



Development and validation of a nomogram for predicting the overall survival in non-small cell lung cancer patients with liver metastasis

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Background: Among all metastatic lesions in non-small cell lung cancer (NSCLC), liver metastasis (LM) is the most lethal site with a median survival of less than 5 months. Few studies exclusively report on prognostic factors for these unique patients. We aimed to construct and validate a practical model to predict the prognosis of NSCLC patients with LM.

Methods: Cases of NSCLC with LM diagnosed between 2010 and 2015 were collected from the Surveillance, Epidemiology, and End Results (SEER) database, and were randomly split into training and validation cohort (7:3). The overall survival (OS) was measured from diagnosis until date of death or last follow-up. Cox regression analyses were performed to identify potential predictors of the model. A nomogram incorporating those independent factors was constructed and validated by the concordance index (C-index) and calibration plots. The decision curve analysis (DCA) and a risk stratification system were used to evaluate its clinical value.

Results: A total of 2,367 cases were selected for analysis and randomized to the training cohort (n=1,677) and the validation cohort (n=690). The patients were mainly male (59.3%), married (83.1%) and White (77.3%). Apart from LM, 54.2%, 26.7%, and 36.7% of patients also present with bone, brain, and lung metastases, respectively. The median follow-up was 4.0 months for all patients and 23 months for alive cases. The median OS was 5 months [interquartile range (IQR), 2–11 months]. Sex, age, race, grade, T stage, bone metastasis, brain metastasis, surgery, and chemotherapy were identified as the independent risk factors of the OS and used to develop the nomogram. The calibration curves exhibited excellent agreement between the predicted and actual survival in both the training and validation set, with a C-index of 0.700 [95% confidence interval (CI): 0.684–0.716] and 0.677 (95% CI: 0.653–0.701), respectively. The DCA and the risk classification system further supported that the prediction model was clinically effective.

Conclusions: This is the first study to build a prediction model for NSCLC patients with LM. It aids in treatment decisions, focused care, and physician-patient communication. The global prospective data is needed to further improve this model.

Keywords: Liver metastasis (LM); nomogram; non-small cell lung cancer (NSCLC); Surveillance, Epidemiology, and End Results (SEER); overall survival (OS)

Submitted May 25, 2023. Accepted for publication Sep 28, 2023. Published online Oct 26, 2023.

doi: 10.21037/tcr-23-899

View this article at: <https://dx.doi.org/10.21037/tcr-23-899>

Introduction

As the first leading cause of tumor-related death worldwide, lung cancer is still a severe threat to global health (1). Of all lung cancer cases, more than 85% are non-small cell lung cancer (NSCLC) (2,3). Among them, up to 57% present with metastatic lesions at diagnosis (1). As distant metastasis contributes to a large portion of NSCLC-related death, the prognosis of metastatic NSCLC patients remains dismal (4). Although sites of distant metastases are equivalent in the American Joint Committee on Cancer (AJCC) stage system, previous studies revealed that the survival of patients varies with sites of metastases (5-7). Further, liver metastasis (LM) is the most lethal site compared with other metastatic lesions, with a median survival of only 3–5 months (5,6,8,9).

Despite the enormous progress of novel therapeutic modalities, including molecular targeted therapy and immunotherapy, the clinical outcome of NSCLC patients with LM has only marginally improved. The impact of LM on the therapeutic effect of first-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in EGFR-mutant NSCLC was investigated in a multicenter study. It reported that patients with EGFR mutation and LM had significantly shorter progression-free survival (PFS) and overall survival (OS) than those without LM (10). Similarly, Meng and colleagues revealed that EGFR-TKIs failed to improve the clinical outcomes in patients with EGFR-mutant NSCLC and LM (11). In the setting of immunotherapy, preclinical

studies revealed that LM diminished immunotherapy efficacy systemically by creating an ‘immune desert’ state (12,13). Similar results from multiple studies also indicated resistance to immunotherapy in NSCLC patients with LM (12,14-17). Therefore, it is necessary to predict the individualized survival of this unique group of patients.

