Original Article
Development and validation of nomograms for predicting survival in small cell lung cancer patients with brain metastases: a SEER population-based analysis

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Abstract: Objective: To develop prognostic nomograms for overall survival (OS) and cancer-specific survival (CSS) probabilities in small cell lung cancer (SCLC) patients with brain metastasis (BM). Methods: SCLC patients with BM from the Surveillance, Epidemiology, and End Results (SEER) database (2010-2015) were randomly allocated to training (n=1771) and validation (n=757) cohorts. Independent prognostic factors for OS and CSS were determined using univariate and multivariate Cox regression analyses in the training cohort, and prognostic nomograms for OS and CSS were constructed based on these factors. The efficacy of the nomograms was assessed using area under the receiver operating characteristic (ROC) curves (AUCs), calibration curves, decision curve analysis (DCA), net reclassification index (NRI), and integrated discrimination improvement (IDI), with the TNM staging model as a comparator. Results: Multivariate Cox analysis identified age, sex, race, tumor size, N staging, and presence of liver/bone/lung metastases, chemotherapy, and radiotherapy as independent prognostic factors for both OS and CSS. Prognostic nomograms were developed based on these factors. In both the training and validation cohorts, the AUC values of the nomograms for OS and CSS were significantly above 0.7, surpassing those for TNM staging. Calibration curves demonstrated a high degree of concordance between predicted and actual survival. The constructed nomograms showed superior clinical utility compared to the TNM staging system, as evidenced by NRI, IDI, and DCA. Conclusions: This retrospective study successfully developed and validated prognostic nomograms for SCLC patients with BM, providing valuable tools for oncologists to enhance prognosis evaluation and guide clinical decision-making.

Keywords: Small cell lung cancer, brain metastases, nomogram, overall survival, cancer-specific survival, SEER

Introduction

Small cell lung cancer (SCLC), comprising 13-15% of all lung carcinoma cases, is characterized by its highly malignant and aggressive nature [1]. Known for rapid growth and early widespread metastases, approximately 70% of SCLC patients are diagnosed with advanced and distantly metastasized tumors [2]. SCLC demonstrates a notable predilection for brain metastases (BMs), with 10-20% of patients presenting with BMs at initial diagnosis - a figure that may exceed 50% after chemotherapy and radiotherapy [3]. Clinical manifestations of BMs vary and include headaches, nausea, vomiting, seizures and neurological dysfunctions, significantly impacting patients' quality of life [4]. Current treatment options for SCLC patients with BM encompass whole-brain radiotherapy, stereotactic radiotherapy, chemotherapy, and emerging immunotherapies [5-7]. While these treatments offer symptom relief and modest survival extension, prognosis remains poor due to advanced disease and frequent multiorgan metastasis, with an average survival of approximately 5 months [8]. Given the high incidence and grave clinical implications of SCLC patients with BM, coupled with the scarcity and limitations of existing prognostic models, the development of an accurate prognostic

model is imperative. Such a model would enable clinicians to more precisely assess patient prognosis, thereby facilitating tailored treatment strategies, and offer patients and their families informed expectations for better medical decision-making.

As big data and machine learning technologies advance rapidly, database-driven survival prediction models have garnered increased attention. The Surveillance, Epidemiology, and End Results (SEER) database, covering approximately 34.6% of American cancer patients, serves as a valuable resource for real-world cancer research. By harnessing data from the SEER database, researchers can develop predictive models to estimate survival outcomes for specific patient populations, thereby offering robust support for clinical decision-making. Nomograms, also known as nomographs, are graphical tools utilized in survival analysis. They translate complex statistical models into visually intuitive graphics, enabling the prediction of event probabilities. Renowned for their intuitiveness, individualization, integration of multiple factors, simplicity, and flexibility, nomograms have gained widespread acceptance in survival prediction across various cancers [9-12].

Despite the widespread utilization of the SEER database in cancer survival prediction research [9-11, 13, 14], studies specifically targeting survival prediction for SCLC patients with BM remain scarce. Moreover, existing studies on prognostic models for SCLC patients with BM often focus on a limited number of predictive factors, overlooking other significant variables that could influence survival. Additionally, they may lack a comprehensive prognosis prediction approach, often concentrating solely on patient overall survival (OS) or cancer-specific survival (CSS) [15-17]. Hence, this retrospective study aims to develop a predictive model based on the SEER database for both OS and CSS, integrating multiple potential determinants, to offer a more accurate and comprehensive prediction of outcomes for SCLC patients with BM.

Materials and methods

Patient selection and data acquisition

Information on SCLC patients with BM registered between 2010 and 2015 in the SEER database (URL: https://seer.cancer.gov/data/) was obtained using SEER*Stat (v8.4.2). Inclusion criteria comprised: (i) patients diagnosed between 2010 and 2015; (ii) initial diagnosis of pathologically confirmed SCLC (primary sites: lung and bronchus; ICD-O-3 codes: 8002/3, 8041/3, 8042/3, 8043/3, 8044/3, and 8045/3) with concurrent BM; (iii) absence of other diagnosed tumors besides SCLC; and (iv) age at diagnosis between 18 and 80 years. Exclusion criteria included: (i) incomplete demographic information (e.g., age, sex, race, and marital status); (ii) deficient clinical pathology data such as tumor laterality, tumor size, T stage, and N stage; (iii) inadequate follow-up information; and (iv) unknown cause of death. Refer to **Figure 1** for the screening process. Ultimately, 2528 SCLC patients were selected and randomized into training (1771 cases) and validation (757 cases) sets at a ratio of 7:3.

Variables selected for this retrospective analysis included age, sex, race, marital status, tumor size, primary tumor site, tumor laterality, histologic grading, T staging, N staging, liver/bone/lung metastases, chemotherapy, radiotherapy, and surgical procedures. Tumor size and age were continuous variables, and their optimal cutoff values were determined using the X-tile program, converting them into categorical variables (tumor size categories: ≤19 mm, 20-44 mm, ≥45 mm; age categories: ≤64, 65-69, ≥70), as illustrated in Figure S1. Overall survival (OS), defined as the interval from diagnosis to death or the last follow-up for any reason, and cancer-specific survival (CSS), defined as the time from diagnosis to cancer-specific death or the last follow-up, served as the primary endpoints of our study. Due to the anonymous nature of the SEER database, ethics committee approval was waived.

