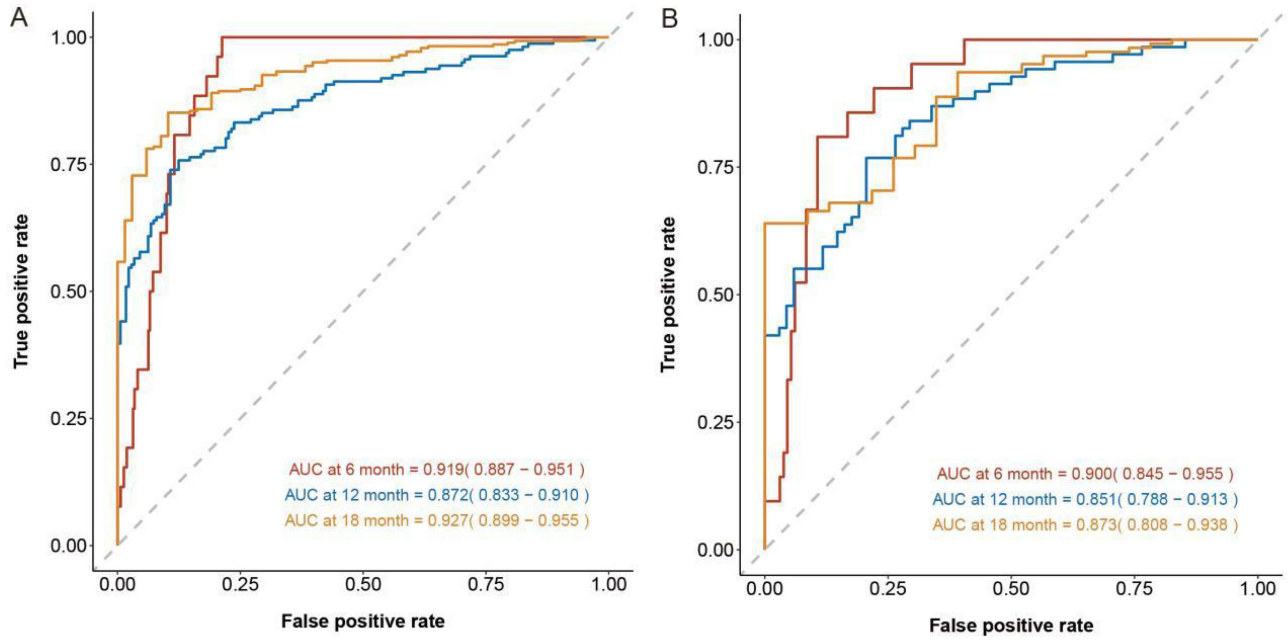

Figure 5 Receiver operating characteristic curves for 6 months, 12 months, and 18 months probability of OS in patients with LCBM in the training (**A**) and validation set (**B**).

