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Mining prognostic factors of extensive-stage small-cell lung cancer patients using nomogram model

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Abstract

This study is to establish the nomogram model and provide clinical therapy decision-making for extensive-stage small-cell lung cancer (ES-SCLC) patients with different metastatic sites using the Surveillance, Epidemiology, and End Results (SEER) Program.

A total of 10,025 patients of ES-SCLC with metastasis from January 2010 to December 2016 were enrolled from the SEER database. All samples were randomly divided into a derivation cohort and a validation cohort, and the derivation cohort was divided into 6 groups by different metastatic sites: bone, liver, lung, brain, multiple organs, and other organs. Using Cox proportional hazards models to analyze candidate prognostic factors, screening out the independent prognostic factors to establish the nomogram. Compare the different models by Net reclassification improvement and integrated discrimination improvement. Concordance index (C-index) and the calibration curve were used to verify the prediction efficiency of the nomogram in the derivation cohort and validation cohort.

In the derivation cohort, the median overall survival was 7 months. The overall survival rates at 6-month, 1-year, and 2-year were 55.07%, 24.61%, and 7.56%, respectively. The median survival time was 10, 8, 7, 9, 7, and 6 months for the 6 groups of different metastatic sites: other, bone, liver, lung, brain, and multiple organs, respectively. Age, sex, race, T, N, distant metastatic site, and chemotherapy were contained in the final nomogram prognostic model. The C-index was 0.6569777 in the derivation cohort and 0.8386301 in the validation cohort.

The survival time of ES-SCLC patients with different metastatic sites was significantly different. The nomogram can effectively predict the prognosis of individuals and provide a basis for clinical decision-making.

Abbreviations: AI = American Indian/Alaska native, AIC = Akaike information criterion, API = Asian or Pacific Islander, Chemo = chemotherapy, C-index = concordance index, DM = distant metastatic site, ES-SCLC = extensive-stage small-cell lung cancer, IDI = integrated discrimination improvement, NRI = net reclassification improvement.

Keywords: extensive-stage small-cell lung cancer, multiple metastatic, nomogram model, prediction, Surveillance, Epidemiology, and End Results

1. Introduction

The small-cell lung cancer (SCLC) accounts for 16% of all lung cancer, which is characterized by rapid growth, early metastatic spread, and widespread dissemination.[1] Approximately two-thirds of SCLC patients showed significant metastasis at the time of clinical diagnosis,[2] which was classified as ES-SCLC. Liver, brain, bone, adrenals, and lungs are the most common metastatic sites in ES-SCLC patients,[1] which is the main factor for the failure of treatment and poor prognosis. Despite the rapid development of clinical oncology, the prognosis of ES-SCLC is still very poor at present, with the survival time of 60% to 70% of patients ranging from 7 to 11 months, and only 2% of patients reaching the 5-year survival period.[3] To this kind of patient, except the routine chemotherapy, the treatment method is various, but the curative effect is not satisfactory. A previous study[4] based on large cohort data revealed that the survival time of ES-SCLC patients varied with different metastatic sites. Therefore, predicting the patient's survival time based on the patient's metastatic site was essential for the choice of treatment decisions. In this study, the nomogram was established to analyze the survival time of ES-SCLC patients from the SEER database and the individualized patient survival prediction can provide accurate clinical decision-making.

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HG, YD, and TQ contributed equally to the work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Patients and methods

2.1. Patients enrollment

We applied the SEER database of incidence-seer 18 Regs Custom Data with additional treatment fields and the data of the November 2017 Sub (1973–2016) version, which concluded at the end of 2016. This study takes cases of ES-SCLC in adults over 18 years old as the research object. All patients were divided randomly into a derivation cohort and a validation cohort. Pathologic types include ICD-O-3 Hist 8041/3 small cell carcinoma, NOS; 8042/3 oat cell carcinoma; 8043/3 small cell carcinoma, fusiform cell; 8044/3 small cell carcinoma, intermediate cell; 8045/3 combined small cell carcinoma. Because the database did not clearly record the distant metastatic sites before 2010, only cases from 2010 to 2016 were selected in this study. The purpose of this study was to analyze the survival of different metastatic sites of ES-SCLC, so cases with no distant metastasis and cases with unclear metastatic sites were excluded. Cases in which the cause of death was unclear or died of other causes should also be excluded. Figure 1 illustrates the screening flow chart of patients in SEER database.