Statistical analysis

For data analysis, we utilized R software (v4.1.2). Descriptive statistical analyses were conducted to examine the baseline characteristics of all enrolled patients. Continuous variables were described using the median (first quartile; third quartile) and compared using the Kruskal-Wallis H test. Frequencies and percentages were calculated for categorical data such as sex, race, and tumor staging, and comparisons were made using chi-square tests. Univariate and multivariate Cox regression analyses were performed to identify significant
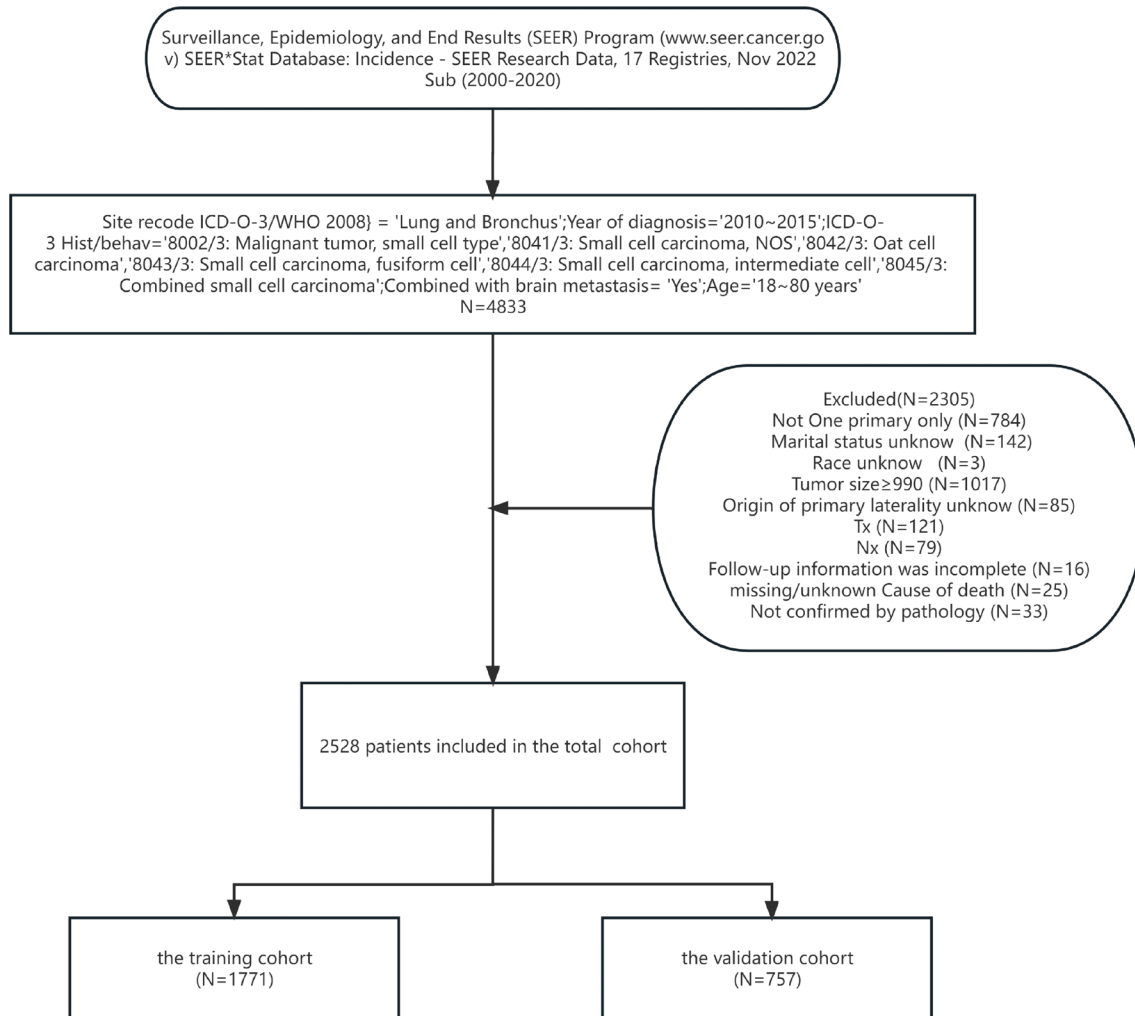
Figure 1. Patient selection flow chart.

prognostic factors affecting OS and CSS. Independent prognostic factors were determined through multivariate Cox regression analysis, which was used to construct nomograms for predicting OS and CSS. The discriminative capacities of the models were evaluated using the concordance index (C-index; range: 0.5-1) and receiver operating characteristic (ROC) curves, with a C-index above 0.7 indicating excellent discriminatory power and a higher area under the curve (AUC) signifying better discriminative ability. Calibration curves, with 1000 bootstrap resamplings, were employed for accuracy assessment. Additionally, to assess whether the novel nomogram models outperform the conventional TNM staging system in predictive performance, we utilized the net reclassification index (NRI) and integrated

discrimination improvement (IDI). Decision curve analysis (DCA) determined the clinical utility of the predictive model. All tests were two-tailed, and statistical significance was defined as P-values <0.05.

Results

Patient baseline characteristics

Among the 2528 eligible SCLC patients with BM retrieved from the SEER database, 1771 were allocated to the training cohort, while 757 were assigned to the validation cohort. Demographic and clinicopathological characteristics are summarized in **Table 1**. The predominant age at onset was ≤64 years (49.6%). Male and female patients were nearly evenly distributed, comprising 54.3% and 45.7%,

Table 1. Baseline characteristics of the training and validation cohorts

Variables	Total	Training cohort	Validation cohort	P value
Number of patients	2528	1771	757	
Sex (%)				
Female	1155 (45.7)	809 (45.7)	346 (45.7)	0.990
Male	1373 (54.3)	962 (54.3)	411 (54.3)	
Age (%)				
≤64	1253 (49.6)	885 (50.0)	368 (48.6)	0.052
65-69	557 (22.0)	368 (20.8)	189 (25.0)	
≥70	718 (28.4)	518 (29.2)	200 (26.4)	
Race (%)				
White	2169 (85.8)	1516 (85.6)	653 (86.3)	0.909
Black	255 (10.1)	181 (10.2)	74 (9.8)	
Others	104 (4.1)	74 (4.2)	30 (4.0)	
Marital status (%)				
Married	2065 (81.7)	1447 (81.7)	618 (81.6)	0.968
Single	463 (18.3)	324 (18.3)	139 (18.4)	
T (%)				
T0	15 (0.6)	8 (0.5)	7 (0.9)	0.174
T1	321 (12.7)	210 (11.9)	111 (14.7)	
T2	661 (26.1)	462 (26.1)	199 (26.3)	
T3	558 (22.1)	397 (22.4)	161 (21.3)	
T4	973 (38.5)	694 (39.2)	279 (36.9)	
N (%)				
N0	374 (14.8)	253 (14.3)	121 (16.0)	0.413
N1	191 (7.6)	137 (7.7)	54 (7.1)	
N2	1399 (55.3)	973 (54.9)	426 (56.3)	
N3	564 (22.3)	408 (23.0)	156 (20.6)	
Tumor size (%)				
≤19 mm	256 (10.1)	170 (9.6)	86 (11.4)	0.064
20-44 mm	849 (33.6)	578 (32.6)	271 (35.8)	
≥45 mm	1423 (56.3)	1023 (57.8)	400 (52.8)	
Radiation (%)				
Yes	1883 (74.5)	1308 (73.9)	575 (76.0)	0.267
No/unknown	645 (25.5)	463 (26.1)	182 (24.0)	
Chemotherapy (%)				
Yes	1848 (73.1)	1301 (73.5)	547 (72.3)	0.532
No/unknown	680 (26.9)	470 (26.5)	210 (27.7)	
Surgery (%)				
Yes	581 (23.0)	417 (23.5)	164 (21.7)	0.303
No/unknown	1947 (77.0)	1354 (76.5)	593 (78.3)	
Bone metastasis (%)				
Yes	720 (28.5)	513 (29.0)	207 (27.3)	0.408
No/unknown	1808 (71.5)	1258 (71.0)	550 (72.7)	
Liver metastasis (%)				
Yes	789 (31.2)	556 (31.4)	233 (30.8)	0.760
No/unknown	1739 (68.8)	1215 (68.6)	524 (69.2)	
Lung metastasis (%)				
Yes	442 (17.5)	312 (17.6)	130 (17.2)	0.788
No/unknown	2086 (82.5)	1459 (82.4)	627 (82.8)	

