Original Article

Brain metastases in newly diagnosed lung cancer: epidemiology and conditional survival

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Background: The brain serves as the primary site for metastasis in patients with both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The presence of lung cancer with brain metastasis (LCBM) is a debilitating condition associated with considerable morbidity and mortality. The objective of this study was to assess the incidence and survival rates of LCBM in the United States population.

Methods: We analyzed a total of 9,212 patients diagnosed with LCBM between 2010 and 2015, extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Our analysis assessed the incidence, relative survival, and conditional survival (CS) of LCBM. We utilized the Kaplan-Meier method to estimate overall survival and determine CS at year y+x after x years of survival, following the formula $CS(y|x) = CS(y+x)/CS(x)$. Prognostic factor selection was performed using the least absolute shrinkage and selection operator (LASSO) regression approach, and multivariate Cox regression was employed to demonstrate the impact of these predictors on outcomes and construct a CS-based nomogram.

Results: The overall age-adjusted incidence rate of LCBM was 5.82 cases per 100,000, with a slight decline observed during our study period. Patient relative survival showed a continuous decline with increasing age. CS analysis revealed that the 5-year CS rate for patients initially diagnosed with LCBM adjusted from 3% to 13%, 28%, 52%, and 73% over successive years of survival (1–4 years). Identified predictors included age at diagnosis, sex, race, tumor size, tumor grade, surgery, radiotherapy, and chemotherapy. These predictors, along with the CS formula, were employed to develop a CS-based nomogram for real-time prognosis prediction. Calibration curve, area under the time-dependent receiver operating characteristic (ROC) curve, concordance index (c-index), and decision curve analysis (DCA) demonstrated the model's strong predictive capabilities.

Conclusions: This study deepened our understanding of LCBM patients, summarizing their epidemiological characteristics and CS patterns. We successfully developed a novel CS-based nomogram model for dynamic survival estimation, offering real-time and personalized prognostic information that is clinically valuable.

Keywords: Lung cancer with brain metastasis (LCBM); Surveillance, Epidemiology, and End Results (SEER); incidence; survival; nomogram

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Introduction

Lung and bronchus primary cancer stands as the foremost cause of cancer-related mortality, boasting a disheartening 5-year survival rate of only 19%. Its prevalence has escalated to an important health dilemma, bearing profound medical and socioeconomic ramifications in both developing and developed nations (1-3). One significant factor contributing to the poor prognosis of these patients is the diagnosis of lung cancer at an advanced stage, where therapeutic efficacy is currently limited. Despite notable advancements in treatment modalities such as targeted molecular therapies and immunotherapies, survival outcomes for patients with tumor distant metastases remain frustratingly low (3,4). Brain metastasis is predominant among both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients (5), constituting a debilitating condition associated with significant morbidity and mortality (1,6,7). Some studies have reported that 16% to 22% of lung cancer patients eventually develop brain metastases (3,8). However, despite efforts by some research groups with smaller sample sizes to determine the prognosis of lung cancer with brain metastasis (LCBM), there remains a lack of large-scale studies examining the incidence and survival rates of patients with LCBM.

Conditional survival (CS) serves as a valuable metric predicting the likelihood of a patient surviving for an additional year after having survived for x years since their cancer diagnosis (9-11). The advantageous nature of CS lies in its ability to provide dynamic, real-time prognostic estimates. However, it often overlooks the clinicopathological features of cancer patients. Certain clinical factors, such as age, tumor histology, tumor grade, and treatment information, have been identified as influential in the survival of patients with LCBM (7,12,13). However, the combined effect of these factors in predicting CS for these patients is yet to be thoroughly investigated.

Therefore, this study utilized the Surveillance, Epidemiology, and End Results (SEER) database to perform a thorough analysis of the epidemiological characteristics and CS of patients with LCBM. Additionally, we merged the conventional nomogram model, which can integrate prognostic factors to predict survival, with CS analysis to develop a novel CS-based nomogram model. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-776/rc).

Highlight box

Key findings

- This study deepened our understanding of lung cancer with brain metastasis (LCBM), summarizing their epidemiological characteristics and conditional survival (CS) patterns. We successfully developed a novel CS-based nomogram model for dynamic survival estimation.

What is known and what is new?

- Certain clinical factors, such as age, tumor histology, tumor grade, and treatment information, have been identified as influential in the survival of patients with LCBM. However, the combined effect of these factors in predicting CS for these patients is yet to be thoroughly investigated.
- This study significantly contributes to our understanding of LCBM patients. Our findings provide a comprehensive overview of their epidemiological characteristics and CS patterns. And a novel CS-based nomogram model was successfully established.

