Original Article

Development and validation of nomograms to predict early death in non-small cell lung cancer patients with brain metastasis: a retrospective study in the SEER database

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Background: Throughout the course of non-small cell lung cancer (NSCLC), a lot of patients would develop brain metastasis (BM) associated with the poor prognosis and high rate of mortality. However, there have been few models to predict early death (ED) from NSCLC patients with BM. We aimed to develop nomograms to predict ED in NSCLC patients with BM.

Methods: The NSCLC patients with BM between 2010 and 2015 were selected from the Surveillance, Epidemiology, and End Result (SEER) database. Our inclusion criteria were as follows: (I) patients were pathologically diagnosed as NSCLC; (II) patients who suffered from BM. The patients were randomly divided into 2 cohorts at the ratio of 7:3, for training and validation cohorts, respectively. The univariate and multivariate logistic regression methods were managed to identify risk factors for ED in NSCLC patients with BM. Two nomograms were established and validated by calibration curves, receiver operating characteristic (ROC) curves, and decision curve analysis (DCA). The follow-up data included survival months, causes of death, vital status. Death that occurred within 3 months of initial diagnosis is defined as ED and the endpoints were all-cause ED and cancer-specific ED.

Results: A total of 4,920 NSCLC patients with BM were included and randomly divided into 2 cohorts (7:3), including the training (n=3,444) and validation (n=1,476) cohorts. The independent prognostic factors for all-cause ED and cancer-specific ED included age, sex, race, tumor size, histology, T stage, N stage, grade, surgical operation, radiotherapy, chemotherapy, bone metastasis, and liver metastasis. All these variables were used to establish the nomograms. In the nomograms of all-cause and cancer-specific ED, the areas under the ROC curves were 0.813 (95% CI: 0.799–0.837) and 0.808 (95% CI: 0.791–0.830) for the training dataset as well as 0.835 (95% CI: 0.805–0.862) and 0.824 (95% CI: 0.790–0.849) for the validation dataset, respectively. Besides, the calibration curves proved that the predicted ED was consistent with the actual value. DCA suggested a good clinical application.

Conclusions: The nomograms can be used to predict the specific probability of a patient's death, which aids in treatment decisions and focused care, as well as in physician-patient communication.

Keywords: Non-small cell lung cancer (NSCLC); brain metastasis (BM); nomogram; early death (ED); Surveillance, Epidemiology, and End Result (SEER) database

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Introduction

The non-small cell lung cancer (NSCLC) is the predominant form of lung cancer, accounting for 80–85% of all the patients with lung cancer, including the subtypes of lung adenocarcinoma (LUAD), squamous cell carcinoma (SQCC), adenosquamous carcinoma (ADSQC), and large-cell lung carcinoma (LCLC), which are different at the sites of origin as well as the histological characteristics (1). The main sites for NSCLC metastasis include bone, brain, and adrenal gland along the liver, among which brain metastasis (BM) is the most common, with 10% found at the time of diagnosis, and 40–50% developed during the course of the disease. NSCLC patients with BM have been found to be associated with the poor prognosis and high rate of mortality. The median overall survival (OS) period among the untreated patients was reported to be only 1–3 months, and the 1-year survival rate was 10–20% (2).

With the advances of diagnostic techniques, the detection rate of BM on patients with NSCLC is also getting higher, making it one of the hotspots in cancer research. In recent years, whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT) have become the primary treatments in addition to the surgical resection. Besides, insights into the biology of the disease have also triggered the research and development of novel treatments, such as immune checkpoint inhibitors and targeted drugs. Thus, the prognosis, as well as the life quality of NSCLC patients with BM, have been improved to a certain extent.

Yet, only a few studies have paid attention to the early death (ED) of NSCLC patients with BM, of which ED is defined as the death in a short time after the diagnosis. To understand the underlying causes, it is necessary to deeply explore the prognostic factors of ED on NSCLC patients with BM. Shen *et al.* (3) reported the prediction model of lung cancer with BM. The results found that age, race, gender, pathological type, grade, tumor stage, bone metastasis, liver metastasis, and marital status were independent risk factors for ED. However, the model did not include the protective factors of surgery, radiotherapy, and chemotherapy and could not assess the risk of ED in patients who received treatment. In addition, other scholars (4) reported that predictive models for ED and long-term survival prediction in NSCLC patients with BM after stereotactic radiosurgery (SRS). The study found that age, sex, extracranial metastases, World Health Organization (WHO) performance status, and Gross Tumor Volume (GTV) largest BM were prognostic factors for survival. However, the inclusion of this study was limited to patients treated with SRS. These nomograms cannot be used for patients treated with other modalities than SRS alone for newly diagnosed BM of NSCLC. To date, no ED prediction models have been reported for patients with NSCLC with BM using the Surveillance, Epidemiology, and End Result (SEER) database. The large sample size of the SEER database, which accounts for about 28% of the entire US population, is more accurate for predicting ED outcomes compared to the results of prediction model studies with small sample sizes and single centers. Our study aimed at establishing a nomogram prediction model to predict the risk probability of the ED among NSCLC patients with BM, providing a basis for the individualized treatment and improving the prognosis of patients. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2323/rc).

Highlight box

Key findings

- Two nomograms were valuable in predicting the specific probability of a patient's death.

What is known and what is new?

- Patients with NSCLC developed BM associated with the poor prognosis and high rate of mortality.
- We developed nomograms to predict ED in NSCLC patients with BM.

What is the implication, and what should change now?

- The nomograms might have a potential in providing references for the selection of the treatment strategies for NSCLC patients with symptomatic BM in clinical practice.

Methods

Patients

This was a retrospective study based on the SEER database, an open-access database covering more than 28% of the US population. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The NSCLC patients with BM between 2010 and 2015 were selected from SEER database. Our inclusion criteria were as follows: (I) patients were pathologically diagnosed as NSCLC; (II) patients who suffered from BM. Besides, the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) was applied to limit the pathological

types (adenocarcinoma: 8140, 8250, 8255, 8260, 8310, 8480–8481, 8574; ADSQC: 8560; SQCC: 8070–8072, 8074; large cell carcinoma: 8012; other: 8010, 8013, 8020–8022, 8031–8032, 8046, 8050, 8252–8253, 8430, 8490) and tumor sites (C34.0-C34.3, C34.8-C34.9). The exclusion criteria were as follows: (I) patients with stage T0, Tx or NX; (II) patients with the histological grade unknown; (III) patients with the race unknown; (IV) patients with the tumor size unknown; (V) patients with the status of bone metastasis unknown; (V) patients with the status of liver metastasis unknown; (VII) patients with the marital status unknown at the diagnosis; (VIII) patients with the information of surgeries unknown; (IX) patients who were diagnosed based on the autopsy only.