Primary lesion site (%)				
Main bronchus	283 (11.2)	196 (11.1)	87 (11.5)	0.943
Upper lobe	1382 (54.7)	973 (54.9)	409 (54.0)	
Middle lobe	100 (4.0)	70 (4.0)	30 (4.0)	
Lower lobe	556 (22.0)	389 (22.0)	167 (22.1)	
Overlapping lesion of lung	30 (1.2)	23 (1.3)	7 (0.9)	
Lung, NOS	177 (7.0)	120 (6.8)	57 (7.5)	
Laterality (%)				
Left	1106 (43.8)	759 (42.9)	347 (45.8)	0.166
Right	1422 (56.2)	1012 (57.1)	410 (54.2)	
Grade (%)				
Grade I	2 (0.1)	2 (0.1)	0 (0.0)	0.328
Grade II	8 (0.3)	4 (0.2)	4 (0.5)	
Grade III	234 (9.3)	159 (9.0)	75 (9.9)	
Grade IV	351 (13.9)	257 (14.5)	94 (12.4)	
Unknown	1933 (76.5)	1349 (76.2)	584 (77.1)	
OS (median [IQR])	5.00 [2.00, 10.00]	6.00 [2.00, 10.00]	5.00 [2.00, 11.00]	0.524

Others refer to American Indian/Alaska Native/Asian/Pacific Islander populations; NOS, not otherwise specified; IQR, inter-quartile range; OS, overall survival.

respectively, with the majority being Caucasian (85.8%). A significant proportion of patients were married (81.7%). The upper lobe was the most common primary tumor location (54.7%), and tumor size ≥45 mm was the most prevalent category (56.3%). The right side was the most frequently affected (56.2%). Among T staging categories, the majority of patients (38.5%) were classified as stage T4, while in N staging, most were categorized as stage N2 (55.3%). Pathological grade was predominantly unknown (76.5%), followed by grade IV (13.9%). Concurrent bone metastasis was observed in 28.5% of patients, liver metastasis in 31.2%, and lung metastasis in 17.5%. The majority of patients (74.5%) underwent radiotherapy, while a smaller proportion (23.0%) underwent surgery, and 73.1% received chemotherapy. Patients had a median follow-up of 5 months (2.00 months, 10.00 months). No statistically significant differences were observed in demographic characteristics between the training and validation cohorts (P>0.05).

Univariate and multivariate Cox analyses of prognostic factors for OS and CSS

Univariate Cox analysis in the training cohort revealed significant associations between age, sex, race, tumor size, N staging, liver/bone/lung metastases, surgery, chemotherapy, and radiotherapy with both OS and CSS prognosis

(P<0.05). Subsequently, multivariate Cox analysis confirmed the independence of age, sex, race, tumor size, N staging, liver/bone/lung metastases, chemotherapy, and radiotherapy as prognostic factors (P<0.05). Refer to **Tables 2** and **3** for details of univariate and multivariate Cox regression analyses for OS and CSS rates in the training cohort.

Development of prognostic nomograms

Utilizing the ten identified independent prognostic factors (age, sex, race, tumor size, N staging, liver/bone/lung metastases, chemotherapy, and radiotherapy), prognostic nomograms were formulated to predict the 6-, 12-, and 24-month probabilities of OS and CSS for SCLC patients with BM (**Figure 2**). Notably, chemotherapy, race, and N stage exerted the most significant influence on patient prognosis in the nomograms, followed by age, tumor size, liver metastasis, radiotherapy, lung metastasis, bone metastasis, and sex. Each prognostic factor was quantified as a specific score, and the cumulative scores were utilized to forecast OS and CSS at 6, 12, and 24 months.

Validation of prognostic nomograms

The performance of the nomograms was assessed using the C-index, AUC, calibration curves, and DCA. In the training set, the nomo-

Table 2. Univariate and multivariate Cox analyses of overall survival in the training cohort

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
≤64	Reference		Reference	
65-69	1.181 (1.045, 1.335)	0.008	1.110 (0.981, 1.257)	0.098
≥70	1.505 (1.349, 1.679)	<0.001	1.378 (1.232, 1.543)	<0.001
Sex				
Female	Reference		Reference	
Male	1.121 (1.021, 1.232)	0.017	1.143 (1.038, 1.259)	0.006
Race				
White	Reference		Reference	
Black	0.950 (0.814, 1.109)	0.518	0.888 (0.759, 1.039)	0.137
Other	0.786 (0.620, 0.996)	0.046	0.634 (0.497, 0.808)	<0.001
Marital status				
Married	Reference			
Single	0.967 (0.856, 1.091)	0.584		
Grade				
Grade I	Reference			
Grade II	2.489 (0.455, 13.618)	0.293		
Grade III	2.198 (0.544, 8.878)	0.269		
Grade IV	2.189 (0.544, 8.816)	0.27		
Unknown	2.441 (0.609, 9.787)	0.208		
Laterality				
Left	Reference			
Right	0.985 (0.896, 1.083)	0.75		
Liver metastasis				
Yes	Reference		Reference	
No/unknown	0.692 (0.625, 0.767)	<0.001	0.767 (0.684, 0.859)	<0.001
Bone metastasis				
Yes	Reference		Reference	
No/unknown	0.760 (0.685, 0.844)	<0.001	0.856 (0.764, 0.960)	0.008
Lung metastasis				
Yes	Reference		Reference	
No/unknown	0.786 (0.695, 0.889)	<0.001	0.834 (0.735, 0.947)	0.005
T				
T0	Reference			
T1	1.244 (0.614, 2.520)	0.545		
T2	1.244 (0.618, 2.503)	0.54		
T3	1.426 (0.708, 2.871)	0.321		
T4	1.447 (0.721, 2.906)	0.299		
N				
N0	Reference		Reference	
N1	0.986 (0.800, 1.216)	0.896	1.058 (0.857, 1.306)	0.602
N2	1.266 (1.100, 1.457)	0.001	1.504 (1.298, 1.742)	<0.001
N3	1.337 (1.141, 1.567)	<0.001	1.526 (1.292, 1.802)	<0.001
Primary Site				
Main bronchus	Reference			
Upper lobe	0.987 (0.846, 1.152)	0.87		
Middle lobe	0.985 (0.747, 1.299)	0.914		