The data on race, sex, age, American Joint Committee on Cancer (AJCC) 7th edition TNM staging, different metastatic site, and chemotherapy were extracted for all cases. In the SEER database, only 4 sites of distant metastasis were recorded: bone, liver, lung, and brain. According to the research needs, all cases were divided into 6 groups by different metastatic sites: bone; liver; lung; brain; multiple organs; others organs, specifically refers to the exception of bone, liver, lung, brain metastases. This study was approved by the Chang An Hospital Ethics Committee (approval no: CA2019-001-023; Xi'an, China)

2.2. Survival analysis

The life-table method was used to calculate the survival time of different metastatic sites. The survival curve was drawn by the Kaplan–Meier method, and the survival difference was evaluated by the Log-rank test. Categorical variables were grouped based on clinical findings, and decisions on the groups were made before modeling.

2.3. Prognostic factors analysis

The COX proportional risk model was used for multivariate analysis of candidate prognostic factors in the derivation cohort. Independent prognostic factors were screened by the backward LR method.

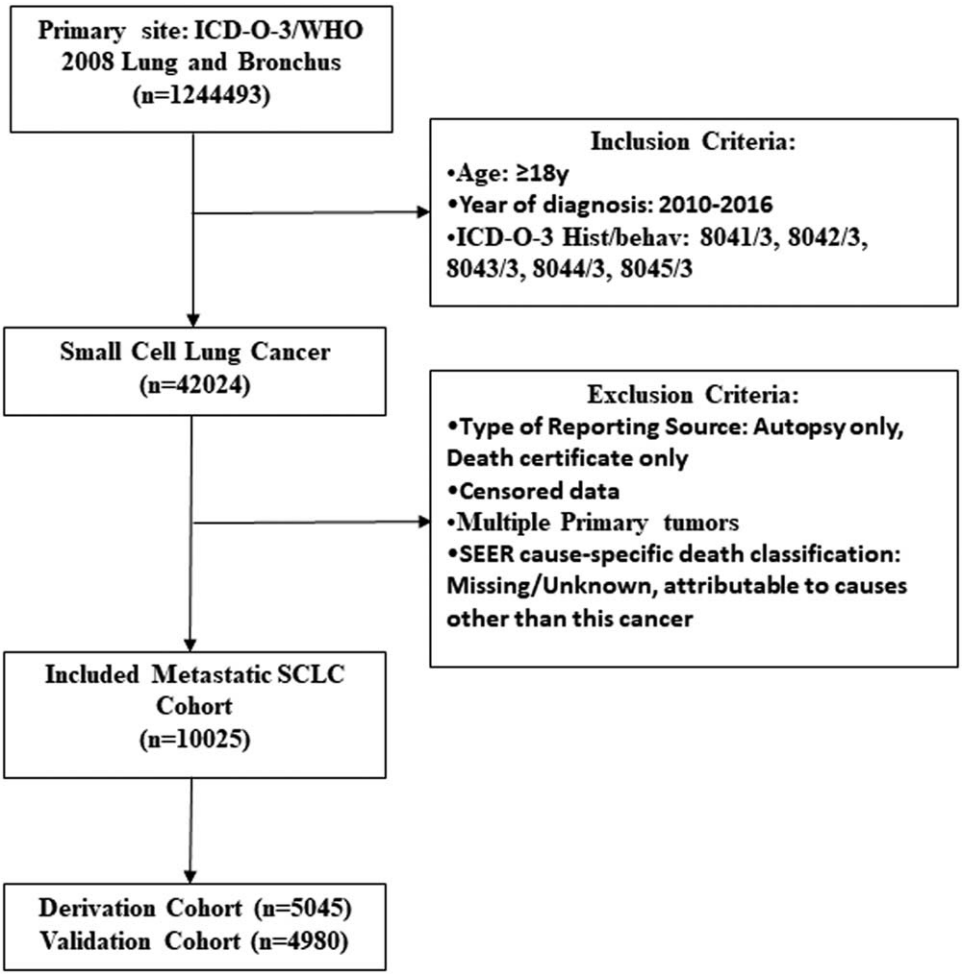

Figure 1. The screening flow chart of patients in Surveillance, Epidemiology, and End Results database.