What is the implication, and what should change now?

- This model holds the potential to enhance clinical decision-making and optimize disease management strategies for LCBM patients. The inclusion of additional prognostic factors such as biological markers would enhance the predictive capacity of our model, and external validation is warranted.

Methods

Data source

In our study, we analyzed cases extracted from the SEER database. The SEER program gathers incidence and survival data from population-based state cancer registries, covering approximately 35% of the population in the U.S. (14). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since SEER data are publicly accessible, no Institutional Review Board approval is required.

Study population

We conducted a retrospective analysis on lung cancer patients diagnosed with brain metastasis from 2010 to 2015. Cases diagnosed by autopsy or death certificate were excluded, along with patients with unknown detailed information.

Variable declaration

Demographic variables, including age at diagnosis, gender

(male or female), race (White, Black, or other), insurance status (insured or uninsured), and marital status (single or married), were obtained from the SEER database. The optimal cutoff values for age were identified as ≤61, 62–77, or ≥78 years using the X-tile program (see Figure S1). Tumor characteristics, such as primary tumor sites, the total number of (*in situ*/malignant) tumor sites, tumor size, and histological types, were also collected. Tumor size was categorized as <3, ≥3 and <5, ≥5 and <7, and ≥7 cm. Histological types were grouped as adenocarcinoma, squamous cell carcinoma (SCC), SCLC, NSCLC, and others. Additionally, treatment information including surgery, radiotherapy, and chemotherapy was also extracted.

Statistical analysis

Incidence, trends, and relative survival

Using the SEER*Stat statistical software, we initially investigated the incidence, trends, and relative survival among LCBM patients diagnosed from 2010 to 2015. Relative survival rate is a specialized measure that adjusts for all causes of death except cancer. Using the Ederer II method, relative survival was determined by comparing observed survival with expected survival derived from the general U.S. population, matched for age, sex, and race (15).

CS analysis

CS plays a crucial role in assessing the long-term survival of patients diagnosed with cancer. The CS formula, $CS(y|x) = CS(y+x)/CS(x)$, calculates the probability of a patient's survival for y additional years, given they have already survived x years following their LCBM diagnosis. CS(x) and CS(y+x) were estimated using the Kaplan-Meier method for x- and (x+y)-year survival.

CS-based nomogram development and validation

We randomly divided eligible patients into training and validation groups at a 7:3 ratio. The least absolute shrinkage and selection operator (LASSO) regression analysis with 10-fold cross-validation was then conducted in the training cohort to identify prognostic predictors, avoiding overfitting. These factors were further analyzed via multivariate Cox regression to confirm their significance as prognostic indicators. Utilizing these factors, we developed a predictive nomogram model incorporating the CS formula for personalized and dynamic survival prediction.

Finally, the model underwent evaluation and validation in both the training and validation groups. The model's accuracy was assessed through calibration plots generated from 1,000 bootstrap samples, and discrimination was evaluated using the area under the time-dependent receiver operating characteristic (ROC) curve (AUC) and concordance index (c-index). Additionally, decision curve analysis (DCA) was employed to assess the clinical utility of the nomogram, measuring the net benefit of nomogram-guided medical interventions.

All statistical tests were two-sided, with $P<0.05$ considered statistically significant. All statistical analyses were performed using R software (version 4.1.0).

Results

Baseline characteristics

According to the defined inclusion and exclusion criteria, a total of 9,212 patients diagnosed with LCBM were included in our study, with 6,448 in the training group and 2,764 in the validation group. Patient demographics and tumor characteristics are detailed in *Table 1*. In the entire cohort, 3,343 patients (36.3%) were under 61 years old, 4,655 (50.5%) were aged between 62 and 77 years, and 1,214 (13.2%) were over 78 years old. The majority of patients were male (53.6%), and most were of White ethnicity (79.4%). Adenocarcinoma (53.2%) was the most common histological type of tumors, followed by SCC (13.6%), NSCLC (10.0%), and SCLC (9.1%). Tumors were predominantly located in the upper lobe (57.2%). Surgery was performed on only 582 LCBM patients (6.3%), while the majority underwent radiotherapy (78.6%). Additionally, 5,259 cases (57.1%) opted for chemotherapy.

Incidence of LCBM

The age-adjusted incidence rate of LCBM was 5.82 per 100,000 during the study period, as depicted in *Figure 1A*. Subsequently, we analyzed the annual incidence of patients across various age groups. Our findings revealed a significant increase in incidence with age, peaking among individuals aged 70 to 79 years, followed by a decline (*Figure 1B*).