Lower lobe	1.101 (0.926, 1.309)	0.274		
Overlapping lesion of lung	0.807 (0.523, 1.244)	0.331		
Lung, NOS	1.036 (0.825, 1.302)	0.76		
Chemotherapy				
Yes	Reference		Reference	
No/unknown	3.497 (3.132, 3.905)	<0.001	3.774 (3.347, 4.256)	<0.001
Radiation				
Yes	Reference		Reference	
No/unknown	1.740 (1.563, 1.937)	<0.001	1.296 (1.159, 1.450)	<0.001
Surgery				
Yes	Reference		Reference	
No/unknown	1.169 (1.046, 1.305)	0.006	1.056 (0.942, 1.184)	0.353
Tumor size				
≤19 mm	Reference		Reference	
20-44 mm	1.146 (0.964, 1.361)	0.122	1.104 (0.928, 1.313)	0.263
≥45 mm	1.260 (1.070, 1.484)	0.006	1.348 (1.142, 1.591)	<0.001

Table 3. Univariate and multivariate Cox analyses of cancer-specific survival in the training cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
≤64	Reference		Reference	
65-69	1.175 (1.037, 1.331)	0.011	1.106 (0.975, 1.255)	0.118
≥70	1.523 (1.363, 1.702)	<0.001	1.393 (1.243, 1.562)	<0.001
Sex				
Female	Reference		Reference	
Male	1.139 (1.035, 1.254)	0.008	1.164 (1.055, 1.284)	0.002
Race				
White	Reference		Reference	
Black	0.930 (0.794, 1.090)	0.372	0.873 (0.744, 1.026)	0.098
Other	0.766 (0.601, 0.978)	0.032	0.622 (0.485, 0.798)	<0.001
Marital status				
Married	Reference			
Single	0.955 (0.844, 1.081)	0.464		
Grade				
Grade I	Reference			
Grade II	4.956 (0.553, 44.416)	0.153		
Grade III	4.194 (0.586, 29.994)	0.153		
Grade IV	4.251 (0.596, 30.330)	0.149		
Unknown	4.666 (0.656, 33.188)	0.124		
Laterality				
Left	Reference			
Right	0.987 (0.897, 1.087)	0.798		
Liver metastasis				
Yes	Reference		Reference	
No/unknown	0.685 (0.617, 0.760)	<0.001	0.763 (0.679, 0.856)	<0.001
Bone metastasis				
Yes	Reference		Reference	
No/unknown	0.754 (0.678, 0.838)	<0.001	0.853 (0.759, 0.958)	0.007

Lung metastasis				
Yes	Reference		Reference	
No/unknown	0.773 (0.682, 0.875)	<0.001	0.823 (0.724, 0.935)	0.003
T				
T0	Reference			
T1	1.394 (0.656, 2.962)	0.388		
T2	1.392 (0.660, 2.937)	0.386		
T3	1.579 (0.747, 3.336)	0.231		
T4	1.614 (0.766, 3.399)	0.208		
N				
N0	Reference		Reference	
N1	0.990 (0.800, 1.226)	0.93	1.064 (0.858, 1.320)	0.57
N2	1.287 (1.115, 1.485)	0.001	1.529 (1.315, 1.777)	<0.001
N3	1.338 (1.138, 1.574)	<0.001	1.531 (1.291, 1.814)	<0.001
Primary Site				
Main bronchus	Reference			
Upper lobe	0.989 (0.845, 1.159)	0.895		
Middle lobe	1.016 (0.768, 1.344)	0.912		
Lower lobe	1.111 (0.931, 1.325)	0.242		
Overlapping lesion of lung	0.838 (0.543, 1.294)	0.426		
Lung, NOS	1.041 (0.825, 1.313)	0.737		
Chemotherapy				
Yes	Reference		Reference	
No/unknown	3.484 (3.114, 3.899)	<0.001	3.795 (3.358, 4.290)	<0.001
Radiation				
Yes	Reference		Reference	
No/unknown	1.694 (1.518, 1.891)	<0.001	1.262 (1.125, 1.415)	<0.001
Surgery				
Yes	Reference		Reference	
No/unknown	1.188 (1.061, 1.330)	0.003	1.073 (0.955, 1.206)	0.237
Tumor size				
≤19 mm	Reference		Reference	
20-44 mm	1.141 (0.958, 1.358)	0.139	1.103 (0.925, 1.314)	0.275
≥45 mm	1.234 (1.046, 1.457)	0.013	1.321 (1.117, 1.563)	0.001

grams exhibited C-indexes of 0.709 (95% CI 0.695-0.723) for OS and 0.708 (95% CI 0.694-0.723) for CSS, which were consistent with the validation set results of 0.708 (95% CI 0.687-0.729) for both OS and CSS. As illustrated in **Figure 3**, the nomograms demonstrated higher AUCs compared to the TNM staging system for 6-, 12-, and 24-month OS (6-month: 0.772 vs. 0.533; 12-month: 0.754 vs. 0.594; 24-month: 0.766 vs. 0.610) and CSS (6-month: 0.772 vs. 0.533; 12-month: 0.753 vs. 0.595; 24-month: 0.767 vs. 0.611) in the training set, indicating robust predictive ability. Similar findings were observed in the validation set, with the ROC curves showing significantly higher AUCs for the OS nomogram at 6, 12, and 24 months compared to the TNM staging system (6-month: 0.777, 12-month: 0.758, 24-month: 0.759 vs. 0.514, 0.593, 0.665, respectively). Likewise, the CSS nomogram displayed superior AUCs over the TNM staging system (6-month: 0.775, 12-month: 0.759, 24-month: 0.762 vs. 0.513, 0.592, 0.663, respectively). Calibration curves (**Figure 4**) depicted favorable agreement between nomogram predictions and actual observations in both training and validation cohorts, affirming the nomograms' well-calibrated and reliable nature. NRI and IDI values for OS and CSS consistently exceeded 0 in both cohorts at 6, 12, and 24 months, indicating sig-
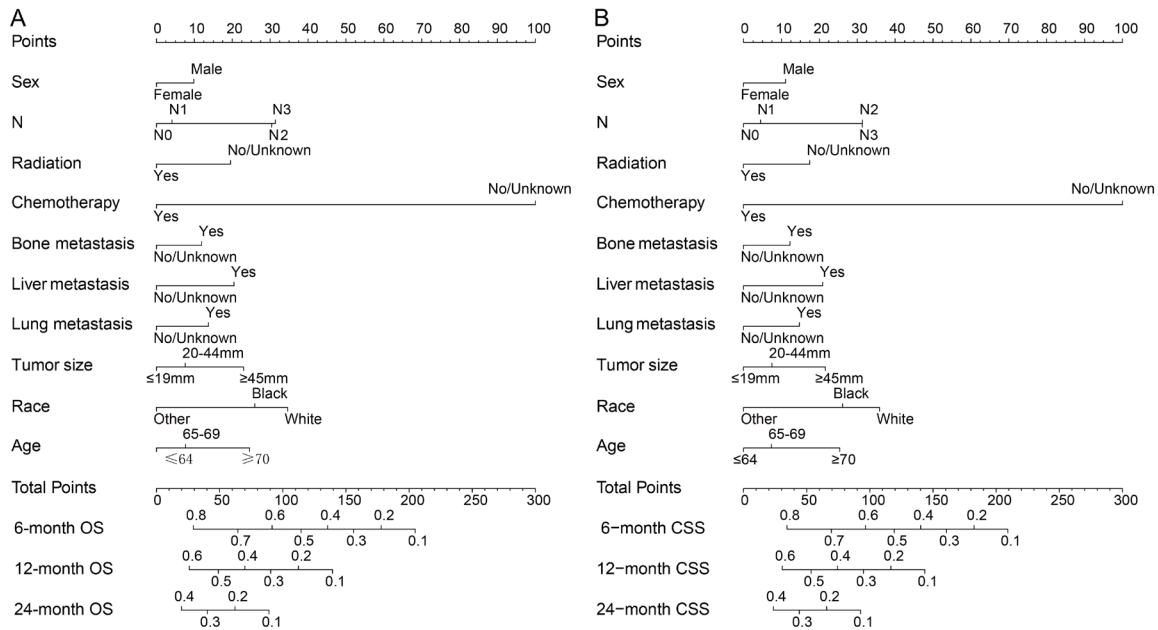
Figure 2. Nomograms for predicting 6-, 12-, and 24-month overall survival (OS; A) and cancer-specific survival (CSS; B) in small-cell lung cancer patients with brain metastases.