2.4. Development of an individualized prediction model

Two different prediction models were established based on these independent prognostic factors, and R 3.6.1 version software was used to calculate net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to compare the advantages and disadvantages of the 2 models and select the best model.

2.5. Validation of the nomogram

Internal validation: Demonstrate the reproducibility of the model and verify it in the Derivation cohort. Calibration curves were plotted to assess the calibration of the nomogram, accompanied by the Hosmer–Lemeshow test. To quantify the discrimination performance of the nomogram, Harrell C-index was measured. The nomogram was subjected to bootstrapping validation (1000 bootstraps resamples) to calculate a relatively corrected C-index.

External validation: Demonstrate the transportability and generalizability of the model and verify it in the validation cohort. The expected survival rate for each case was calculated in the validation cohort using the regression model and the baseline survival rate from the derivation cohort. Then, the COX regression analysis was performed again with the expected survival rate as the only independent variable in the validation cohort. And finally, the C-index and calibration curve were derived based on the regression analysis.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 24.0 software. All the data were expressed as the mean ± standard deviation. Statistical significance was determined as $P < .05$. The nomogram was established by R 3.6.1 version software on the basis of multivariable COX analysis in the derivation cohort.

3. Results

3.1. Patient characteristics

A total of 10,025 SCLC patients with metastatic were chosen from the SEER database. Among them, 8796 patients died by the end of follow-up, accounting for 87.7% of the total cases. The age ranged from 19 to 94 years old, with a median age of 66 years old. Except for Race ($P = .028$), there was no selection bias of clinical characteristics between the derivation cohort and the validation cohort, which is shown in Table 1.

Table 1

Characteristics of ES-SCLC patients in derivation cohort and validation cohort.

Prognostic factors	Derivation cohort, n (%)	Validation cohort, n (%)	P
Total	5045	4980	
Age			.471
<45	55 (1.1)	63 (1.3)	
≥45, <55	584 (11.6)	575 (11.5)	
≥55, <65	1597 (31.7)	1571 (31.5)	
≥65, <75	1787 (35.4)	1823 (36.6)	
≥75	1022 (20.3)	948 (19.0)	
Race			.028*
White	4398 (87.2)	4251 (85.4)	
Black	460 (9.1)	511 (10.3)	
Others	187 (3.7)	218 (4.4)	
Sex			.376
Male	2636 (52.2)	2558 (51.4)	
Female	2409 (47.8)	2422 (48.6)	
T			
T0	55 (1.1)	56 (1.1)	.551
T1a	208 (4.1)	239 (4.8)	
T1b	244 (4.8)	258 (5.2)	
T2a	683 (13.5)	665 (13.4)	
T2b	387 (7.7)	360 (7.2)	
T3	1179 (23.4)	1195 (24.0)	
T4	2289 (45.4)	2207 (44.3)	
N			.225
N0	635 (12.6)	609 (12.2)	
N1	345 (6.8)	300 (6.0)	
N2	2765 (54.8)	2813 (56.5)	
N3	1300 (25.8)	1258 (25.3)	
DM			.342
Others	947 (18.8)	906 (18.2)	
Bone	550 (10.9)	525 (10.5)	
Brain	664 (13.2)	669 (13.4)	
Liver	749 (14.8)	820 (16.5)	
Lung	352 (7.0)	341 (6.8)	
Multiorgans	1783 (35.3)	1719 (34.5)	
Chemo			.553
Yes	4058 (80.4)	4029 (80.9)	
No	987 (19.6)	951 (19.1)	

DM = distant metastatic site.

3.2. Survival analysis

The median survival time of the derivation cohort was 7 months. The 6-month, 1-year, and 2-year survival rates were 55.07%, 24.61%, and 7.56%, respectively (Fig. 2A). The median survival time was 10, 8, 7, 7, 9, and 6 months in the 6 metastatic site groups of the other organs, bone, brain, liver, lung, and multiple organs, respectively, shown in Table 2. The Kaplan–Meier survival curves of different metastatic sites are described in Figure 3A, and the Log-rank method showed a significant difference in survival between the groups ($\chi^2 = 251.826$, $P = .000$).