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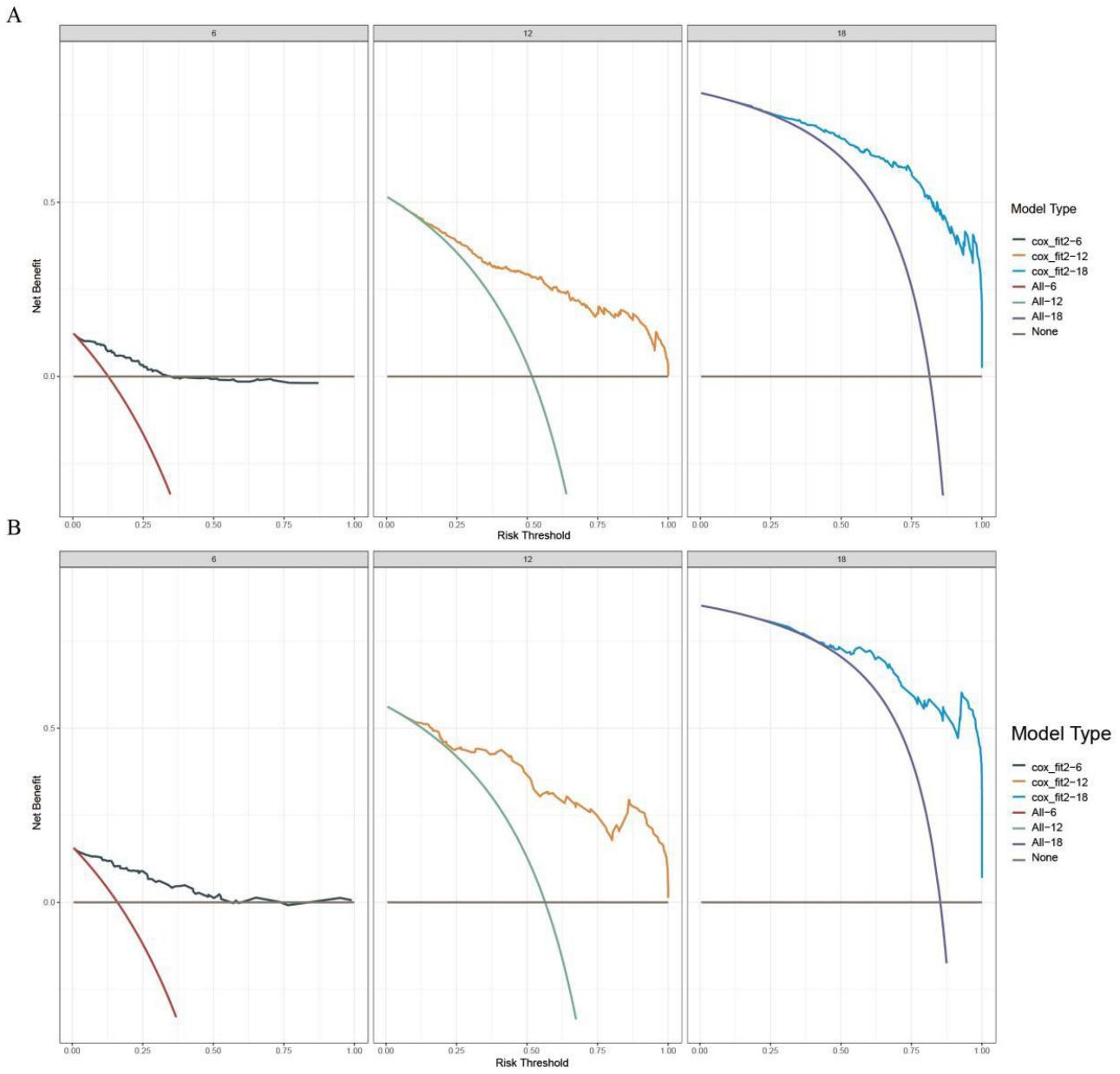

Figure 6 Decision curve analysis of the training and validation sets. Decision curve analysis of the nomogram for predicting the 6 months, 12 months and 18 months OS in the training set (**A**)and the 6 months, 12 months and 18 months OS in the validation set (**B**) of patients with LCBM.

Web-Based Dynamic Nomogram

The authors developed a web-based dynamic nomogram to facilitate clinical application and generalization. By accurately inputting information on various independent prognostic factors, it can predict OS in LCBM patients (https://huyiba.shinyapps.io/QiuS/), thereby helping clinicians utilize the nomogram model more effectively.

Discussion

In this study, we investigated the differential clinical characteristics of bone metastasis-predisposing brain metastases and the prognostic impact of EGFR mutation status. To eliminate histological confounding factors, this analysis was restricted to data with histologically confirmed LC as the sole metastatic origin via brain tissue. Notably, bone metastatic tumors demonstrated increased probabilities of skull invasion and meningeal invasion. Concurrently, we followed

survival outcomes in EGFR mutation-positive patients and developed a nomogram prediction model through univariate/multivariate analyses to estimate 6-/12-/18-month postoperative overall survival rates.

Recent studies reveal tumor cells can bypass the blood-brain barrier via anatomical conduits[7] (eg peri-vascular spaces of vertebral vessels and cranial emissary veins) to directly invade the leptomeninges.[15,16] Once breaching the leptomeninges, malignant cells rapidly disseminate through the subarachnoid space and cerebrospinal fluid (CSF) circulation, forming diffuse LM.[17] As LM is unresectable, clinical management primarily involves palliative interventions like CSF diversion (eg, Ommaya reservoir chemotherapy) or diagnostic biopsies, yet prognosis remains dismal with a median survival of ~4 months.[18–20] Our findings indicate about 70% of skull metastasis patients developed concurrent LM, potentially attributable to skull-leptomeningeal anatomical contiguity: tumor cells synchronously or sequentially colonized skull and leptomeninges via emissary veins before invading adjacent tissues,[21,22] corroborating the "bone metastasis and intracranial invasion" pathway as an alternative to classical hematogenous spread.[7] Histopathological analysis showed skull metastases exclusively originated from NSCLC (adenocarcinoma 39%, squamous cell carcinoma 18.7%, large cell carcinoma 9%), while SCLC was absent—likely due to its indolent skull metastatic behavior (prolonged latency from primary LC to skull metastasis) and rapid intracranial progression once intracranially seeded,[23,24] precluding surgical candidacy.[25,26] These findings suggest skull metastasis may serve as a sentinel marker for impending LM,[27] though the preventive value of early interventions (eg, metastatic lesion resection) requires validation through prospective studies.[28]