nificant improvement. Consequently, the newly developed nomogram models exhibited markedly enhanced predictive performance compared to the TNM staging model (**Tables 4**, **5**). Furthermore, DCA curves (**Figure 5**) demonstrated the clinical utility of the nomograms, indicating superior net clinical benefits across a wide threshold probability range for predicting 6-month, 12-month, and 24-month OS and CSS compared to the traditional TNM staging system.

Discussion

This study successfully developed a nomogram model for predicting the prognosis of SCLC patients with BM, accurately forecasting both OS and CSS. The AUC values for OS and CSS exceeded 0.7 in both the training and validation cohorts, indicating the model's strong discriminative ability. Furthermore, calibration curves and DCA curves confirmed the model's good calibration and clinical applicability in addition to its discriminative ability. While the TNM staging system is widely used for outcome assessment in SCLC patients with BM, it has significant limitations since patient prognosis is influenced by multiple factors beyond TNM stage alone, as evidenced in previous studies [18-23]. Our model exhibited superior predictive accuracy and clinical applicability compared to

the traditional TNM staging system. These findings suggest that our models can more accurately reflect the prognostic landscape of SCLC patients with BM by considering a broader range of factors. The improved accuracy may be attributed to the inclusion of multiple independent prognostic markers identified by the multivariate model, which are closely linked to the survival outcomes of SCLC patients. By incorporating various factors, our model can more comprehensively capture the complex interactions that impact patient prognosis.

In previous research, earlier survival prediction models for SCLC patients with BM often focused solely on either OS or CSS [24]. Furthermore, the variable selection in these studies might not have fully considered the extensive factors influencing prognosis, potentially limiting the clinical applicability of the predictive models. In contrast, our study offers several advantages:

(i) Comprehensiveness: Our study simultaneously predicts both OS and CSS, providing a more comprehensive prognostic view. This dual prediction model enables physicians to assess not only the potential survival duration of patients but also the impact of the tumor on their quality of life, facilitating more holistic clinical decision-making.
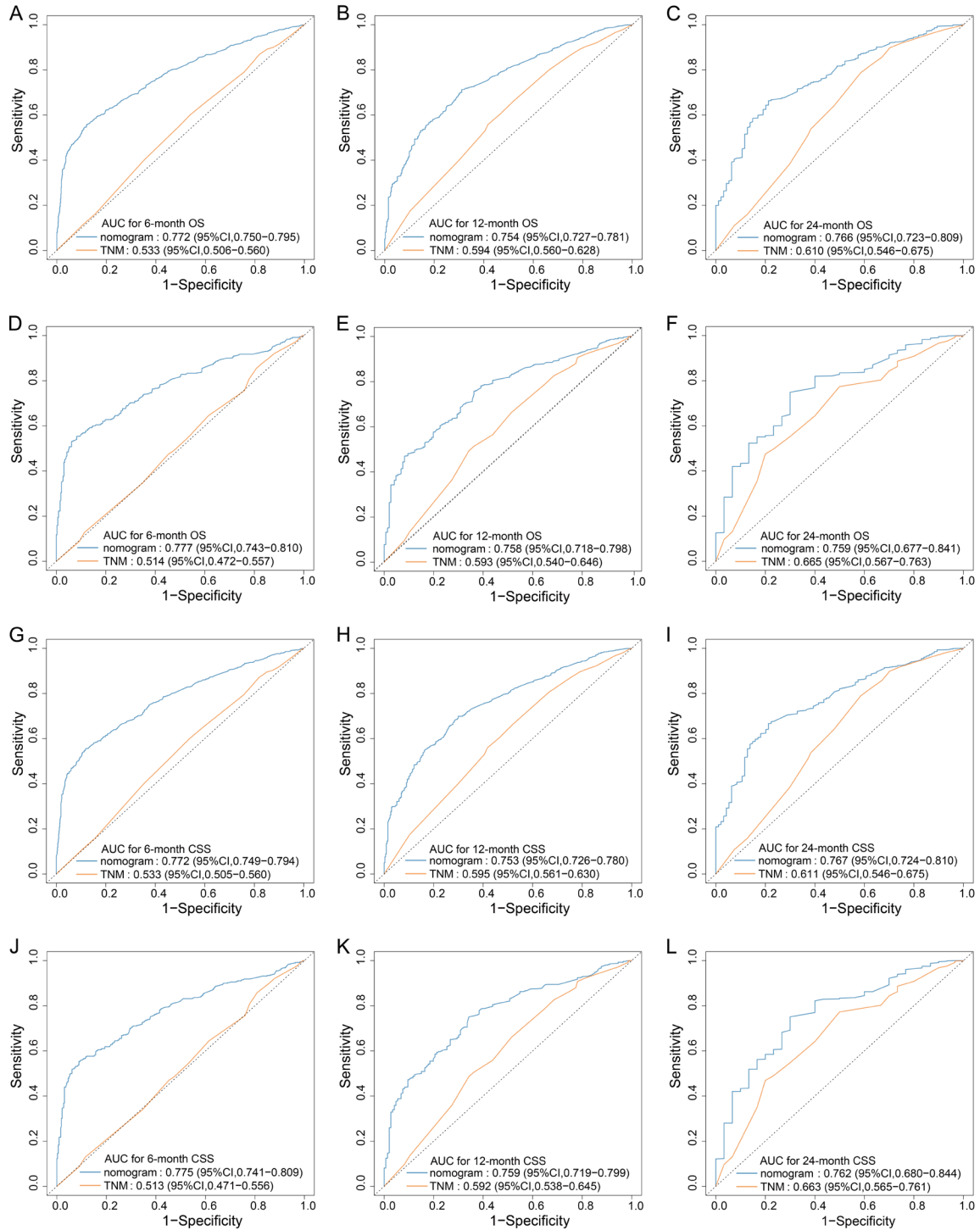
Figure 3. ROC curves of nomograms and the TNM staging system for predicting OS and CSS in the training and validation cohorts at 6, 12, and 24 months. A-C. ROC curves to predict OS in the training cohort at 6, 12, and 24 months; D-F. ROC curves to predict OS in the validation cohort at 6, 12, and 24 months; G-I. ROC curves to predict CSS in the training cohort at 6, 12, and 24 months; J-L. ROC curves to predict CSS in the validation cohort at 6, 12, and 24 months.