And the median survival time of the validation cohort was 8 months. The 6-month, 1-year, and 2-year survival rates were 56.57%, 24.44%, and 6.85%, respectively (Fig. 2B). The median survival time was 9, 9, 7, 7, 9, and 7 months in the 6 metastatic site groups of the other organs, bone, brain, liver, lung, and multiple organs, respectively. The Log-rank method showed a significant difference in survival between the groups ($\chi^2 = 218.851$, $P = .000$) (Fig. 3B).

3.3. Prognostic factors analysis

Multivariate analysis of Cox regression models including age, sex, race, T, N, metastatic sites, and chemotherapy. The results in Table 3 show that these 7 factors were independent prognostic factors affecting survival ($P < .05$). There were significant differences among 6 groups of metastatic sites except for brain metastasis ($P = .574$).

3.4. Development of an individualized prediction model

Mod1 was established by the independent prognostic factors including age, sex, race, T, N, metastatic site and chemotherapy,

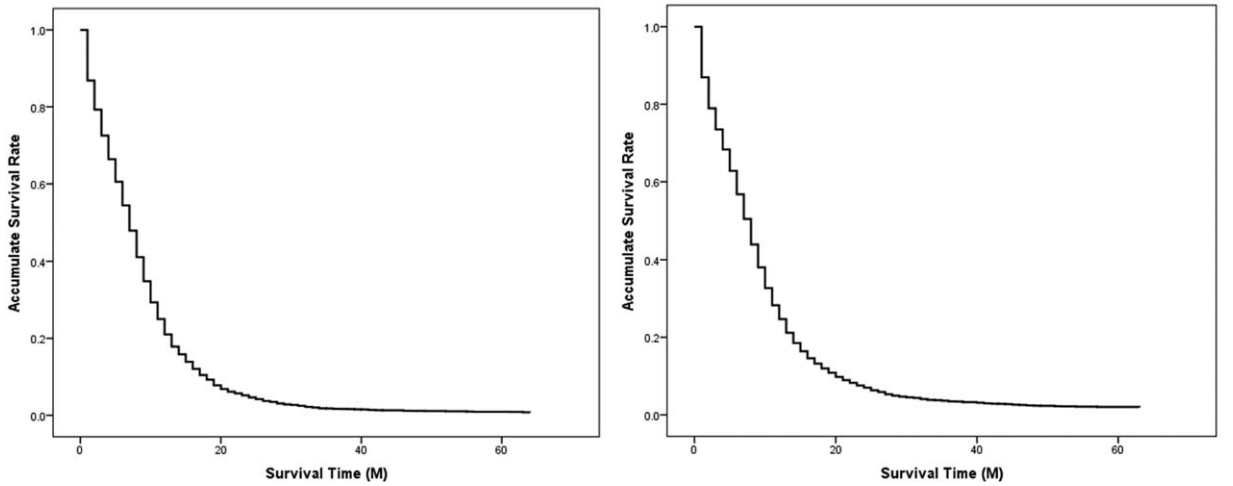

Figure 2. Overall survival in derivation cohort (A) and validation cohort (B).

and Mod2 was established without race. The prediction ability of Mod2 was equivalent compared with that of Mod1 (NRI 0.006, 95% confidence interval [CI] −0.139 to 0.090, $P = .786$), and the prediction ability was improved by 0.1% (IDI −0.001, 95% CI −0.008 to 0.002, $P = .856$), but there was no statistical difference.

3.5. Establish the nomogram

Taking Mod2 as the final model, 6 prognostic factors including age, sex, T, N, metastatic site and chemotherapy were selected to establish the nomogram. According to the levels of each prognostic factor, the individualized survival probability of patients with different metastatic sites was inquired at 6 months, 1 year, and 2 years (Fig. 4).

3.6. Validation of the nomogram

Nomogram was validated in terms of its discrimination and calibration. The C-index in the derivation cohort and validation cohort is 0.6569777 and 0.8386301, respectively. And the calibration curve in Figure 5 shows that the nomogram can effectively predict the prognosis.