Survival analysis of lung cancer patients with or without brain metastasis

Next, we compared the relative survival of lung cancer patients with and without brain metastasis. As depicted in *Figure 1C*, LCBM patients exhibited a dismal prognosis.

Table 1 Characteristics of patients with LCBM

Parameters	Total cohort (N=9,212), n (%)	Training cohort (N=6,448), n (%)	Validation cohort (N=2,764), n (%)
Age at diagnosis			
≤61 years	3,343 (36.3)	2,307 (35.8)	1,036 (37.5)
62–77 years	4,655 (50.5)	3,282 (50.9)	1,373 (49.7)
≥78 years	1,214 (13.2)	859 (13.3)	355 (12.8)
Race			
White	7,318 (79.4)	5,105 (79.2)	2,213 (80.1)
Black	1,119 (12.1)	782 (12.1)	337 (12.2)
Others	775 (8.4)	561 (8.7)	214 (7.7)
Sex			
Male	4,939 (53.6)	3,419 (53.0)	1,520 (55.0)
Female	4,273 (46.4)	3,029 (47.0)	1,244 (45.0)
Tumor site			
Main bronchus	376 (4.1)	265 (4.1)	111 (4.0)
Upper lobe	5,268 (57.2)	3,688 (57.2)	1,580 (57.2)
Middle lobe	396 (4.3)	296 (4.6)	100 (3.6)
Lower lobe	2,483 (27.0)	1,714 (26.6)	769 (27.8)
Others	689 (7.5)	485 (7.5)	204 (7.4)
Coexistence with other malignancy			
No	7,518 (81.6)	5,263 (81.6)	2,255 (81.6)
Yes	1,694 (18.4)	1,185 (18.4)	509 (18.4)
Histology			
Adenocarcinoma	4,903 (53.2)	3,464 (53.7)	1,439 (52.1)
SCC	1,249 (13.6)	836 (13.0)	413 (14.9)
SCLC	842 (9.1)	585 (9.1)	257 (9.3)
NSCLC	921 (10.0)	647 (10.0)	274 (9.9)
Others	1297 (14.1)	916 (14.2)	381 (13.8)
Grade			
Grade I	322 (3.5)	224 (3.5)	98 (3.5)
Grade II	2,033 (22.1)	1,426 (22.1)	607 (22.0)
Grade III	6,042 (65.6)	4,242 (65.8)	1,800 (65.1)
Grade IV	815 (8.8)	556 (8.6)	259 (9.4)
Tumor size			
<3 cm	1,877 (20.4)	1,311 (20.3)	566 (20.5)
≥3 and <5 cm	2,908 (31.6)	2,058 (31.9)	850 (30.8)
≥5 and <7 cm	2,170 (23.6)	1,517 (23.5)	653 (23.6)
≥7 cm	2,257 (24.5)	1,562 (24.2)	695 (25.1)

Table 1 (*continued*)

Table 1 (*continued*)

Parameters	Total cohort (N=9,212), n (%)	Training cohort (N=6,448), n (%)	Validation cohort (N=2,764), n (%)
Surgery			
No	8,630 (93.7)	6,025 (93.4)	2,605 (94.2)
Yes	582 (6.3)	423 (6.6)	159 (5.8)
Radiotherapy			
No	1,971 (21.4)	1,389 (21.5)	582 (21.1)
Yes	7,241 (78.6)	5,059 (78.5)	2,182 (78.9)
Chemotherapy			
No	3,953 (42.9)	2,771 (43.0)	1,182 (42.8)
Yes	5,259 (57.1)	3,677 (57.0)	1,582 (57.2)
Insurance status			
No	382 (4.1)	247 (3.8)	135 (4.9)
Yes	8,830 (95.9)	6,201 (96.2)	2,629 (95.1)
Marital status			
Single	4,144 (45.0)	2,934 (45.5)	1,210 (43.8)
Married	5,068 (55.0)	3,514 (54.5)	1,554 (56.2)

LCBM, lung cancer with brain metastasis; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