The following clinical variables were extracted in the present study: sex, age (≤65, 66–71, and >71 years), race (white, black, and other), marital status, grade (grade I, grade II, grade III, and grade IV), histologic type (LUAD, ADSQC, SQCC, LCLC, and Other), tumor size (≤46, 47–70, and >70 mm), T stage (T1, T2, T3, and T4), N stage (N0, N1, N2, and N3), surgery, radiotherapy, chemotherapy, bone metastasis, liver metastasis. The collinearity of variables was evaluated by variation inflation factors. All the data were randomly divided into two groups (70% for the train group, 30% for the validation group) with "caret" R package. The collected follow-up data included survival months, causes of death, vital status. ED was defined as the death within 3 months following the time of the initial diagnosis and the endpoints were all-cause ED and cancer-specific ED.

Statistical analysis

Data analysis was conducted using R software (version 3.5.2; http://www.r-project.org) as well as SPSS software (version 21; IBM Corp, Armonk, NY, USA). Data extraction was carried out using SEER*Stat software (version 8.4.0.1; http://seer.cancer.gov/seerstat/). The categorized data were presented as numbers and percentages. Univariate and multivariate logistic regression analyses were used to determine the risk factors in the training cohort. The variables with p-values <0.05 in the multivariate regression analysis were used to develop nomograms. Based on the results of the multivariate logistic regression analyses, two nomograms were developed to separately predict the risk of all-causes ED and cancer-specific ED. Receiver operating characteristic (ROC) curves were adopted to evaluate the discriminatory ability of the nomograms. The higher the area under the curve (AUC) was, the better the accuracy would be. AUC values vary from 0.5 to 1.0, where 0.5 represents random chance, and 1.0 represents full compliance. AUC value greater than 0.7 means a reasonable estimate (5). Besides, the calibration curves representing the agreement between the observed outcome and the predicted probabilities were adopted to evaluate the nomograms' performance. Decision curve analysis (DCA) was conducted to assess the clinical utility in all the patients and quantified the net benefits at different threshold probabilities. Two-tailed P value <0.05 was considered to be statistically significant.

Results

Demographic and clinical characteristics of NSCLC patients with BM

In total, 4,920 patients of NSCLC patients with BM diagnosed between 2010 and 2015 in the SEER database were selected and randomly divided into 2 cohorts at the ratio of 7:3, including the training (n=3,444) and validation (n=1,476) cohorts. The process for patient selection is shown in *Figure 1*.

As shown in *Table 1*, 53.5% of the patients were younger than 65 years; and the number of male patients was slightly higher than that of female (54.4% *vs.* 45.6%); besides, white-skinned patients were of a much higher percentage than that of the black-skinned ones (77.9% *vs.* 11.7%); the proportions of LUAD, SQCC, ADSQC and LCLC were 65.8%, 15.7%, 1.7% and 1.6%, respectively; the patients with Gleason grade III were much more compared to others. In addition to BM, liver metastasis and bone metastasis were recognized in 14.6% and 30.2% on the patients respectively; surgical treatment, radiotherapy, chemotherapy were performed in 6.0%, 78.4% and 56.3% of the patients; among all NSCLC patients with BM, 43.3% had ED and 41.1% died of lung cancer (*Table 1*).

The characteristics of patients in training set and validation set were shown in *Table 2*.

Identification of prognostic factors for ED

There was no significant statistical collinearity among the independent predictors (Table S1). Based on the results of the univariate logistic regression analysis (*Table 3*), all the significant variables in the univariate analysis, including the age, sex, race, marital status, Gleason grade, tumor size,

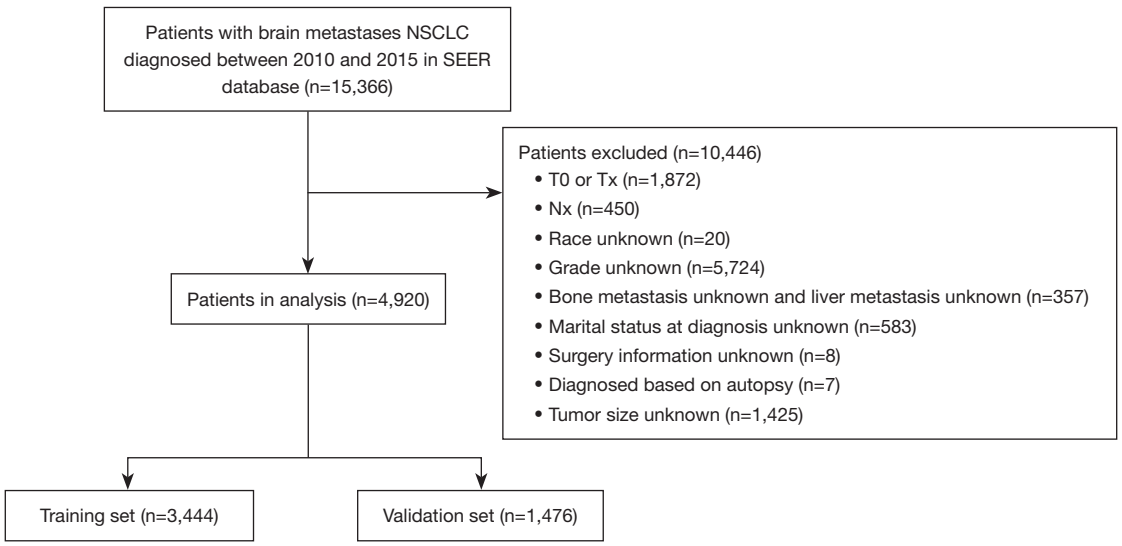

Figure 1 The flowchart of patient selection from the SEER database. NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Result.

histology, Tumor Node Metastasis (TNM) classification of the tumor, surgery, radiation, chemotherapy, bone metastasis, liver metastasis were included in the multivariate logistic regression analysis (*Table 4*), and the results showed that the variables except the marital status and Gleason grade were identified as the independent factors to predict the all-cause ED; Besides, the variables except the sex and marital status were identified as the independent factors to predict the cancer-specific ED.

Establishment of the nomogram prediction models

Using the prognostic factors of the multivariate logistic regression in the training cohort, the nomogram prediction models were established (*Figure 2A*,*2B*). The total score could be calculated by summing up the points of each variable, suggesting each patient's all-cause/cancer-specific probabilities of ED.