The tumor node metastasis (TNM) staging system remains the most frequently used tool to predict patient prognosis. However, TNM classification only assesses the anatomic factors and fails to incorporate them as continuous variables (18). Previous studies showed that some demographic factors, including histology, age, and race, were significantly associated with prognosis in patients with metastatic NSCLC (19-21). Moreover, the factors like metastatic sites and treatment modalities have also been recognized as important prognostic factors of NSCLC patients with LM (9). Thus, developing a practical, convenient, and accurate model with the combination of these crucial predictors is essential. Nomograms, in recent decades, have served as a method to improve cancer prognostication (18). Based on statistical regression models, the nomograms provide more accessible results by integrating diverse determinant variables and graphically depicting them with intuitive graphs. Sporadic reports have created the nomograms for predicting the outcomes in metastatic NSCLC (22-25), whereas the nomogram specifically for the prediction of prognosis in patients with LM specifically has not been established.

As one of the largest and most comprehensive cancer registries in the United States (US), the Surveillance, Epidemiology, and End Results (SEER) database covers about 28% of the entire US population. It provides detailed information on a wide range of cancer cases, including patient demographics, tumor characteristics, treatment modalities, and vital status. It also provides long-term follow-up data, often spanning several decades, and continually updates its data. Further, SEER records follow standardized data collection and reporting protocols, ensuring uniformity and quality across all participating cancer registries. This consistency minimizes data discrepancies and errors, which are crucial for building reliable predictive models. Therefore, the SEER database is more accurate for predicting the OS compared to the results of prediction model studies with small sample sizes and single centers.

Herein we propose to construct an accurate and efficient nomogram for NSCLC with LM based on records extracted from the SEER database. With this tool, improved clinical

Highlight box

Key findings

- A practical nomogram was developed and validated to predict the overall survival of non-small cell lung cancer (NSCLC) patients with liver metastasis (LM). Furthermore, the clinical value of the nomogram was confirmed by a risk stratification system.

What is known and what is new?

- In spite of a relatively low frequency, LM is considered the worst prognostic factor among all metastatic sites in NSCLC patients. A practical and convenient model to predict the survival of this unique group of patients is essential.
- This is the first study to build a prediction model focusing on the overall survival of NSCLC patients with LM.

What is the implication, and what should change now?

- The predictive model can be used to assist clinicians in applying personalized treatment.
- This user-friendly tool can allow physicians to identify the subgroup of patients requiring closer attention.

decision-making and patient-clinician communication can be achieved. We present this article in accordance with the TRIPOD reporting checklist (available at <https://tcr.amegrouppublishing.com/article/view/10.21037/tcr-23-899/rc>).

Methods

Patient selection and data elements

Metastatic lung cancer cases diagnosed between 2010 and 2015 were selected from the SEER database using the SEER*Stat software (v8.3.5). Overall, 144,302 records were collected. The inclusion criteria were as follows: lung cancer was the first primary tumor; cases without other malignant cancers; NSCLC confirmed by histology according to the International Classification of Disease (ICD) code O-3; LM. Subtypes of histology included in the study were as follows: adenocarcinoma (ADC; ICD-O-3: 8140, 8141, 8144, 8250, 8251, 8255, 8260, 8310, 8323, 8480), squamous cell carcinoma (SCC; ICD-O-3: 8070–8075, 8083, 8084), and other NSCLC (ICD-O-3: 8012, 8013, 8030–8035). In contrast, cases ineligible for analysis were excluded: patients with an OS time of less than 1 month and patients with incomplete information [blanks, unknown, or not available (N/A)]. Ultimately, 2,367 patients were included for analysis. The detailed flow diagram of data collection is shown in [Figure S1](#). The study was performed in accordance with the Declaration of Helsinki (as revised in 2013). As public and anonymous data were used, according to the ethics guidelines, neither informed consent nor approval of an ethics committee was required.