4. Discussion

The ES-SCLC patients with multiple organ metastatic were treated with chemotherapy, radiotherapy, or supportive care because of its late onset and short survival expectations. Treatment choices were often made based on expected survival time and response to the treatment. However, there are a lot of prognostic factors, including demographics, tumor-related, and therapy-related characteristics. Analysis based on 14 trials showed that sex, age, PS (performance status), creatinine levels, and a number of metastatic sites were important prognostic factors of ES-SCLC.[5] Furthermore, there was a significant interaction between sex and PS within ES-SCLC, suggesting that PS was highly prognostic in males, with no significant impact on females. Our previous study[6–8] tried to find several strong prognostic factors to establish a prognostic scoring system to predict survival. Sculier et al[9] established a Recursive Partitioning Analysis (RPA) grading system by screening out 4 prognostic factors including TNM staging, PS, age, and gender through the analysis of cases from the international staging database of the International Association for the Study of Lung Cancer. In this study, our result showed that race, sex,

Table 2

Survival statistics of different metastatic sites in ES-SCLC.

Distance metastatic		6-mo survival rate	1-yr survival rate	2-yr survival rate	Median survival time
Derivation cohort	Total	55.07	24.61	7.56	7
	Others	66.02	37.16	15.05	10
	Bone	61.25	28.23	6.01	8
	Brain	52.89	28.13	9.80	7
	Liver	52.41	20.45	4.88	7
	Lung	62.34	32.90	14.76	9
	Multiorgan	47.78	15.43	2.83	6
Validation cohort	Total	56.57	24.44	6.85	8
	Others	64.23	35.20	13.83	9
	Bone	61.98	29.11	7.77	9
	Brain	53.42	27.46	8.82	7
	Liver	53.01	21.90	4.11	7
	Lung	63.48	36.30	13.96	9
	Multiorgan	52.41	15.08	2.16	7

ES-SCLC = extensive-stage small cell lung cancer.

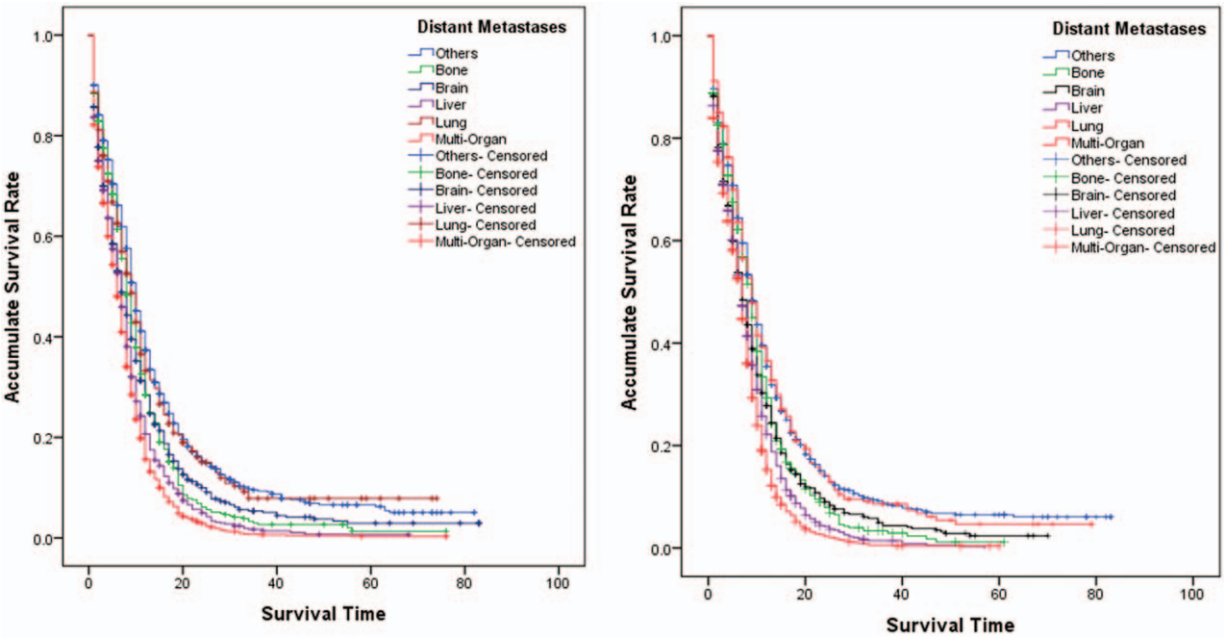

Figure 3. Kaplan–Meier analysis of survival by different distant metastatic sites in derivation cohort (A) and validation cohort (B).