Validation of the nomogram prediction models

For the nomogram models of all-cause and cancer-specific ED, ROC curves showed that the AUCs were 0.813 (95% CI: 0.799–0.837) and 0.808 (95% CI: 0.791–0.830) in the training cohort and 0.835 (95% CI: 0.805–0.862) and 0.824 (95% CI: 0.790–0.849) in the validation cohort, respectively (*Figure 3*). The calibration curves of the nomogram in patients also demonstrated a good agreement between the observed outcome and the predicted probabilities (*Figure 4*). Besides, the results of DCA indicated good clinical utilities of the nomogram models (*Figure 5*).

Discussion

Despite significant therapeutic advances in the treatment of NSCLC with BM, patients with symptomatic BMs are often left remained untreated because of the known low survival rate. Except for the locoregional treatment options, there are no other specific indications in the international guidelines for the treatments of NSCLC patients with BM, resulting in poor prognosis of these patients, and this has become a worrying problem worldwide. However, previous studies only paid attention to the long-term survival of patients, leaving the ED not being fully explored. As reported, the definition of ED differs in studies, mostly defined as the death 30 days to 3 months after the first diagnosis. In our study, ED was defined as death within three months. Although previous study (3) has revealed the prognostic factors of ED for the patients with lung cancer and BM, there are few studies for NSCLC patients with BM. Our study not only found out the risk factors of the all-cause/cancer-specific ED among NSCLC patients with BM, but also discovered the protective factors for them. The nomogram prediction models were also established, showing a good predictive ability. Besides, the validation of the nomograms demonstrated a consistency between

Table 1 Baseline Characteristics of NSCLC patients with brain metastasis

Characteristic	Variable	Overall (n=4,920)	No early death (n=2,788)	All-cause early death (n=2,132)	Cancer-specific early death (n=2,021)
Age, years	≤65	2,632 (53.5)	1,687 (60.5)	945 (44.3)	902 (44.6)
	66–71	1,011 (20.5)	530 (19.0)	481 (22.6)	446 (22.1)
	>71	1,277 (26.0)	571 (20.5)	706 (33.1)	673 (33.3)
Sex	Male	2,677 (54.4)	1,413 (50.7)	1,264 (59.3)	1,187 (58.7)
	Female	2,243 (45.6)	1,375 (49.3)	868 (40.7)	834 (41.3)
Race	White	3,832 (77.9)	2,129 (76.4)	1,703 (79.9)	1,617 (80.0)
	Black	577 (11.7)	324 (11.6)	253 (11.9)	237 (11.7)
	Other	511 (10.4)	335 (12.0)	176 (8.3)	167 (8.3)
Marital	Married	2,682 (54.5)	1,600 (57.4)	1,082 (50.8)	1,020 (50.5)
	Unmarried	2,238 (45.5)	1,188 (42.6)	1,050 (49.2)	1,001 (49.5)
Grade	I	188 (3.8)	124 (4.4)	64 (3.0)	60 (3.0)
	II	1,260 (25.6)	835 (29.9)	425 (19.9)	400 (19.8)
	III	3,325 (67.6)	1,757 (63.0)	1,568 (73.5)	1,487 (73.6)
	IV	147 (3.0)	72 (2.6)	75 (3.5)	74 (3.7)
Tumor size, mm	≤46	2,287 (46.5)	1,392 (49.9)	895 (42.0)	841 (41.6)
	47–70	1,515 (30.8)	879 (31.5)	636 (29.8)	602 (29.8)
	>70	1,118 (22.7)	517 (18.5)	601 (28.2)	578 (28.6)
Histology	LUAD	3,237 (65.8)	1,998 (71.7)	1,239 (58.1)	1,173 (58.0)
	ADSQC	83 (1.7)	48 (1.7)	35 (1.6)	33 (1.6)
	SQCC	770 (15.7)	364 (13.1)	406 (19.0)	385 (19.0)
	LCLC	78 (1.6)	40 (1.4)	38 (1.8)	37 (1.8)
	Other	752 (15.3)	338 (12.1)	414 (19.4)	393 (19.4)
T	T1	492 (10.0)	331 (11.9)	161 (7.6)	147 (7.3)
	T2	1,520 (30.9)	946 (33.9)	574 (26.9)	545 (27.0)
	T3	1,343 (27.3)	708 (25.4)	635 (29.8)	604 (29.9)
	T4	1,565 (31.8)	803 (28.8)	762 (35.7)	725 (35.9)
N	N0	1,180 (24.0)	705 (25.3)	475 (22.3)	450 (22.3)
	N1	488 (9.9)	294 (10.5)	194 (9.1)	180 (8.9)
	N2	2,386 (48.5)	1,296 (46.5)	1,090 (51.1)	1,028 (50.9)
	N3	866 (17.6)	493 (17.7)	373 (17.5)	363 (18.0)
Surgery	No	4,627 (94.0)	2,556 (91.7)	2,071 (97.1)	1,970 (97.5)
	Yes	293 (6.0)	232 (8.3)	61 (2.9)	51 (2.5)
Radiation	No/Unknown	1,062 (21.6)	386 (13.8)	676 (31.7)	628 (31.1)
	Yes	3,858 (78.4)	2,402 (86.2)	1,456 (68.3)	1,393 (68.9)
Chemotherapy	No/Unknown	2,151 (43.7)	607 (21.8)	1,544 (72.4)	1,459 (72.2)
	Yes	2,769 (56.3)	2,181 (78.2)	588 (27.6)	562 (27.8)
Bone metastasis	No	3,434 (69.8)	2,021 (72.5)	1,413 (66.3)	1,324 (65.5)
	Yes	1,486 (30.2)	767 (27.5)	719 (33.7)	697 (34.5)
Liver metastasis	No	4,203 (85.4)	2,475 (88.8)	1,728 (81.1)	1,623 (80.3)
	Yes	717 (14.6)	313 (11.2)	404 (18.9)	398 (19.7)

Data are presented as n (%). NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; ADSQC, adenosquamous carcinoma; SQCC, squamous cell carcinoma; LCLC, large-cell lung carcinoma.