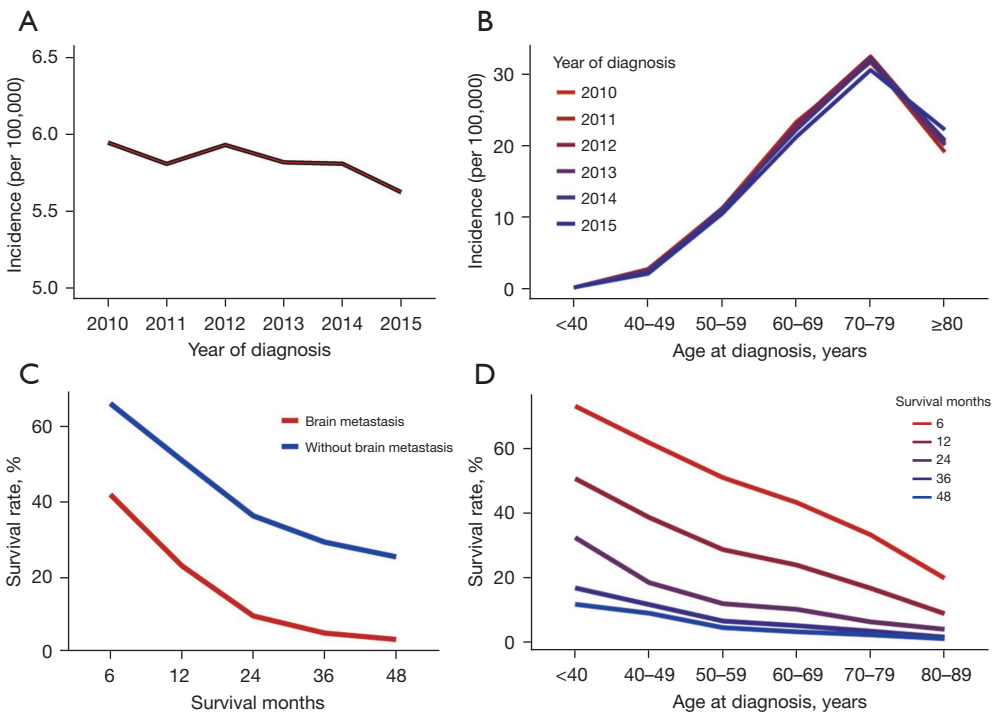

Figure 1 Epidemiology and survival of lung cancer with brain metastasis. (A) Incidence of lung cancer with brain metastasis; (B) incidence of lung cancer with brain metastasis stratified by age groups; (C) relative survival of lung cancer with or without brain metastasis; (D) relative survival of lung cancer with brain metastasis stratified by age groups.

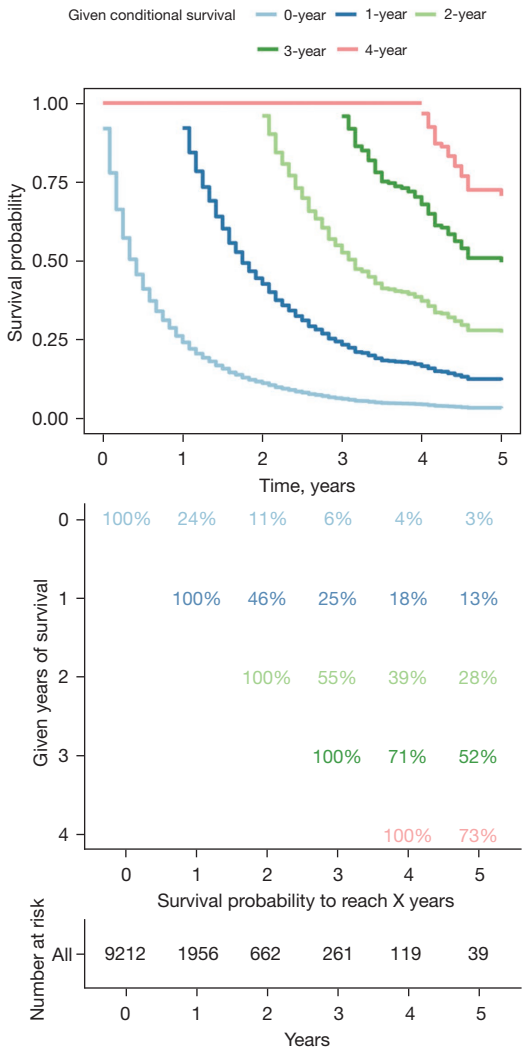

Figure 2 Kaplan-Meier method for estimating conditional survival at 5 years after surviving 0–4 years in LCBM patients. Conditional survival curves and their updated survival data adjusted for survived time. LCBM, lung cancer with brain metastasis.

Furthermore, we conducted additional analysis to assess the impact of age on patient outcomes. As anticipated, the relative survival rate of patients continued to decline with increasing age (*Figure 1D*).

CS of LCBM patients

The overall survival rates for LCBM patients were observed to be 24%, 6%, and 3% for 1, 3, and 5 years, respectively (*Figure 2*). Furthermore, the CS curve illustrated an increasing survival rate for LCBM patients over time, as shown in *Figure 2*. Notably, the 5-year survival rate for patients initially diagnosed with LCBM was adjusted from 3% to 13%, 28%, 52%, and 73% over successive years of survival (1–4 years).