(ii) Broad range of prognostic factors: The construction process of our model analyzed a

wider array of prognostic markers, including age, gender, race, tumor size, metastatic sta-
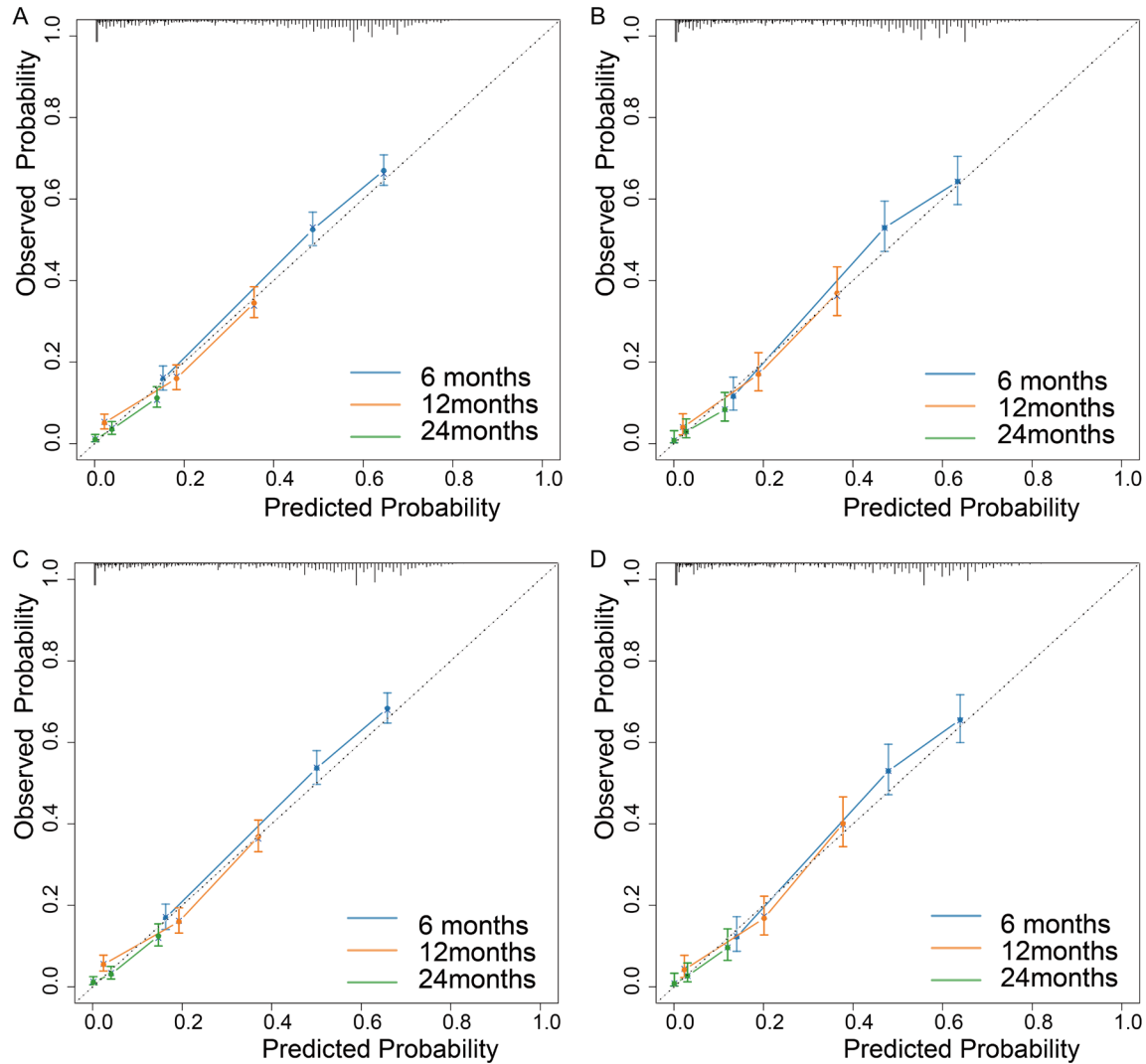
Figure 4. Calibration plots of the nomograms for predicting OS and CSS in training and validation cohorts at 6, 12, and 24 months. A. Calibration plots for 6-, 12-, and 24-month OS prediction in the training cohort; B. Calibration plots for 6-, 12-, and 24-month OS prediction in the validation cohort; C. Calibration plots for 6-, 12-, and 24-month CSS prediction in the training cohort; D. Calibration plots for CSS prediction in the validation cohort at 6, 12, and 24 months.

tus, and treatment plans. Through rigorous statistical methods, independent prognostic factors were selected. This multivariate integration approach not only enhances prediction accuracy but also sheds light on the complex biological and socioeconomic factors influencing patient prognosis.

(iii) Stricter patient selection criteria: Our study employed more stringent patient selection criteria to ensure the consistency of the study population and the reliability of findings. For example, patients with unknown marital status were excluded. Marital status, serving as a proxy measure of social support, is closely correlated with prognoses in cancer patients. By eliminating the unknown category of this variable, potential confounding factors were reduced, making the prognostic model more precise. Additionally, we restricted the age of patients to between 18 and 80 years, which is stricter than previously reported inclusion criteria. Age is a key factor affecting cancer prognosis, and patients of advanced age often have multiple comorbidities, which could confound treatment effects and prognostic assessment. By setting this age limit, our study focused on patient groups whose prognosis is more likely

Table 4. NRI and IDI of the overall survival nomogram compared with TNM stage system

Index	Training cohort			Validation cohort		
	Estimate	95% CI	P value	Estimate	95% CI	P value
NRI (vs. TNM stage System)						
For 6-month Suvival Rate	0.789	0.698-0.869		0.857	0.734-0.975	
For 12-month Suvival Rate	0.741	0.635-0.834		0.753	0.609-0.887	
For 24-month Suvival Rate	0.783	0.570-0.996		0.716	0.456-0.980	
IDI (vs. TNM Stage System)						
For 6-month Suvival Rate	0.213	0.171-0.244	<0.001	0.224	0.172-0.267	<0.001
For 12-month Suvival Rate	0.125	0.092-0.149	<0.001	0.132	0.095-0.168	<0.001
For 24-month Suvival Rate	0.084	0.060-0.121	<0.001	0.089	0.037-0.144	<0.001

IDI, integrated discrimination improvement; NRI, net reclassification index.