Table 2 Baseline characteristics of the training and validation cohorts

Characteristic	Variable	Training cohort (n=3,444)	Validation cohort (n=1,476)
Age, years	≤65	1,827 (53.0)	805 (54.5)
	66–71	714 (20.7)	297 (20.1)
	>71	903 (26.2)	374 (25.3)
Sex	Male	1,875 (54.4)	802 (54.3)
	Female	1,569 (45.6)	674 (45.7)
Race	White	2,679 (77.8)	1,153 (78.1)
	Black	419 (12.2)	158 (10.7)
	Other	346 (10.0)	165 (11.2)
Marital	Married	1,833 (53.2)	849 (57.5)
	Unmarried	1,611 (46.8)	627 (42.5)
Grade	I	125 (3.6)	63 (4.3)
	II	908 (26.4)	352 (23.8)
	III	2,305 (66.9)	1,020 (69.1)
	IV	106 (3.1)	41 (2.8)
Tumor size, mm	≤46	1,592 (46.2)	695 (47.1)
	47–70	1,055 (30.6)	460 (31.2)
	>70	797 (23.1)	321 (21.7)
Histology	LUAD	2,270 (65.9)	967 (65.5)
	ADSQC	61 (1.8)	22 (1.5)
	SQCC	547 (15.9)	223 (15.1)
	LCLC	50 (1.5)	28 (1.9)
	Other	516 (15.0)	236 (16.0)
T	T1	341 (9.9)	151 (10.2)
	T2	1,051 (30.5)	469 (31.8)
	T3	939 (27.3)	404 (27.4)
	T4	1,113 (32.3)	452 (30.6)
N	N0	831 (24.1)	349 (23.6)
	N1	338 (9.8)	150 (10.2)
	N2	1,656 (48.1)	730 (49.5)
	N3	619 (18.0)	247 (16.7)
Surgery	No	3,248 (94.3)	1,379 (93.4)
	Yes	196 (5.7)	97 (6.6)
Radiation	No/Unknown	737 (21.4)	325 (22.0)
	Yes	2,707 (78.6)	1,151 (78.0)
Chemotherapy	No/Unknown	1,495 (43.4)	656 (44.4)
	Yes	1,949 (56.6)	820 (55.6)
Bone metastasis	No	2,368 (68.8)	1,066 (72.2)
	Yes	1,076 (31.2)	410 (27.8)
Liver metastasis	No	2,952 (85.7)	1,251 (84.8)
	Yes	492 (14.3)	225 (15.2)

Data are presented as n (%). LUAD, lung adenocarcinoma; ADSQC, adenosquamous carcinoma; SQCC, squamous cell carcinoma; LCLC, large-cell lung carcinoma.

Table 3 Univariate logistic regression for the risk factors of early death

Variable	Overall early-death			Cancer-specific early-death		
	OR	95% CI	P	OR	95% CI	P
Age (years)						
≤65	Ref.			Ref.		
66–71	1.538	1.291–1.833	<0.001	1.427	1.196–1.703	<0.001
>71	2.060	1.753–2.423	<0.001	2.015	1.714–2.371	<0.001
Sex						
Male	Ref.			Ref.		
Female	0.739	0.645–0.846	<0.001	0.781	0.681–0.895	<0.001
Race						
White	Ref.			Ref.		
Black	1.009	0.819–1.241	0.933	0.986	0.799–1.214	0.891
Other	0.678	0.535–0.855	0.001	0.673	0.529–0.851	0.001
Marital status						
Married	Ref.			Ref.		
Unmarried	1.323	1.155–1.515	<0.001	1.322	1.154–1.516	<0.001
Grade						
I	Ref.			Ref.		
II	0.799	0.545–1.182	0.256	0.797	0.541–1.186	0.255
III	1.414	0.981–2.058	0.066	1.439	0.994–2.106	0.057
IV	1.545	0.916–2.617	0.104	1.712	1.012–2.912	0.046
Tumor size (mm)						
≤46	Ref.			Ref.		
47–70	1.052	0.897–1.233	0.532	1.060	0.902–1.244	0.479
>70	1.813	1.527–2.153	<0.001	1.874	1.578–2.227	<0.001
Histology						
LUAD	Ref.			Ref.		
ADSQC	0.989	0.577–1.658	0.966	1.078	0.629–1.808	0.778
SQCC	1.984	1.644–2.397	<0.001	1.938	1.606–2.341	<0.001
LCLC	1.391	0.787–2.441	0.250	1.518	0.858–2.663	0.146
Other	1.849	1.526–2.243	<0.001	1.838	1.516–2.229	<0.001
T stage						
T1	Ref.			Ref.		
T2	1.130	0.876–1.464	0.349	1.228	0.946–1.602	0.126
T3	1.740	1.347–2.257	<0.001	1.876	1.444–2.450	<0.001
T4	1.795	1.397–2.317	<0.001	1.948	1.508–2.532	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Overall early-death			Cancer-specific early-death		
	OR	95% CI	P	OR	95% CI	P
N stage						
N0	Ref.			Ref.		
N1	0.921	0.709–1.193	0.534	0.923	0.708–1.199	0.549
N2	1.281	1.082–1.518	0.004	1.270	1.071–1.507	0.006
N3	1.116	0.903–1.379	0.309	1.167	0.943–1.444	0.155
Surgery						
No	Ref.			Ref.		
Yes	0.342	0.239–0.480	<0.001	0.297	0.201–0.425	<0.001
Radiation						
No/Unknown	Ref.			Ref.		
Yes	0.344	0.290–0.407	<0.001	0.385	0.325–0.454	<0.001
Chemotherapy						
No/Unknown	Ref.			Ref.		
Yes	0.116	0.099–0.135	<0.001	0.132	0.113–0.154	<0.001
Bone metastasis						
No	Ref.			Ref.		
Yes	1.352	1.170–1.563	<0.001	1.424	1.231–1.648	<0.001
Liver metastasis						
No	Ref.			Ref.		
Yes	1.850	1.527–2.244	<0.001	1.993	1.644–2.418	<0.001

OR, odds ratio; CI, confidence interval; LUAD, lung adenocarcinoma; ADSQC, adenosquamous carcinoma; SQCC, squamous cell carcinoma; LCLC, large-cell lung carcinoma.

the predicted probabilities of ED and the actual value. The results of DCA also proved that the nomograms presented ideal clinical application values in the prediction of the risk of ED among NSCLC patients with BM.

The prognosis of NSCLC patients with BM has been demonstrated to be affected by various factors, including the age, pathological type, the number and size of BM, the different sites of distal metastasis, improper treatment methods, etc. (6-9).