CS-based nomogram development

Based on the training cohort, the LASSO regression method identified eight key prognostic predictors incorporated into the final survival prediction model, including: age at diagnosis, sex, race, tumor size, tumor grade, surgery, radiotherapy, and chemotherapy (*Figure 3*). To ensure accuracy, these variables underwent multivariate Cox analysis to confirm their prognostic value (*Figure 4*). Additionally, multivariate Cox regression analysis was employed to construct a nomogram, assigning varying regression coefficients to selected prognostic factors based on their respective impact on the outcome (*Figure 5*). Unlike traditional predictive models, the CS-based nomogram utilized in this study considered CS, allowing patients to gain insight not only into their 1-, 3-, and 5-year overall survival rates based on their personalized clinicopathologic characteristics but also their 5-year CS rates based on the duration of time since diagnosis.

CS-based nomogram evaluation and validation

Various validation methods were employed to assess the model's performance. Calibration plots for both the training and validation cohorts indicated a strong correlation between the model and actual outcomes (*Figure 6A*,*6B*). These plots closely aligned with the 45-degree line, indicating the model's accuracy in reflecting reality. The c-index of the dynamic CS-nomogram was 0.739 and 0.723 in the training and validation cohorts, respectively. Time-dependent ROCs at 1, 3, and 5 years demonstrated satisfactory discriminatory ability, with AUCs of 0.78, 0.79, and 0.80 in the training group (*Figure 6C*) and 0.77, 0.75, and 0.83 in the validation group (*Figure 6D*). Additionally, DCA curves consistently showed a favorable net benefit whenever medical interventions were initiated based on the CS-nomogram in both the training and validation groups (*Figure 7A*,*7B*).

Discussion

Brain metastasis is an extremely serious sequela remaining the single largest cause of mortality in patients with

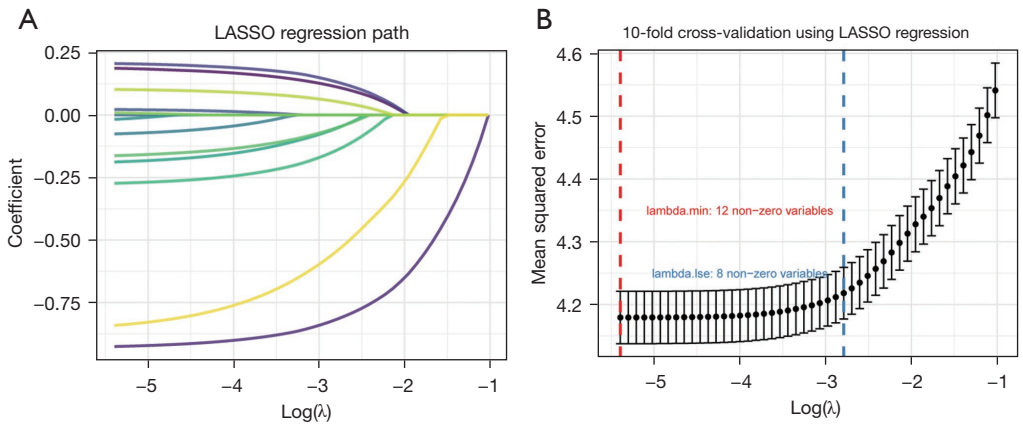

Figure 3 Predictor screening. The LASSO regression model (A) and 10-fold cross-validation technique for predictor selection (B). LASSO, least absolute shrinkage and selection operator.

Variable	HR	Lower 95% CI	Upper 95% CI	P
Age 62–77 years	1.300	1.223	1.383	<0.001
Age ≥78 years	1.460	1.335	1.597	<0.001
Race Black	0.866	0.796	0.941	<0.001
Race others	0.669	0.604	0.740	<0.001
Sex female	0.817	0.774	0.863	<0.001
Tumor site upper lobe	0.772	0.676	0.882	<0.001
Tumor site middle lobe	0.770	0.644	0.922	<0.001
Tumor site lower lobe	0.821	0.715	0.943	0.005
Tumor site others	0.865	0.737	1.015	0.08
Tumor histology SCC	1.200	1.105	1.304	<0.001
Tumor histology SCLC	1.141	1.014	1.284	0.03
Tumor histology NSCLC	1.207	1.102	1.322	<0.001
Tumor histology others	1.092	1.004	1.187	0.04
Tumor grade II	1.138	0.967	1.339	0.12
Tumor grade III	1.616	1.383	1.888	<0.001
Tumor grade IV	1.534	1.269	1.855	<0.001
Tumor size ≥3 and <5 cm	1.107	1.024	1.196	0.01
Tumor size ≥5 and <7 cm	1.237	1.139	1.344	<0.001
Tumor size ≥7 cm	1.358	1.250	1.476	<0.001
Coexistence yes	0.966	0.901	1.037	0.34
Surgery yes	0.411	0.362	0.466	<0.001
RT yes	0.723	0.677	0.772	<0.001
CT yes	0.367	0.347	0.389	<0.001
Marital status yes	0.913	0.863	0.965	0.001
Insurance yes	1.014	0.881	1.167	0.85