Beyond inherent tumor characteristics, postoperative pharmacotherapy sensitivity significantly impacts survival outcomes in LCBM patients.[29,30] Current postoperative management of brain metastases remains understudied, with most approaches extrapolating metastatic potential from primary lung cancer histopathology and imaging features—a paradigm overlooking brain-specific pathological attributes.[30–32] This study exclusively analyzed LCBM histopathological profiles, emphasizing the unique prognostic and therapeutic implications of EGFR signaling axis activation. Within the ASCO-SNO-ASTRO guideline-endorsed multidisciplinary framework (surgery, systemic therapy, radiotherapy),[33] EGFR mutation-positive patients demonstrated superior OS following pharmacotherapy, attributable to: ① Potential transient modulation of local BBB integrity post-surgery, which may facilitate exposure of residual tumor cells to systemically administered EGFR-TKIs with inherent CNS activity (eg, osimertinib);[34–36] ② postoperative molecular profiling identifying T790M secondary mutations in 21% of EGFR-mutant patients,[37] enabling timely TKI resistance management via third-generation TKI escalation;[38] ③ reduced radiation necrosis incidence with TKI combination therapy despite EGFR-mutant patients' heightened neurocognitive vulnerability to whole-brain radiotherapy.[39,40] Our findings validate that EGFR status-guided TKI therapy significantly improves objective response rates and prolongs OS, providing critical evidence for establishing a "pathological confirmation-molecular subtyping-targeted priority" comprehensive LCBM management protocol.

In contrast to most previous prediction models based on presumptive radiological diagnosis (without pathological confirmation), this study utilized a rigorously screened cohort of lung cancer brain metastasis (LCBM) patients who underwent surgical resection with pathological confirmation. We systematically characterized their clinical features and identified maximum tumor diameter, number of metastatic lesions, intratumoral hemorrhage, and extracranial lymphatic invasion as independent prognostic determinants. The nomogram model integrating these variables demonstrated excellent performance in predicting 6/12/18-month overall survival (OS) (sensitivity: 82–91%; specificity: 76–88%), validated by ROC curves, calibration curves, and decision curve analysis (DCA). Its core advantage lies in pathological confirmation eliminating imaging misdiagnosis risks, ensuring cohort homogeneity and data authenticity, thereby significantly enhancing model reliability and accuracy while outperforming comparable studies.

Furthermore, a web-based dynamic nomogram (https://huyiba.shinyapps.io/QiuS/) was implemented to optimize clinical translation. By inputting key prognostic parameters, clinicians can obtain quantitative OS predictions.

Limitation

The retrospective design of this study has inherent limitations: 1) Case selection bias (The exclusive focus on post-neurosurgical cohorts limits generalizability to non-operative LCBM populations); 2) Due to the insufficient sample size of the ALK-positive subgroup (n=29), it was not included in the study cohort separately, which may reduce the statistical

power and requires subsequent large-sample verification. 3) Temporal therapeutic heterogeneity: Prolonged enrollment periods (2015.01–2021.01) introduced confounding through evolving EGFR-TKI generational use (1st/2nd/3rd gen agents), requiring time-stratified efficacy analyses. 4) Unmeasured prognostic variables: Absence of perioperative volumetric analysis (eg residual tumor burden quantification) and treatment fidelity metrics (eg chemotherapy cycle completion rates) may constrain model precision, (5) Competing risk consideration: While non-cancer deaths were infrequent (11.1%), future studies could incorporate Fine-Gray models for comprehensive risk quantification.

Conclusion

This study systematically analyzed the clinical heterogeneity and molecular regulatory mechanism of LCBM, revealed the anatomical association between bone metastasis and meningeal metastasis and the core role of the EGFR signaling axis in prognostic stratification. Meanwhile, the nomogram model constructed by integrating multiple parameters (maximum cross-sectional area of brain metastasis foci, intratumbral hemorrhage, etc) demonstrated excellent predictive efficacy and could quantitatively guide individualized treatment decisions.

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Disclosure

The authors report no conflicts of interest in this work.

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