Table 5. NRI and IDI of the cancer-specific survival nomogram compared with TNM stage system

Index	Training cohort			Validation cohort		
	Estimate	95% CI	P value	Estimate	95% CI	P value
NRI (vs. TNM stage System)						
For 6-month Suvival Rate	0.757	0.677-0.844		0.780	0.663-0.899	
For 12-month Suvival Rate	0.701	0.628-0.834		0.734	0.598-0.888	
For 24-month Suvival Rate	0.791	0.572-0.995		0.720	0.487-0.970	
IDI (vs. TNM Stage System)						
For 6-month Suvival Rate	0.215	0.171-0.243	<0.001	0.222	0.164-0.266	<0.001
For 12-month Suvival Rate	0.127	0.092-0.151	<0.001	0.138	0.099-0.175	<0.001
For 24-month Suvival Rate	0.086	0.060-0.124	<0.001	0.096	0.042-0.155	<0.001

IDI, integrated discrimination improvement; NRI, net reclassification index.

to be influenced by the cancer itself and related treatments.

(iv) More rigorous methodology: Unlike the study by Liang et al. [20], we utilized the X-TILE software to assist in determining optimal grouping cutoffs by minimizing *p* values in survival analysis. This involved analyzing continuous variables such as tumor size and age to determine their optimal cutoff values for grouping. X-TILE's data-driven approach ensures objectivity and reproducibility of the analysis [25]. The software's automated process reduces human selection bias, ensuring that the choice of cutoff values is more accurate and consistent. This approach ensured that the selection of key variables in our study was based on strict statistical evidence, enhancing the scientific rigor and reliability of the prognostic model.

The design choices in our study resulted in findings that diverged from previous research. Multivariate Cox analysis identified age, race, sex, N staging, tumor size, liver/bone/lung dis-

tant metastases, radiotherapy, and chemotherapy as independent prognostic markers for both OS and CSS in SCLC patients with BM. In contrast, the CSS prognostic model for SCLC patients with BM developed by Rong et al. [15] in 2022 did not include tumor size in their analysis, which may explain the significant differences in results between their study and ours. Their findings suggested that surgery was a favorable independent prognostic factor for CSS, while race and sex were not significant. Our results indicated that including minority members, such as Asian patients, was associated with better survival rates, and female gender was favorable for both OS and CSS, with surgery being a non-independent prognostic factor, consistent with previous studies [19, 23]. Furthermore, we found that larger tumor volume was a risk factor for poor prognosis, in line with the findings of Liang et al. [20] in 2023 and Li et al. [16] in 2021. Notably, tumor size was included as a variable in constructing our nomograms.
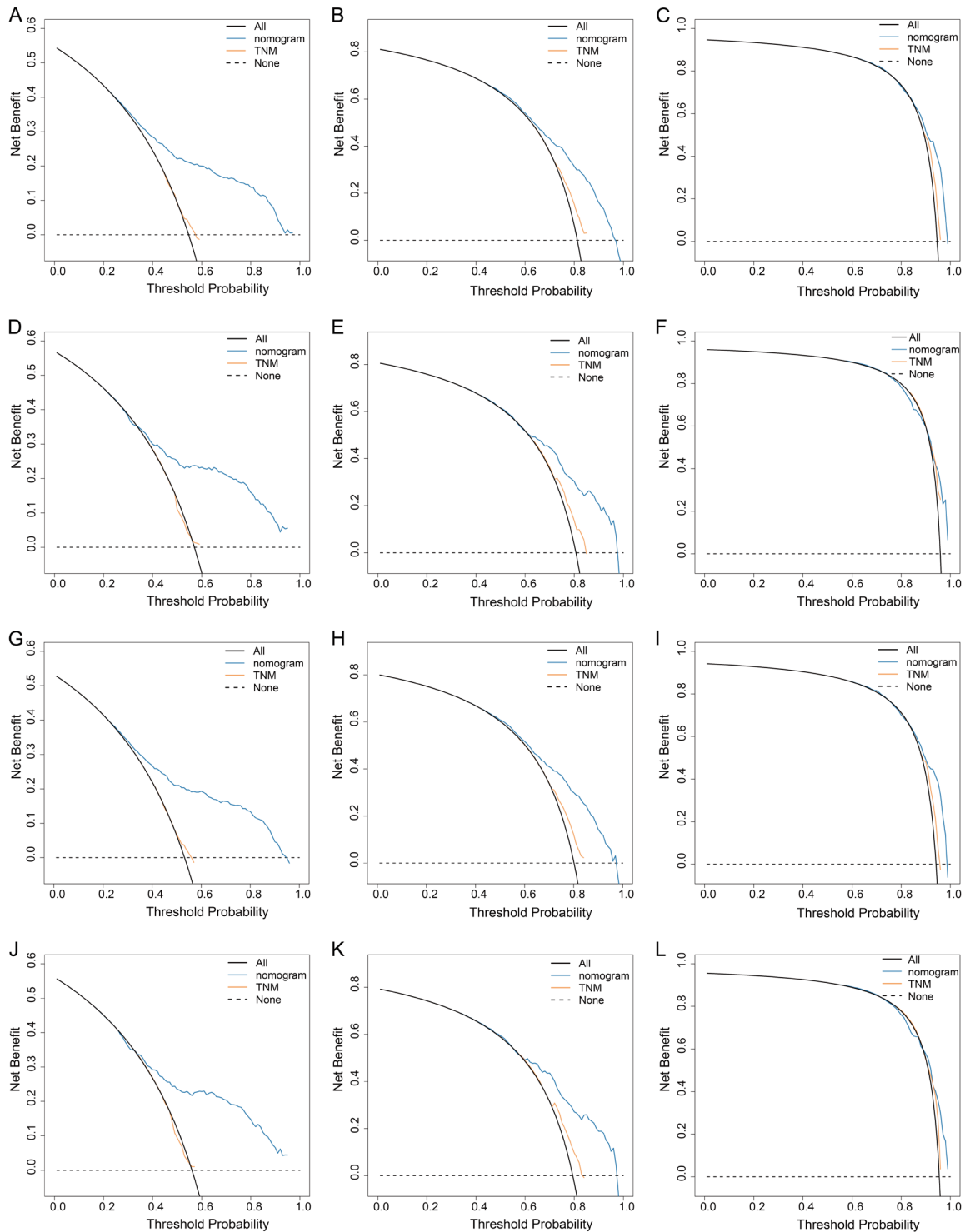
Figure 5. Decision curve analysis (DCA) curves for detecting the predictive value of nomograms and the TNM staging system. DCA plots for 6-, 12-, and 24-month OS in the training cohort (A-C) and the validation cohort (D-F), respectively; DCA plots for 6-, 12-, and 24-month CSS in the training cohort (G-I) and the validation cohort (J-L), respectively.