In total, fifteen variables, including clinical and pathological characteristics, were extracted and retrospectively reviewed in this study. Specifically, clinical factors consisted of sex, age, race, marital status, metastatic lesion, and treatment modalities (surgery, radiotherapy, chemotherapy). Pathological factors included primary site, histology, pathological grade, and TNM stage (based on the 7th edition of the American Joint Committee on Cancer staging). The optimal age-cut-off point was determined based on clinical consideration and prior reports. SEER patient's follow-up is performed by hospital-based and many population-based registries, and generated each month. The time of OS was counted as the period between diagnosis and death from any cause or last follow-up.

Nomogram construction and evaluation

We randomly split all eligible patients into the training and

validation cohort (7:3). Univariate and multivariate Cox regression analyses were applied in the training cohort to determine the parameters for generating the nomogram. The discriminative ability of the final nomogram was quantified by the concordance index (C-index). C-index varies from 0.5 to 1.0, where 0.5 represents random chance and 1.0 indicates a perfect fit. Typically, C-index value greater than 0.65 suggests a reasonable estimation (26-29). The consistency between predicted and actual 3-, 6-, and 12-month OS was displayed in the form of calibration curves. All validations for the model were performed using 1,000-resample bootstrapping. Besides, the decision curve analysis (DCA) was carried out to evaluate the clinical benefit of the nomogram by quantifying net benefits at different threshold probabilities (defined as the proportion of true positives minus the proportion of false positives, weighted by the relative harm of false-positive, and false-negative results) (30). The curves of treat-all-patients scheme (representing the highest clinical costs) and the treat-none scheme (representing no clinical benefit) were plotted as two references. Based on the sum scores of individuals on the nomogram, we further divided cases into high-score and low-score groups with the median score as the cut-off value. The Kaplan-Meier curves and log-rank tests were applied to compare the OS between different risk groups.

Statistical analysis

Variables with $P < 0.05$ in the multivariate analysis were collected as the independent prognostic factors integrated into the nomogram, which was constructed by R software with survival and rms packages. Additionally, the Kaplan-Meier survival analysis and log-rank test were used to evaluate and compare the survival time. R software (version 4.1.0) and Statistical Package for the Social Sciences (SPSS) software (version 25.0.0, International Business Machines Corporation, IBM) were conducted for statistical analyses. All results with two-sided $P < 0.05$ were deemed statistically significant.

Results

Patient demographics

In total, 2,367 records of NSCLC with LM diagnosed between 2010 and 2015 were enrolled in the final analysis. Specifically, 1,677 cases were included in the training set,

while 690 cases were included in the validation set. The baseline demographic features of patients in the three cohorts are summarized in *Table 1*. The patients in this study were mainly male (59.3%), and most cases were married (83.1%) and White (77.3%). The median diagnostic age was 66 years (range, 18–94 years). Adenocarcinoma (ADC) accounted for the largest proportion (63.2%), followed by SCC (32.1%). Apart from LM, 54.2%, 26.7%, and 36.7% of patients also present with bone, brain, and lung metastases, respectively. Regarding treatments, the vast majority of patients did not receive primary tumor resection (96.6%). Meanwhile, 45.4% of patients underwent radiotherapy, and 64.1% had chemotherapy.

Among the total cohort, the median follow-up was 4.0 months [interquartile range (IQR), 2–11 months] for

all patients and 23 months (IQR, 16–35 months) for alive cases. The median OS was 5 months (IQR, 2–11 months). At the last follow-up, the death rate was 94.3%. Further, the 3-, 6-, and 12-month survival rates were 66.8%, 44.0%, and 22.6%, respectively.

Independent prognostic factors for OS

As shown in *Table 2*, eleven characteristics proved to be significantly associated with OS according to the univariate analysis (*Figure S2*). Subsequently, these factors were enrolled in further multivariate analysis. Nine variables (gender, age, race, grade, T stage, bone metastasis, brain metastasis, surgery, and chemotherapy) turned out to be the independent risk predictors for OS (all $P < 0.05$).