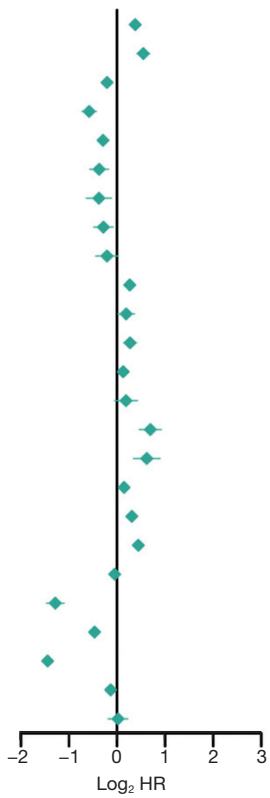

Figure 4 Multivariate Cox regression forest plot confirmed the prognostic value of selected variables. HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; RT, radiotherapy; CT, chemotherapy.

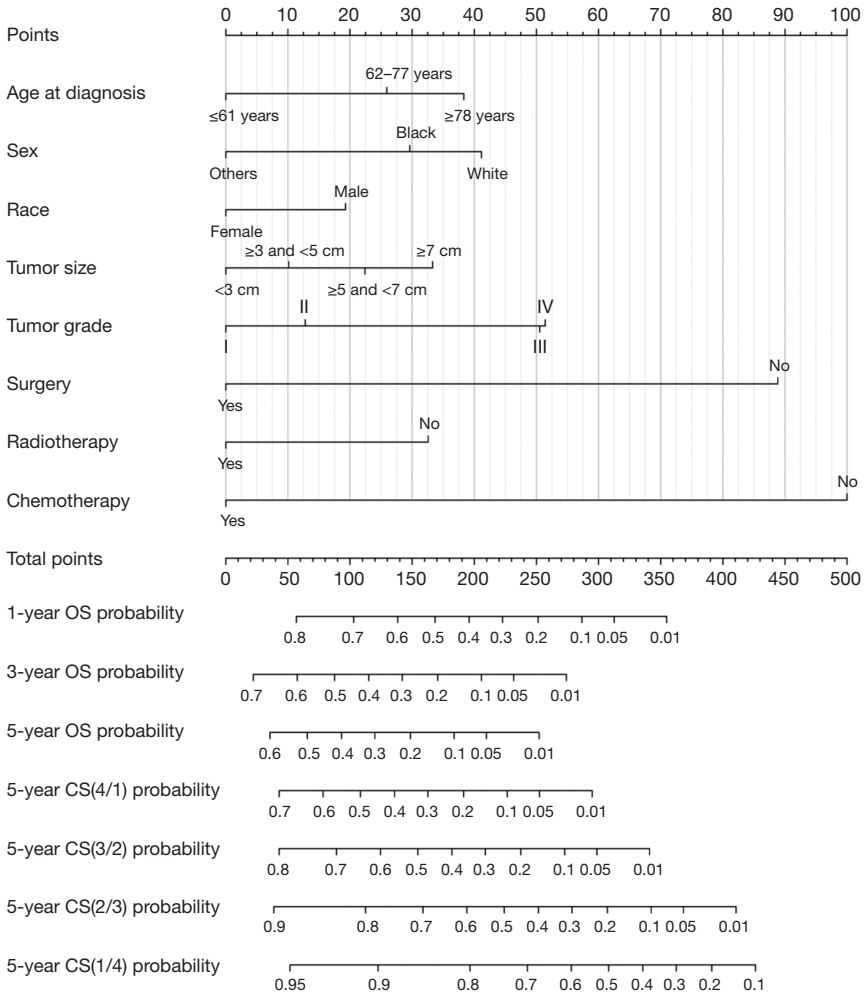

Figure 5 Conditional survival nomogram (CS-based nomogram) for predicting 1-, 3- and 5-year OS and 5-year CS for LCBMs. OS, overall survival; CS, conditional survival; LCBM, lung cancer with brain metastasis.

lung cancer (16). And mounting evidence suggests that improved detection techniques and clinical awareness, as well as changes in the treatment have led to the increased incidence of the LCBM (17). Several recent studies have attempted to deepen understanding of LCBM, but data on its epidemiology and prognosis remain unclear. A better understanding of LCBM can optimize clinical decision-making for healthcare providers during the clinical evaluation stage. Therefore, we conducted a comprehensive analysis of the epidemiological characteristics and CS of LCBM using data extracted from the SEER database.