age, metastatic site, T stage, N stage, and initial chemotherapy were independent prognostic factors, which were consistent with the previous findings.[5,9–13] In addition, male patients over 75 years old, with T3N2 stage and above, multiple organ metastases, and without chemotherapy were adverse prognostic factors.

Although there was metastasis at the time of diagnosis, the survival period of patients was different due to different metastatic

Table 3

COX regression model multivariate analysis for the 2 models in derivation cohort.

	Mod1			Mod2		
Prognostic factors	β	**Exp(β) (95% CI)**	***P***	β	**Exp(β) (95% CI)**	***P***
Race			.006	NA	NA	NA
Black	−0.118	0.801–0.986	.025			
Others	−0.199	0.699–0.961	.014			
Sex	−0.126	0.830–0.936	<.001	−0.122	0.834–0.940	<.001
Age			<.001			<.001
≥45,<55	0.063	0.792–1.433	.677	0.048	0.780–1.411	.753
≥55, <65	0.050	0.787–1.403	.736	0.041	0.781–1.391	.780
≥65, <75	0.175	0.893–1.589	.235	0.162	0.882–1.569	.270
≥75	0.415	1.131–2.028	.005	0.400	1.114–1.997	.007
T			.005			.007
T1a	−0.088	0.661–1.269	.598	−0.079	0.667–1.280	.634
T1b	0.073	0.781–1.484	.654	0.076	0.783–1.487	.643
T2a	−0.033	0.716–1.308	.832	−0.035	0.714–1.305	.820
T2b	0.086	0.800–1.485	.586	0.080	0.795–1.475	.614
T3	0.136	0.852–1.541	.368	0.135	0.851–1.540	.371
T4	0.121	0.841–1.513	.421	0.114	0.836–1.503	.446
N			<.001			<.001
N1	−0.030	0.843–1.118	.680	−0.023	0.848–1.125	.746
N2	0.198	1.108–1.340	<.001	0.203	1.114–1.347	<.001
N3	0.200	1.101–1.357	<.001	0.201	1.101–1.358	<.001
DM			<.001			<.001
Bone	0.298	1.202–1.510	<.001	0.299	1.203–1.512	<.001
Liver	0.311	1.224–1.522	<.001	0.305	1.217–1.512	<.001
Lung	0.459	1.426–1.756	<.001	0.461	1.429–1.760	<.001
Brain	0.039	0.907–1.192	.574	0.041	0.909–1.195	.553
Multiorgan	0.617	1.700–2.021	<.001	0.617	1.700–2.022	<.001
Chemo	−1.098	0.309–0.360	<.001	−1.092	0.311–0.362	<.001

DM = distant metastatic site.