Table 1 Baseline features of patients

Variables	Total cohort	Training cohort	Validation cohort	P value
Gender				0.42
Male	1,403 (59.3)	997 (59.5)	406 (58.8)	
Female	964 (40.7)	680 (40.5)	284 (41.2)	
Age (years)				0.28
<65	1,127 (47.6)	785 (46.8)	342 (49.6)	
≥65	1,240 (52.4)	892 (53.2)	348 (50.4)	
Race				0.37
White	1,829 (77.3)	1,288 (76.8)	541 (78.4)	
Black	326 (13.8)	239 (14.3)	87 (12.6)	
Others	212 (8.9)	150 (8.9)	62 (9.0)	
Primary site				0.14
Upper lobe	1,228 (51.9)	851 (50.7)	377 (54.6)	
Middle lobe	117 (4.9)	87 (5.2)	30 (4.3)	
Lower lobe	660 (27.9)	484 (28.9)	176 (25.5)	
Main bronchus	115 (4.9)	85 (5.1)	30 (4.3)	
Overlapping lesion	247 (10.4)	170 (10.1)	77 (11.3)	
Histology				0.61
Adenocarcinoma	1,497 (63.2)	1,062 (63.3)	435 (63.0)	
SCC	759 (32.1)	531 (31.7)	228 (33.0)	
Others	111 (4.7)	84 (5.0)	27 (4.0)	

Table 1 (continued)

Table 1 (continued)

Variables	Total cohort	Training cohort	Validation cohort	P value
Grade				0.27
Well differentiated (Grade I)	102 (4.3)	70 (4.2)	32 (4.6)	
Moderately differentiated (Grade II)	638 (27.0)	463 (27.6)	175 (25.4)	
Poorly differentiated (Grade III)	1,570 (66.3)	1,104 (65.8)	466 (67.5)	
Undifferentiated (Grade IV)	57 (2.4)	40 (2.4)	17 (2.5)	
T stage				0.43
T1	173 (7.3)	118 (7.0)	55 (8.0)	
T2	611 (25.8)	450 (26.8)	161 (23.3)	
T3	682 (28.8)	483 (28.8)	199 (28.8)	
T4	901 (38.1)	626 (37.4)	275 (39.9)	
N stage				0.73
N0	437 (18.5)	319 (19.0)	118 (17.1)	
N1	197 (8.3)	140 (8.4)	57 (8.3)	
N2	1,192 (50.3)	837 (49.9)	355 (51.4)	
N3	541 (22.9)	381 (22.7)	160 (23.2)	
Metastasis				0.79
Bone	1,284 (54.2)	919 (54.8)	365 (52.9)	
Brain	631 (26.7)	440 (26.2)	191 (27.7)	
Lung	868 (36.7)	593 (35.4)	275 (39.9)	
Marital status				0.66
Unmarried	400 (16.9)	296 (17.7)	104 (15.1)	
Married	1,967 (83.1)	1,381 (82.3)	586 (84.9)	
Surgery				0.34
No	2,287 (96.6)	1,622 (96.7)	665 (96.4)	
Yes	80 (3.4)	55 (3.3)	25 (3.6)	
Radiotherapy				0.39
No	1,292 (54.6)	917 (54.7)	375 (54.3)	
Yes	1,075 (45.4)	760 (45.3)	315 (45.7)	
Chemotherapy				0.11
No	850 (35.9)	604 (36.0)	246 (35.7)	
Yes	1,517 (64.1)	1,073 (64.0)	444 (64.3)	

Data are shown as n (%). SCC, squamous cell carcinoma.