Firstly, it is believed that age is linked with the prognosis of NSCLC patients with BM (10,11). In our results, patients aged ≤65 years presented a lower all-cause risk of ED than those aged >65 years. However, whether sex is related to the prognosis of NSCLC is still controversial. Some studies have reported poorer OS of the elderly male patients with advanced NSCLC (12); except for stage IIIA, all the male patients with SQCC showed a survival disadvantage (13). Comparatively, other studies (14-17) have shown that the OS of the females is higher than that of the males among NSCLC patients. Additionally, Hanagiri *et al.* (18) suggested no apparent correlation between the sex and OS of patients with lung cancer. The different results may be attributed to the small sample size of these studies, the uncertain number of female smokers or passive smokers, and other confounding factors. Our study revealed that the risk of all-cause ED in females was lower than that of males; However, the cancer-specific EDs were not significantly different between the females and the males. The above findings suggest that the different risk probabilities of ED in different sexes of NSCLC patients with BM deserve

Table 4 Multivariate logistic regression for the risk factors of early death

Variable	Overall early-death			Cancer-specific early-death		
	OR	95% CI	P	OR	95% CI	P
Age (years)						
≤65	Ref.			Ref.		
66–71	1.269	1.028–1.566	0.027	1.163	0.943–1.434	0.157
>71	1.537	1.262–1.870	<0.001	1.528	1.258–1.856	<0.001
Sex						
Male	Ref.			Ref.		
Female	0.803	0.679–0.949	0.010	0.873	0.739–1.030	0.108
Race						
White	Ref.			Ref.		
Black	0.842	0.653–1.084	0.183	0.829	0.645–1.065	0.144
Other	0.691	0.521–0.913	0.010	0.689	0.520–0.909	0.009
Marital						
Married	Ref.			Ref.		
Unmarried	1.078	0.910–1.276	0.385	1.087	0.919–1.285	0.328
Grade						
I	Ref.			Ref.		
II	0.869	0.549–1.384	0.551	0.877	0.556–1.394	0.574
III	1.451	0.932–2.278	0.102	1.484	0.956–2.326	0.081
IV	1.827	0.937–3.574	0.077	2.053	1.061–3.990	0.033
Tumor size (mm)						
≤46	Ref.			Ref.		
47–70	0.936	0.766–1.144	0.520	0.928	0.760–1.132	0.462
>70	1.320	1.043–1.672	0.021	1.387	1.099–1.751	0.006
Histology						
LUAD	Ref.			Ref.		
ADSQC	0.913	0.482–1.692	0.775	1.012	0.539–1.864	0.969
SQCC	1.619	1.285–2.042	<0.001	1.575	1.254–1.978	<0.001
LCLC	0.807	0.384–1.685	0.568	0.868	0.417–1.797	0.703
Other	1.345	1.056–1.712	0.016	1.317	1.038–1.671	0.023
T stage						
T1	Ref.			Ref.		
T2	1.129	0.823–1.554	0.453	1.242	0.905–1.712	0.182
T3	1.476	1.057–2.066	0.023	1.550	1.110–2.172	0.010
T4	1.592	1.152–2.208	0.005	1.693	1.225–2.350	0.002

Table 4 (*continued*)

Table 4 (*continued*)

Variable	Overall early-death			Cancer-specific early-death		
	OR	95% CI	P	OR	95% CI	P
N stage						
N0	Ref.			Ref.		
N1	1.155	0.839–1.589	0.376	1.109	0.806–1.523	0.524
N2	1.352	1.097–1.669	0.005	1.281	1.042–1.578	0.019
N3	1.227	0.942–1.598	0.129	1.234	0.950–1.604	0.115
Surgery						
No	Ref.			Ref.		
Yes	0.343	0.227–0.510	<0.001	0.311	0.202–0.469	<0.001
Radiation						
No/Unknown	Ref.			Ref.		
Yes	0.604	0.494–0.739	<0.001	0.680	0.558–0.828	<0.001
Chemotherapy						
No/Unknown	Ref.			Ref.		
Yes	0.116	0.098–0.138	<0.001	0.130	0.109–0.155	<0.001
Bone metastasis						
No	Ref.			Ref.		
Yes	1.586	1.319–1.910	<0.001	1.640	1.366–1.971	<0.001
Liver metastasis						
No	Ref.			Ref.		
Yes	1.654	1.304–2.098	<0.001	1.778	1.407–2.249	<0.001

OR, odds ratio; CI, confidence interval; LUAD, lung adenocarcinoma; ADSQC, adenosquamous carcinoma; SQCC, squamous cell carcinoma; LCLC, large-cell lung carcinoma.

further study in the future.

Secondly, some researchers (19) studied the impact of African descent on the all-cause survival of blacks and whites with NSCLC, and found that the stage and treatments might be important predictive factors. Thus, it could be inferred that with the efforts of early detection and early diagnosis, the racial differences on the survival between the black and white patients with lung cancer may disappear. Our results suggest no statistical difference in the risk of ED between the blacks and whites; however, the risk of the ED in other races (American Indian/Alaska Native/Asian/Pacific Islander) was lower than that in the whites. Compared to the whites, other races only accounted for a small part in our study. Therefore, for the NSCLC patients with BM, the difference in the risk probabilities of the ED among different ethnic groups is necessary to be further confirmed in larger cohorts.

Thirdly, the survival rate of patients with NSCLC has been found to be related to the grade of malignancy (20). In our study, the patients with a higher grade of malignancy presented a higher risk of ED than those with a lower grade of malignancy, and the patients with the tumor size >70 mm in diameter had a high risk of ED. Tumor size has been a known prognostic factor for NSCLC and is usually recognized as the primary determinant of the stage and treatments for the patients (21). In the lung cancer staging system of the International Association for the Study of Lung Cancer (IASLC, 8th edition), it is recommended that 1.0 cm is applied as a cut-off value of the diameter to distinguish the risk of the tumor, i.e., every 1.0 cm increase