Epidemiologically, the overall age-adjusted incidence rate of the LCBM was 5.82 cases per 100,000 and trend was slightly declined during the period of our study. We also compared the incidence in different age groups and found that tumor peak incidence occurred in patients aged 70 to 79 years. Villano *et al.* analyzed cases diagnosed from 2010 to 2011 using the Kentucky Cancer Registry (KCR) and Alberta Cancer Registry (ACR), and reported that the median incidence of stage I/II and III LCBM was 25.6% and 19.3% respectively (18). In addition, the relative survival rates of patients with brain metastasis were much worse than those without brain metastasis. And we further illustrated the effect of age on the relative survival of LCBM patients. These results have potential extensive value of application and may influence screening paradigms, treatment strategies, and clinical trial design for specific subsets of patients with lung cancer.

CS is a method of survival assessment that estimates changes in real-time based on the time survived. We then

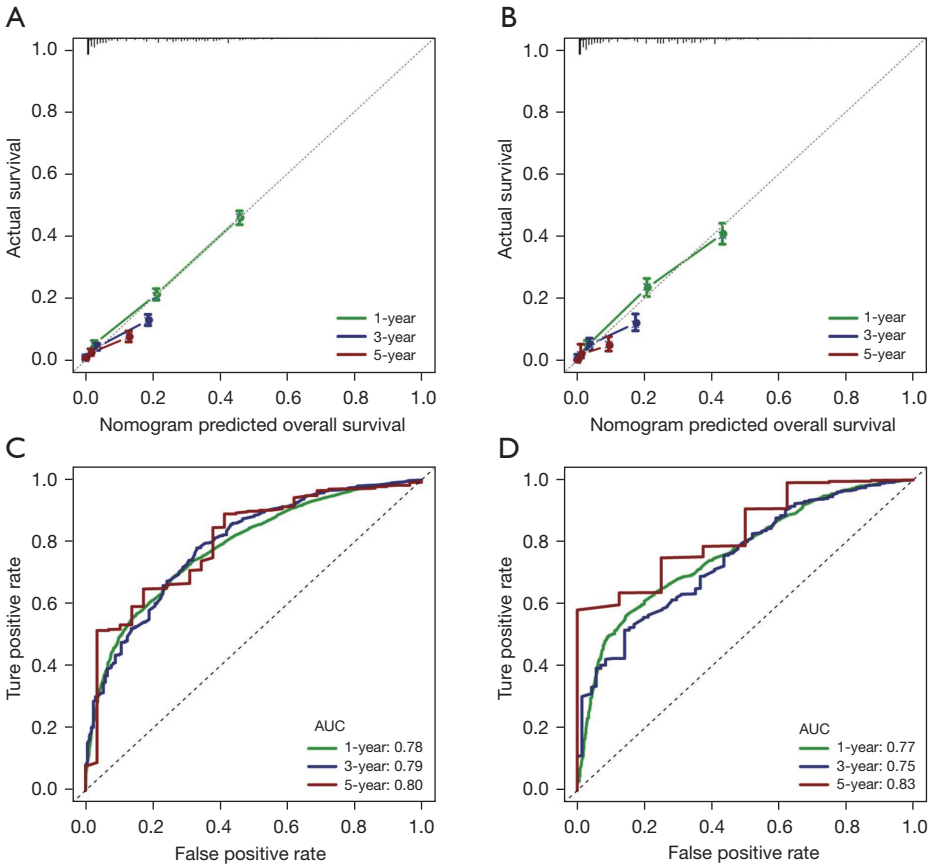

Figure 6 Conditional survival nomogram model evaluation and validation. Calibration plots of the CS-based nomogram for predicting the probability of survival at 1, 3, and 5 years in both training (A) and validation (B) cohorts. Time-dependent ROC curves for assessing the discrimination of the model in both training (C) and validation (D) cohorts. AUC, area under the curve; CS, conditional survival; ROC, receiver operating characteristic.