Table 2 Cox regression analysis in the training cohort

Variables	Median OS (months) (95% CI)	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	P value	HR (95% CI)	P value
Gender					
Male	4.0 (3.5–4.5)	Reference		Reference	
Female	5.0 (4.3–5.7)	0.849 (0.767–0.939)	0.001*	0.899 (0.809–0.998)	0.046*
Age (years)					
<65	5.0 (4.4–5.6)	Reference		Reference	
≥65	4.0 (3.6–4.4)	1.187 (1.075–1.311)	<0.001*	1.134 (1.024–1.257)	0.016*
Race					
White	4.0 (3.6–4.4)	Reference		Reference	
Black	4.0 (3.1–4.9)	1.026 (0.891–1.181)	0.725	0.982 (0.850–1.134)	0.803
Others	7.0 (5.0–9.0)	0.723 (0.604–0.866)	<0.001*	0.803 (0.669–0.964)	0.019*
Primary site					
Main bronchus	4.0 (2.6–5.4)	Reference			
Upper lobe	5.0 (4.4–5.6)	0.847 (0.675–1.063)	0.151		
Middle lobe	6.0 (4.8–7.2)	0.752 (0.553–1.023)	0.069		
Lower lobe	5.0 (4.3–5.7)	0.803 (0.635–1.016)	0.068		
Overlapping lesion	3.0 (2.1–3.9)	0.929 (0.712–1.212)	0.586		
Histology					
Adenocarcinoma	5.0 (4.4–5.6)	Reference		Reference	
SCC	4.0 (3.4–4.6)	1.182 (1.061–1.316)	0.002*	1.112 (0.989–1.251)	0.076
Others	3.0 (2.1–3.9)	1.433 (1.144–1.797)	0.002*	1.251 (0.979–1.600)	0.073
Grade					
Well differentiated (Grade I)	7.0 (4.3–9.7)	Reference		Reference	
Moderately differentiated (Grade II)	6.0 (5.2–6.8)	1.411 (1.072–1.858)	0.014*	1.213 (0.916–1.606)	0.178
Poorly differentiated (Grade III)	4.0 (3.6–4.4)	1.838 (1.408–2.399)	<0.001*	1.565 (1.191–2.055)	0.001*
Undifferentiated (Grade IV)	2.0 (1.3–2.7)	2.582 (1.711–3.859)	<0.001*	1.889 (1.223–2.917)	0.004*
T stage					
T1	7.0 (5.5–8.5)	Reference		Reference	
T2	5.0 (4.3–5.7)	1.302 (1.055–1.606)	0.014*	1.172 (0.945–1.454)	0.149
T3	5.0 (4.3–5.7)	1.270 (1.031–1.565)	0.025*	1.138 (0.919–1.408)	0.235
T4	4.0 (3.5–4.6)	1.443 (1.176–1.769)	<0.001*	1.356 (1.100–1.670)	0.004*
N stage					
N0	5.0 (4.3–5.7)	Reference			
N1	5.0 (3.4–6.6)	0.978 (0.796–1.202)	0.832		
N2	5.0 (4.4–5.6)	1.049 (0.918–1.199)	0.481		
N3	4.0 (3.2–4.9)	1.126 (0.966–1.312)	0.131		

Table 2 (continued)

Table 2 (continued)

Variables	Median OS (months) (95% CI)	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	P value	HR (95% CI)	P value
Bone metastasis					
No	6.0 (5.3–6.7)	Reference		Reference	
Yes	4.0 (3.6–4.4)	1.326 (1.212–1.473)	<0.001	1.403 (1.263–1.558)	<0.001*
Brain metastasis					
No	5.0 (4.6–5.4)	Reference		Reference	
Yes	4.0 (3.3–4.7)	1.147 (1.030–1.285)	0.012*	1.199 (1.055–1.364)	0.005*
Lung metastasis					
No	5.0 (4.5–5.5)	Reference			
Yes	4.0 (3.5–4.5)	1.044 (0.941–1.157)	0.418		
Marital status					
Unmarried	4.0 (3.1–4.9)	Reference			
Married	5.0 (4.6–5.4)	0.983 (0.863–1.120)	0.800		
Surgery					
No	4.0 (3.6–4.4)	Reference		Reference	
Yes	11.0 (7.4–14.6)	0.502 (0.370–0.670)	<0.001*	0.602 (0.445–0.814)	0.001*
Radiotherapy					
No	5.0 (4.4–5.6)	Reference		Reference	
Yes	4.0 (3.4–4.6)	1.116 (1.017–1.235)	0.022*	1.049 (0.938–1.173)	0.403
Chemotherapy					
No	2.0 (1.8–2.2)	Reference		Reference	
Yes	7.0 (6.5–7.5)	0.394 (0.352–0.433)	<0.001*	0.414 (0.371–0.461)	<0.001*

*, P<0.05. OS, overall survival; CI, confidence interval; SCC, squamous cell carcinoma.