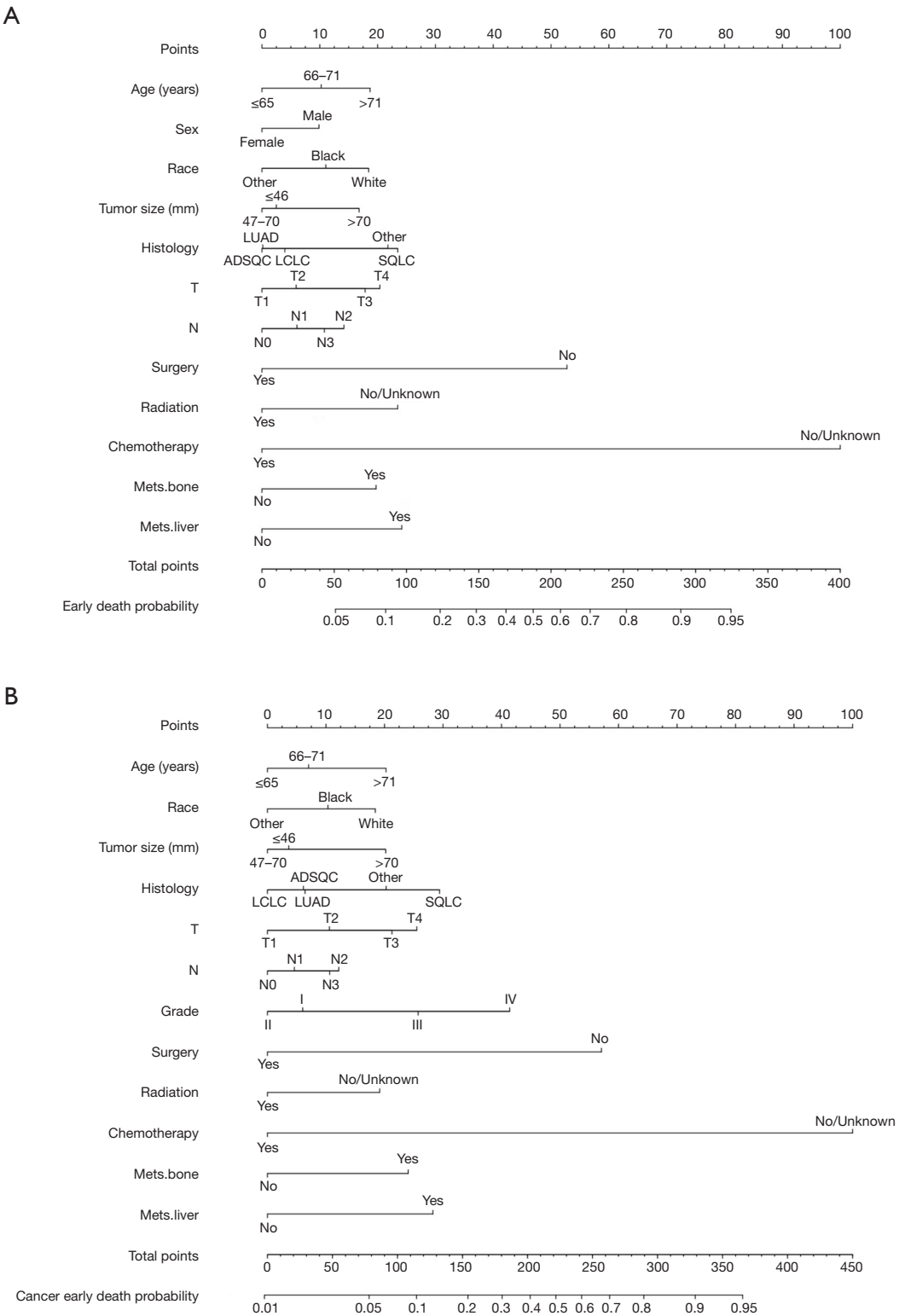

Figure 2 The nomogram prediction model for the all-cause (A) and cancer-specific (B) early death of NSCLC patients with brain metastasis in the training cohort. NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; ADSQC, adenosquamous carcinoma; LCLC, large-cell lung carcinoma; SQLC, squamous cell lung carcinoma.

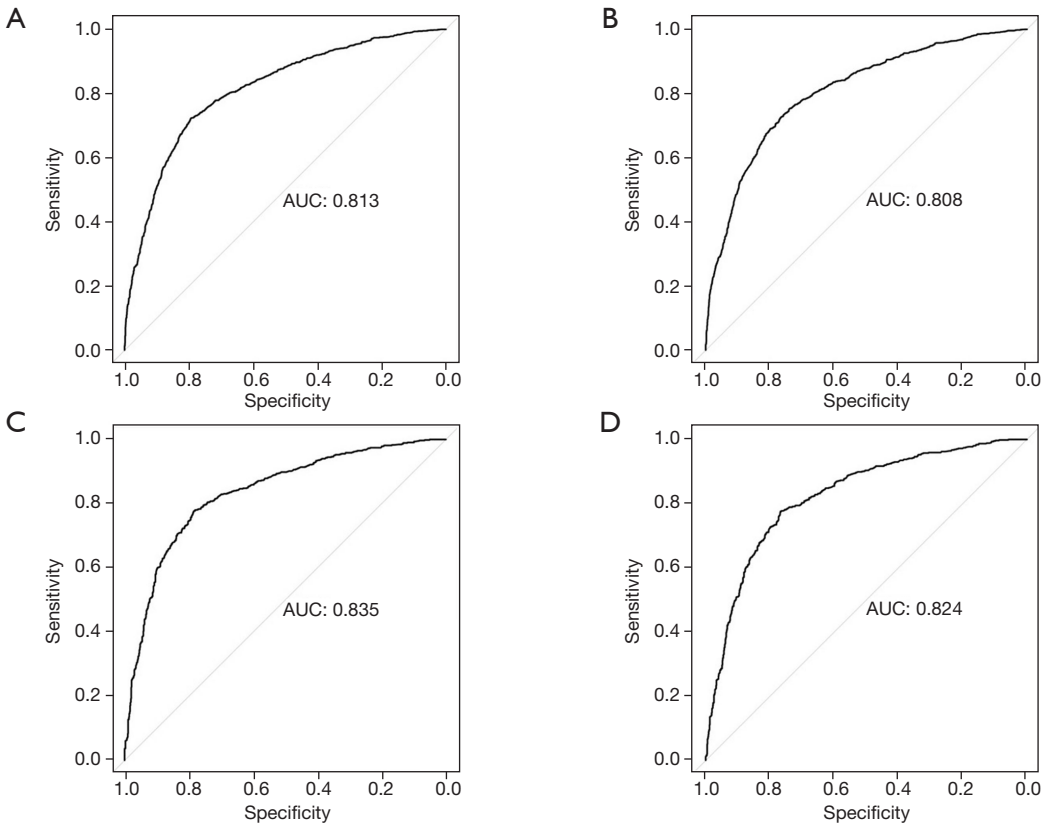

Figure 3 ROC curves for the nomograms of the all-cause early death and the cancer-specific early death in the training cohort (A,B) as well as in the validation cohort (C,D). ROC, receiver operating characteristic; AUC, area under the curve.

in the maximum diameter of the tumor will lead to a worse probability of the prognosis of the patients (22).

Fourthly, the prognosis of NSCLC patients is closely related to clinicopathological features, such as the tumor stage, the pathological classification, and the location of the primary tumor (23,24). Lopez Guerra *et al.* (25) showed that the survival rate of patients with LUAD was higher than those with SQCC, but Chansky *et al.* (26) reported the opposite results; Puri *et al.* (27) reported that the prognosis was not obvious between the patients with LUAD and SQCC, possibly related to the clinical characteristics as well as the sample sizes. In our study, the results of logistic regression suggest that the risk of ED from SQCC was higher than that of LUAD; however, the risks of ED in the patients with ADSQC and LCLC were not significantly different from those with LUAD.