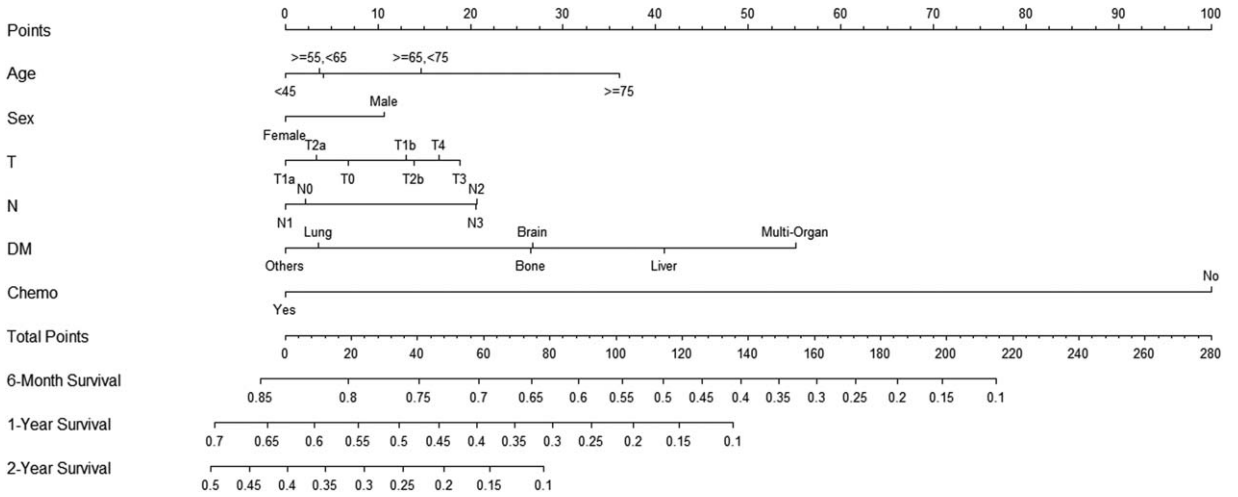

Figure 4. Nomogram for the different metastatic site in extensive-stage small-cell lung cancer patients.