Nomogram construction and validation

Based on the results above, a nomogram integrating all independent risk factors was constructed for the prediction of OS (Figure 1). By summing up the points of each variable on the point-scale axis, the total score of individual patients could be calculated, and patients' 3-, 6-, and 12-month survival probabilities can be estimated. For example, a patient is 70 years old Asian female, grade II SCC, T4 stage with bone and brain metastasis, and she has received chemotherapy but not surgery. Her total points are 180, and the probabilities of 3-, 6-, and 12-month survival are 0.68, 0.5, and 0.28, respectively. As illustrated in the nomogram, chemotherapy contributed the most significant proportion to the OS, followed by grade and surgical resection. Bone

metastasis and T stage presented a moderate impact on survival; on the contrary, gender and age showed a relatively small effect on survival.

What is more, the nomogram exhibited good discriminative ability and accuracy at predicting OS. The C-index was 0.700 [95% confidence interval (CI): 0.684–0.716] in the training dataset and 0.677 (95% CI: 0.653–0.701) in the validation dataset. Meanwhile, the calibration curves confirmed an excellent consistency between the observed and predicted survival probabilities in both cohorts (Figure 2).

Clinical value of the nomogram

DCA evaluated the net benefit of patients in both cohorts,

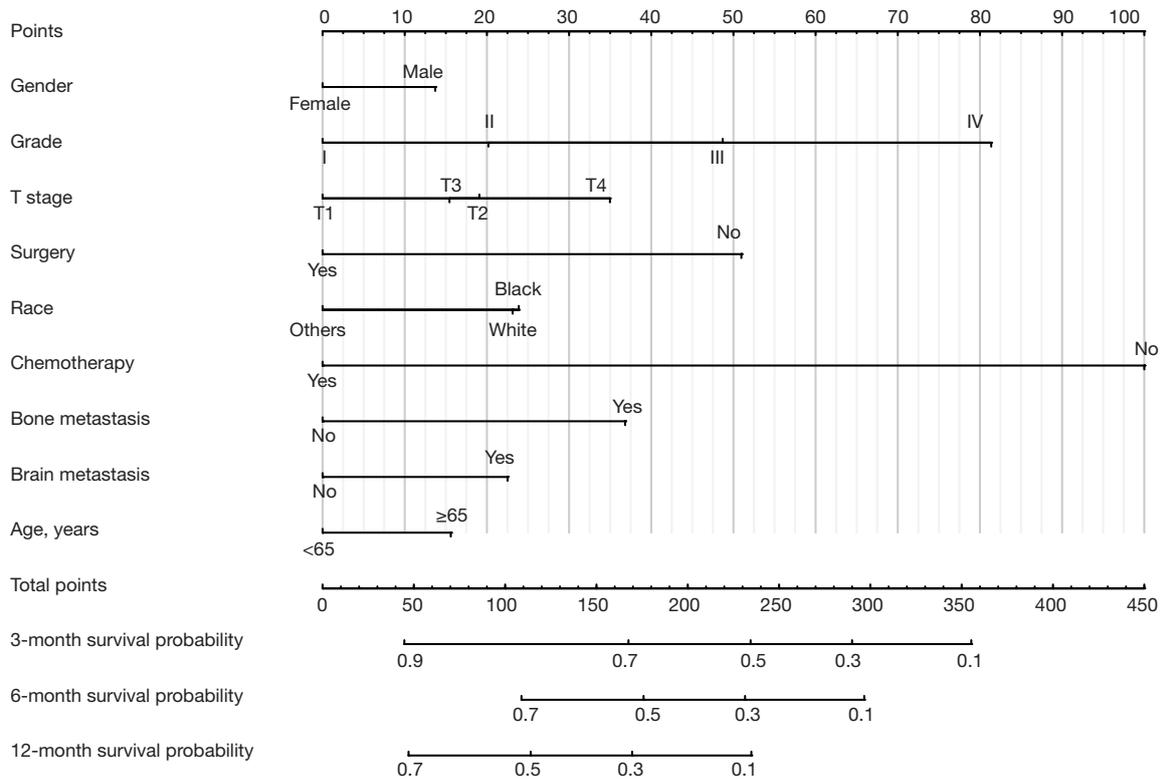


Figure 1 Nomogram for the prediction of 3-, 6- and 12-month overall survival in NSCLC patients with liver metastasis. NSCLC, non-small cell lung cancer.

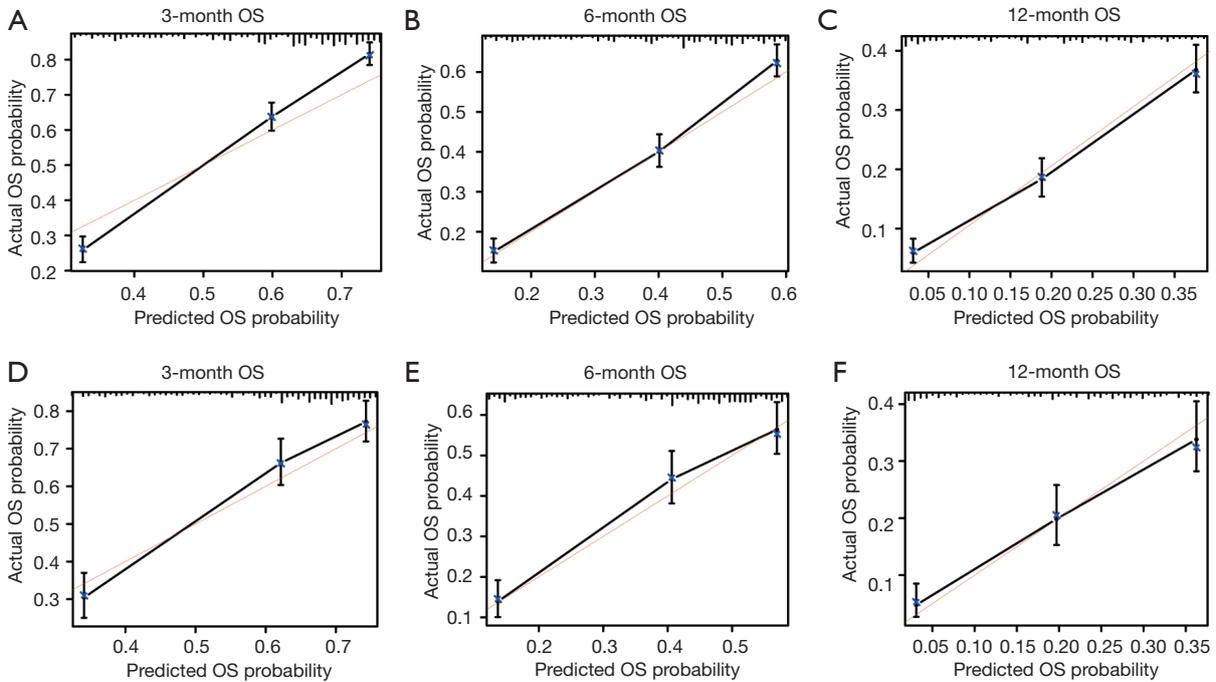


Figure 2 Calibration of the nomogram. Calibration curves at 3-, 6-, and 12-month in the training cohort (A-C) and the validation cohort (D-F). The ideal equality between them is depicted by the 45-degree red line. OS, overall survival.