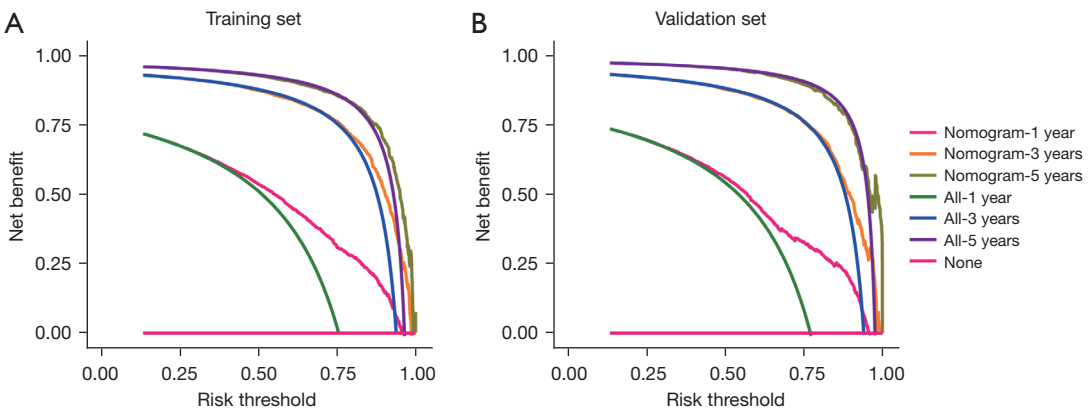

Figure 7 Decision curve analysis of the CS-based nomogram in both training (A) and validation (B) cohorts. The x-axis represents the percentage of threshold probability, whereas the y-axis represents the net benefit, calculated by adding the true positives and subtracting the false positives. CS, conditional survival.

described the CS pattern of LCBM patients and found that despite the advanced stage of LCBM, long-term survival improved significantly for each additional year patients lived. The analysis of the CS revealed a significant increase in the 2nd year post-diagnosis [CS(1|1) =46%], with a gradual improvement continuing in the following years. Therefore, the findings of the CS analysis indicating a significant enhancement in the possibility of survival could alleviate the anxiety of cancer patients, increase their confidence in overcoming the disease, and improve their overall quality of life. Moreover, understanding this dynamic survival pattern may help establish cost-effective methods for LCBM surveillance, including determining the appropriate duration and intensity of follow-up.

The prognostication of patients in real-time is not only time-dependent, but also subject to variations based on individual clinicopathological characteristics (19,20). To address this, a dynamic CS-nomogram was also developed in our study. We employed the LASSO regression to avoid overfitting or underfitting the mode and finally identify eight prognostic factors for our CS-based nomogram model establishment. Finally, we constructed and internally validated a CS prediction model for these patients. This is the first study, to the best of our knowledge, to develop a CS-based nomogram integrating easily-obtained variables together in determining risk of death for LCBM patients. Our prognostic model demonstrated exceptional predictive ability and could be practically implemented in clinical settings to accurately forecast the dynamic and real-time life expectancy of patients with LCBM. Additionally, mutational profiling indicated that an elevated frequency of genetic mutation facilitated the development of diverse patterns of brain metastasis (21,22). Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) positive have been found to be associated with more frequent brain metastases in patients with lung cancer (23-25). Efforts are actively underway to investigate the impact of various cancer-related factors, including distinct categories of genes that drive metastasis, on the progression of tumors (16,26-28). While our analysis was limited by the lack of genomic data available through the SEER database, we were able to achieve effective dynamic predictions by incorporating basic clinicopathological features.

There are several limitations that should be considered in the present study. The first may be the retrospective nature of the SEER database-based study and selection bias may be virtually brought in. Second, detailed information on treatment variables such as surgical procedures, immunotherapy, chemotherapy regimens, and radiation dose/technology which related to patient outcomes are not collected by SEER database. Third, we only analyzed patients based on the initial diagnosis of LCBM, data on tumor recurrence was unavailable in SEER database. Lastly, the inclusion of additional prognostic factors such as biological markers would enhance the predictive capacity of our model, and external validation is warranted.

Conclusions

Despite its limitations, this study significantly contributes to our understanding of LCBM patients. Our findings provide a comprehensive overview of their epidemiological characteristics and CS patterns. Through LASSO analysis, we identified eight prognostic factors, facilitating the development of a novel CS-based nomogram model for dynamic survival estimation. This model holds the potential to enhance clinical decision-making and optimize disease management strategies for LCBM patients.

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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-24-776/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-776/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-776/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). Since the study relied on the SEER database, which was freely available to the public (http://

seer.cancer.gov/seerstat/), the requirement for ethical approval was waived.

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