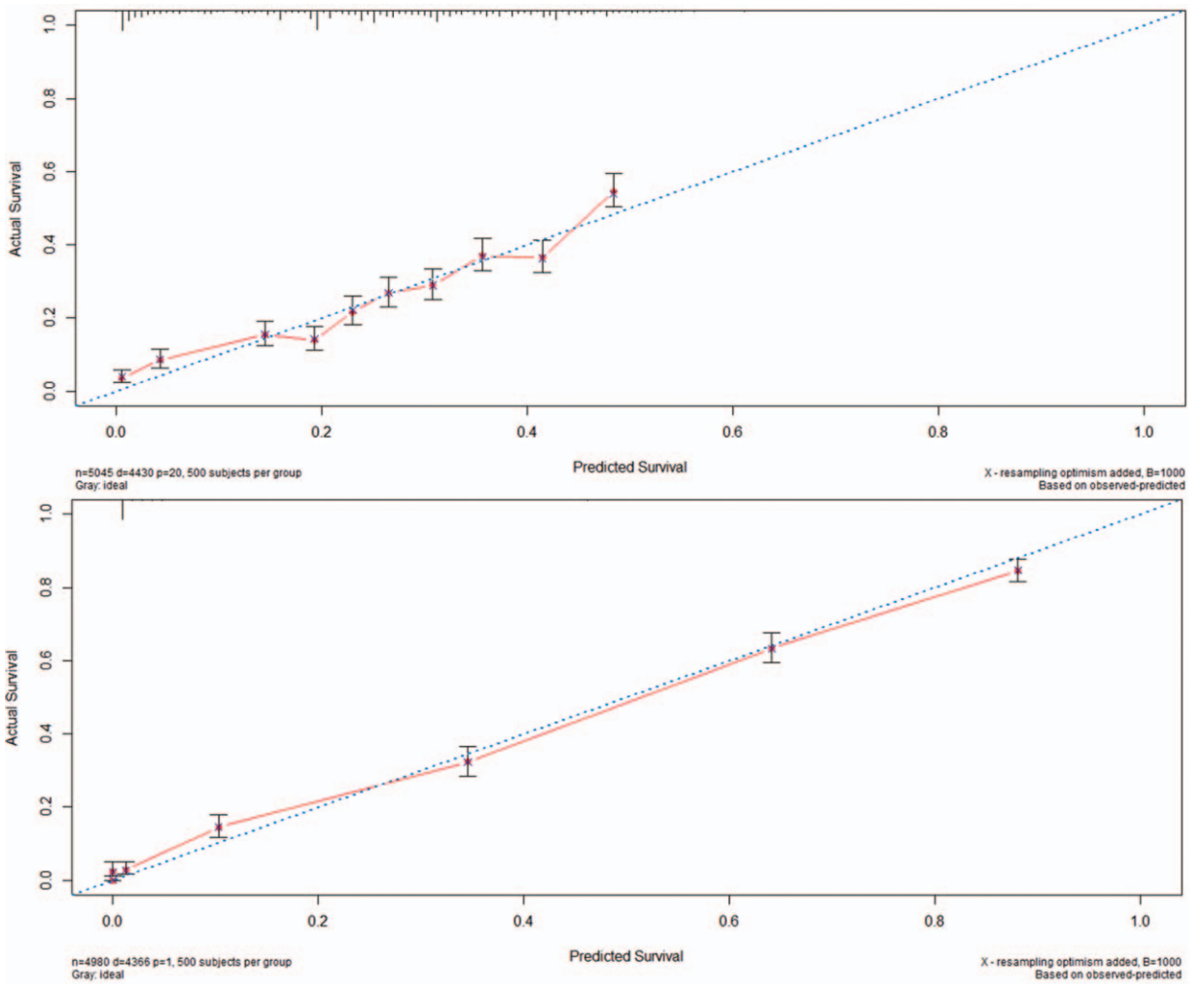

Figure 5. Calibration plot for nomogram of (A) derivation cohort mod2 and (B) validation cohort.

sites and the number of metastatic sites.[4] Therefore, it is very important to predict the survival time of patients according to the different metastatic sites and the number of metastatic sites. However, there was still a lack of studies on the correlation between different metastatic sites and prognosis. Foster et al[5] found that the number of metastatic tumors was an important prognostic factor, but he ignored the impact of metastatic sites on survival. At present, studies had indicated that the most common metastatic sites of ES-SCLC were liver, brain, bone, lung, and adrenal gland.[14] In this study, 42.8% of the patients were initially diagnosed with liver metastasis, followed by bone metastasis, brain metastasis, and lung metastasis. Survival analysis showed that patients with liver metastasis and multiple organ metastases had the shortest survival period, which was consistent with the report of Cai et al.[4] The decrease of survival expectation caused by liver metastasis may be related to the decrease of liver function caused by liver metastatic tumors, and the occurrence of severe symptoms such as jaundice and ascites, which lead to the decrease of patients' quality of life.

The significance of the clinical prognostic model was that patients could be grouped according to their survival expectations before treatment, so as to determine whether a specific treatment scheme was worthy of implementation. Chemotherapy, as the most important treatment for ES-SCLC, had been proved to prolong survival time by many types of research.[13,15,16] In this study, 80.7% of the patients were initially treated with chemotherapy, so chemotherapy was included as the baseline covariate of the model. Race, as a covariable, showed independent prognostic significance in multivariate analysis, but 86.3% of the patients in this study were white, and there was a selection bias between the derivation cohort and the validation cohort. Therefore, 2 models were established in this study, the former included race and the latter excluded. Comparing the prediction ability of the 2 models, it was found that they were equivalent (NRI 0.006, 95% CI −0.139 to 0.090, $P = .786$), and the overall predictive ability of the model was reduced by 0.1% (IDI −0.001, 95% CI −0.008 to 0.002, $P = .856$) after race were excluded, but there was no statistical difference. Considering selection bias, a nomogram was established without race.

The greatest significance of our research was that through nomogram individualized predict survival for patients with newly diagnosed ES-SCLC with different metastatic sites. To help doctors select patients with long expected survival time for active treatment, to benefit from survival. For patients with short expected survival time, overtreatment should be avoided and supportive treatment should be used instead. The shortcoming of our study as follows: First, the relevant treatment information was insufficient. For example, studies have proved that thoracic radiotherapy could also improve the survival time of patients with ES-SCLC.[15,17,18] Second, there was a lack of patient physical status score and laboratory examination information, which has been proven to be predictive of survival.

5. Conclusion

The survival time of ES-SCLC patients with different metastatic sites was significantly different. The nomogram model can effectively predict the survival of individuals and provide a basis for clinical decision-making.

Author contributions

Conceptualization, SH and HG; Data curation, HG, TQ, and YD; Formal analysis, SH, XH, TQ, and YD; Funding acquisition, XZ and HG; Methodology, HG and SH; Resources, HG; Supervision, XZ and SH; Writing—original draft, SH and HG; Writing—review & editing, SH and HG. All authors read and approved the final manuscript.

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Supervision: Xiaozhi Zhang.
Validation: Tao Qi.
Writing – original draft: Hongxiang Gao.

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