Fifthly, TNM staging has been demonstrated to be the most important factor in the evaluation of the prognosis of NSCLC patients (26). The more advanced stage usually indicates a worse prognosis. Our study found that the risks of ED in T3 and T4 stages were much higher than that in T1 stage, and the risk probability of ED in N2 stage was much higher than that in N0 stage.

According to the results of the multivariate logistic regression, the risk probability of ED of patients with surgical treatments was lower than those without surgical treatment. Cautions should be taken when treating NSCLC patients with BM with surgeries. Besides, the complications and tumor recurrence after surgeries need to be considered as well. Studies have reported that the surgical treatment of lung cancer with BM could significantly improve the survival rate of patients. A retrospective study (28) found the median OS of 13 NSCLC patients with BM reached up to approximately 94 months, and two studies (29,30) have reported that the five-year survival rate of NSCLC patients with surgical treatments was 11–36%. Another study (31) of 17 patients reported similar results. These findings suggest that surgical treatment has a potential in prolonging the

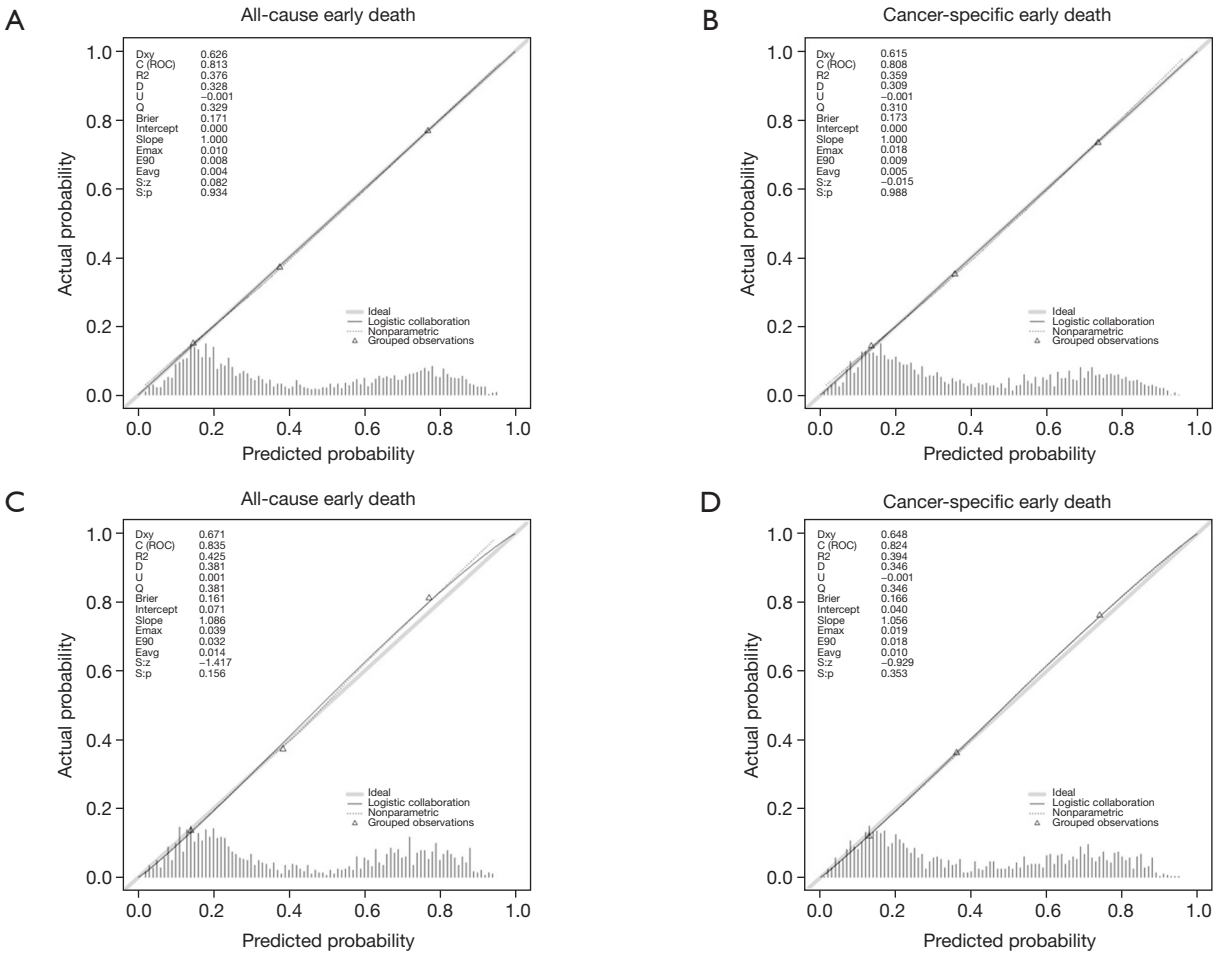

Figure 4 Calibration plots for the nomograms of the all-cause early death and the cancer-specific early death in the training cohort (A,B) as well as in the validation cohort (C,D).

survival rate and reducing the mortality of NSCLC patients with BM.

Radiotherapy is another important treatment for BM, among which WBRT and SRT have been recognized as the main radiotherapies for NSCLC patients with BM according to the guidelines of the National Cancer Comprehensive Network (NCCN). As reported, the effective rate of WBRT for NSCLC patients with BM is 70–90% (32); however, some studies revealed that the median OS after WBRT was as less as 3–6 months (33), and may result in serious neurological complications (34,35). In contrast, SRT could bring more benefits and less damage to the surrounding normal tissues, and control the progression of BM safely and quickly, thus relieving the neurological symptoms of patients. One study proved that SRT is an effective treatment associated with a high local control rate and a low morbidity for NSCLC patients with BM (36). Nowadays, SRT has gradually become an essential method for the clinical treatment of NSCLC patients with BM. In our study, compared to those without radiotherapy, patients with radiotherapy showed a lower risk of ED, which was consistent with the above results.