Ultimately, the AUC values for our CSS prognostic model at 6 months and 12 months were higher than those constructed by Rong et al. [15] (0.772, 0.753 vs. 0.723, 0.737). Additionally, the OS prediction model for SCLC patients with BM based on the SEER database

created by Shan et al. [17] in 2021 had limitations, as only a few variables (age, sex, race, marital status, T staging, N staging, etc.) were analyzed. This led to results significantly different from ours. Their model had a subpar AUC value, with the 1-year OS AUC being only 0.606, lower than our 0.754, indicating limited predictive ability, and lacked validation in a validation cohort and clinical applicability.

Li et al. [16] developed an OS prediction model in 2021 based on the SEER database, incorporating seven variables: age, race, tumor size, N staging, surgery, radiotherapy, and chemotherapy. However, their model lacked multiple crucial factors analyzed in our study, such as liver/lung/bone metastases, primary tumor site, laterality, and pathological grade. Additionally, they did not validate their constructed model, which limits its comprehensiveness and rigor compared to ours.

Similarly, Liang et al. [20] constructed an OS prediction model for SCLC patients with BM in 2023 using the SEER database, covering a comprehensive range of variables in their analysis. However, their study had certain flaws in the selection criteria, such as including cases with an unknown marital status, potentially introducing bias. Moreover, they did not adopt a scientifically rigorous method for categorizing continuous variables like age and tumor size, which may have introduced subjectivity and potential selection bias. Their study results diverged from ours and previous research, as they found that radiation therapy was not a significant independent prognostic factor, which contradicts current clinical experience and guidelines [7, 26-28]. They also believed that this difference may be related to the lack of detailed radiation therapy implementation plans in the SEER database. In the end, the AUC value of the SCLC combined with BM patient OS prediction model they constructed was lower than our model, indicating poor discriminative ability and accuracy.

In summary, our prognostic prediction model has higher AUC values than models developed by previous researchers, demonstrating superior discriminative ability and accuracy.

Despite significant advancements in developing predictive models for OS and CSS in SCLC patients with BM, our study design exhibits some deficiencies. First, our research relies on the SEER database, which, while encompassing a broad demographic and geographical distribution, may not fully represent patient populations globally or in specific countries/regions. Consequently, our predictive model may require additional validation in different populations, such as those in China. Additionally, the SEER database's data are subject to entry and reporting standard limitations, potentially leading to missing data or imprecise categorization. Vital information such as smoking status, comorbidities, biomarkers, molecular mutation characteristics, patients' life quality and functional status, duration from diagnosis to treatment, specific radiation therapy implementation plans, and immunotherapy are missing, which could impact the interpretation of the results. Second, the retrospective research design cannot completely eliminate selection and information biases. Despite our efforts to control these biases with strict inclusion and exclusion criteria, unknown or unmeasured confounding factors may still exist. Third, while our model provides accurate prognosis predictions for SCLC patients with BM, its application in actual clinical practice requires further research and validation. Clinical decision-support tools need to consider various factors, including treatment feasibility, patient preferences, and cost-effectiveness. Lastly, this study only underwent internal validation and currently lacks further validation with multicenter external data. Future research should involve prospective studies in a more diverse population to validate the generalizability and clinical applicability of our model externally. Exploring other prognostic factors, such as comorbidities, immunotherapy, biomarkers, patient quality of life, and functional status, and using other statistical methods to test and optimize the model are also important directions for future research. Nonetheless, our study still provides valuable insights into the prognosis prediction of SCLC patients with BM and lays the groundwork for subsequent research.

This study successfully constructed and validated a prognostic model for predicting OS and CSS in SCLC patients with BM by integrating multiple independent prognostic factors, including age, sex, race, tumor size, metastatic status, and treatment modalities. These factors were carefully selected and validated,

ensuring the model's high accuracy and clinical applicability. The model provides a robust and innovative tool for prognostic assessment in clinical settings, significantly contributing to the improvement of treatment strategies and prognosis evaluation for SCLC patients with BM.

Acknowledgements

The authors extend our sincere thanks to the SEER Program, and to all participating patients and research personnel involved in this study.

Disclosure of conflict of interest

None.

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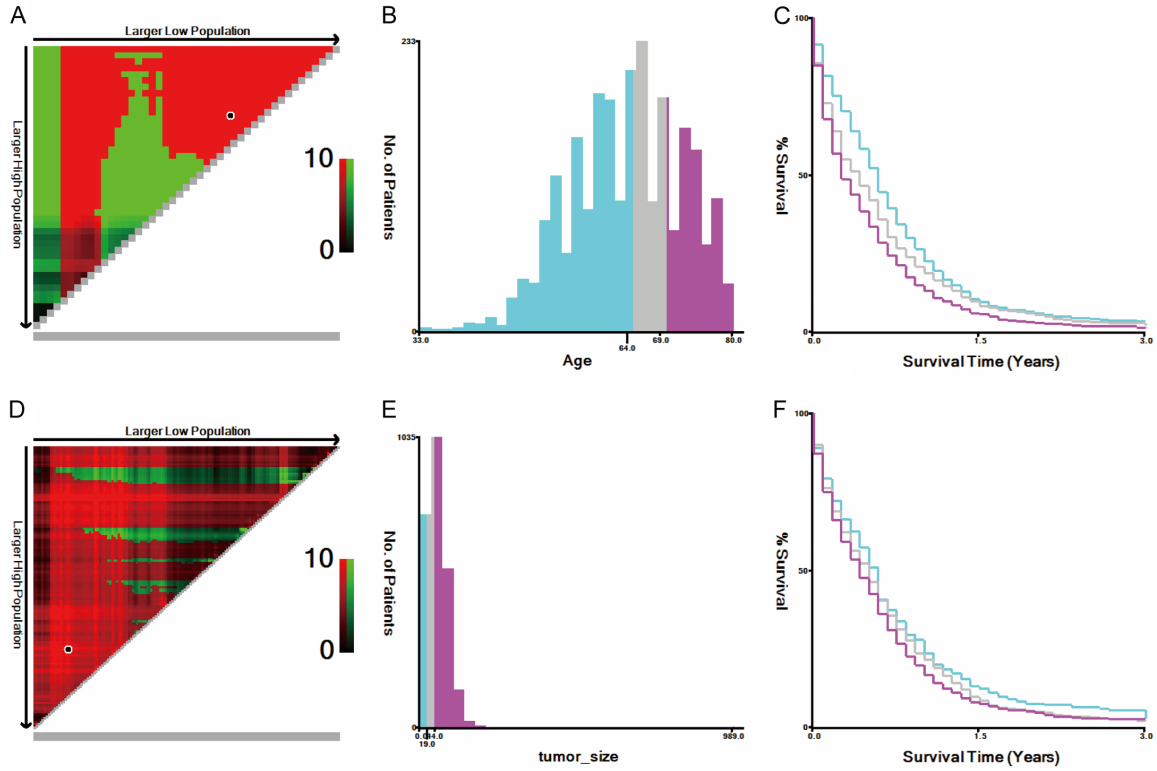
Figure S1. Identification of the optimal cutoff values for age (A-C) and tumor size (D-F) based on OS and CSS via X-tile software analysis. The results revealed that the optimal cutoff point for age was 64 and 69 years, and the optimal cutoff point for tumor size was 19 and 44 mm.