Chemotherapy is not only the pillar to treatment for advanced NSCLC patients but also an essential part of the comprehensive multidisciplinary treatment for NSCLC patients with BM. Currently, the platinum combined with third-generation cytotoxic drugs has been a classic scheme of chemotherapy for NSCLC patients with BM (37,38). Pemetrexed has achieved a good efficacy in treating NSCLC patients with BM (39), and the response rate of intracranial metastasis was 30.8%. In addition, temozolomide could penetrate the blood-brain barrier due to its low molecular

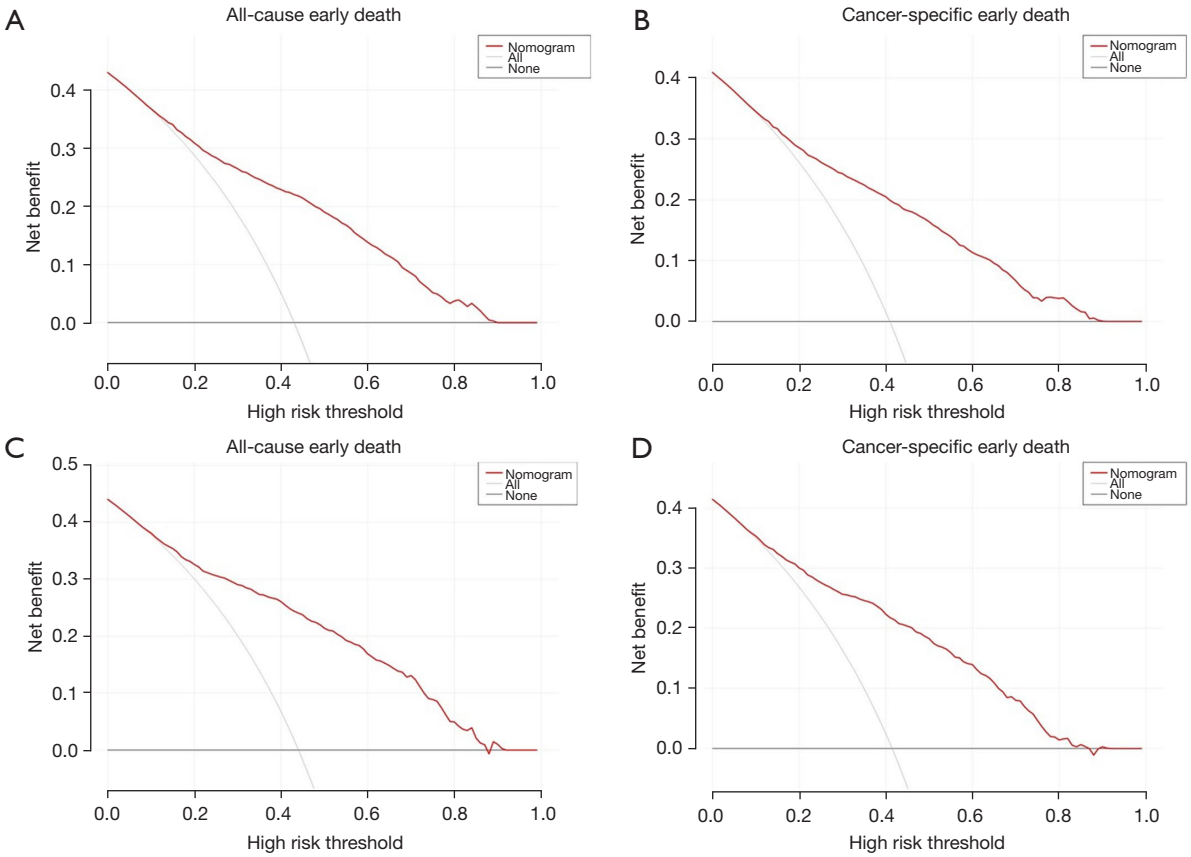

Figure 5 Decision curve analysis for the nomograms of the all-cause early death and the cancer-specific early death in the training cohort (A,B) as well as in the validation cohort (C,D).

weight and lipophilic properties and it has an excellent therapeutic effect on BM. It is often combined with WBRT to improve the disease control rate (DCR) of intracranial metastasis (38). Several clinical studies have shown that as a systemic treatment, chemotherapy combined with WBRT can not only improve the response rate and prolong the survival rate but also tolerate the toxic reactions (37,40,41). Our results showed that the chemotherapy significantly exerted a protective effect on the ED, suggesting the risk probability of ED of patients who received the chemotherapy was considerably lower than those did not receive the chemotherapy.

Rief *et al.* (42) found that the OS rate of patients with single bone metastasis of lung cancer at 6 and 12 months was 76.7% and 47.2%, respectively, significantly higher than those with metastasis at other sites (60.0% and 34.0%); comparatively, the OS of patients with multiple bone metastases and pathological fractures was much poorer. Ren *et al.* (43) also analyzed the data in the SEER database in the United States, and found that among patients with LUAD and small cell lung cancer, patients with liver metastasis had the worst prognosis compared to those with metastasis at other single organs. Similarly, Tamura *et al.* (44) and Wu *et al.* (45) also demonstrated a very poor prognosis of NSCLC patients with liver metastasis. The progression-free survival (PFS) of patients without liver metastasis was significantly longer than those with liver metastasis (11.2 *vs.* 6.7 months). Our results demonstrated that patients with bone/liver metastasis had a higher risk probability of ED than those without bone/liver metastasis, which complied with the above results.

Our study also had some limitations. Firstly, it was a retrospective study, including only the patients with complete data, suggesting inevitable bias. Secondly, specific information about the systemic treatment of the patients was absent, especially the particular types of surgeries, dose of the radiotherapy, and drugs for the chemotherapy. Thirdly, due to the lack of the data on adrenal metastasis

in the SEER database, some other distant metastatic sites of lung cancer were not involved in this study, such as adrenal metastasis, skin metastasis and splenic metastasis. In addition, information on single or multiple metastases was also not recorded in the SEER database. Fourth, in recent years, the types of gene mutations, targeted therapies, and immunotherapies also have exerted a significant impact on the prognosis of patients with lung cancer. However, we didn't obtain the relevant data. Finally, despite of the internal validation, the included patients were limited to the United States. Thus, the clinical utilities of the nomogram prediction models still need to be validated through a cohort in other countries and ethnic groups in the future.

Conclusions

In summary, we established two comprehensive nomogram prediction models for the ED among NSCLC patients with BM, which might have a potential in providing references for the selection of the treatment strategies for NSCLC patients with symptomatic BM in clinical practice.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2323/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2323/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Statistical collinearity of the predictors

Predictors	Variation inflation factors
Age	1.056
Sex	1.046
Race	1.009
Marital	1.047
Grade	1.105
Tumor size	1.213
Histology	1.122
T stage	1.227
N stage	1.090
Surgery	1.061
Radiation	1.095
Chemotherapy	1.151
Bone metastasis	1.109
Liver metastasis	1.090

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