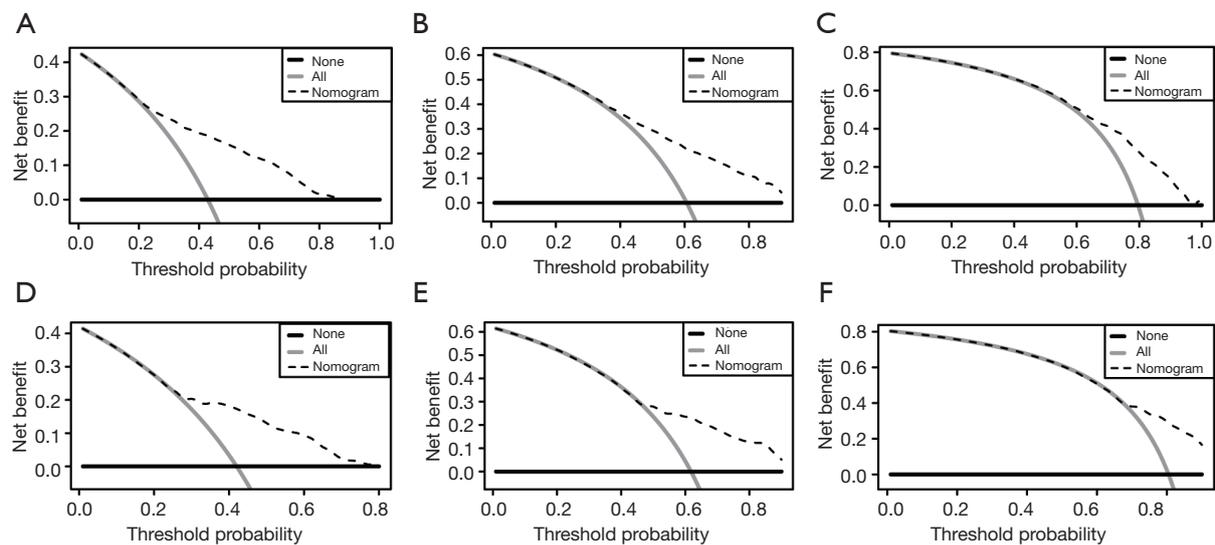


Figure 3 The DCA to evaluate the nomogram. Decision curves at 3-, 6-, and 12-month in the training cohort (A-C) and the validation cohort (D-F). DCA, decision curve analysis.

indicating a favorable clinical value of the proposed nomogram (Figure 3). Moreover, the total points of individuals were calculated based on the nomogram, and all patients were classified into two risk groups. The Kaplan-Meier survival analysis indicated that patients with lower scores achieved a significantly longer survival time than patients with higher scores ($P < 0.0001$), providing solid evidence of the strong predictive ability of the model (Figure 4).

Discussion

In spite of a relatively low frequency (3–7%) (6,31,32), LM is considered the worst prognostic factor among all metastatic sites in NSCLC patients (8,33). The estimated OS of these patients is usually less than 6 months (5,6,15). Thus, predicting individual survival is critical to personalize treatment strategies and improve physician-patient communications. In this study, a nomogram was built to assess the OS probabilities of NSCLC patients with LM. Further analysis confirmed the model's predictive ability and clinical value, which is highly significant for stratifying risk groups.

Our study revealed that sex, race, age, grade, and T stage were independent predictors of OS, consistent with prior studies (5,22,23). In addition to these classical risk factors, we found that in NSCLC patients with LM, the presence of bone or brain metastasis was significantly correlated with

poor outcomes, whereas the impact of lung metastasis in the same group was negligible. Several reports have noted that the outcome among different metastatic sites varies (8,33). Yang *et al.* (34) pointed out that the prognosis in NSCLC patients with multiorgan metastases was substantially more unfavorable than those with single organ metastasis. All the evidence strongly supports metastatic heterogeneity in NSCLC. In terms of histologic types, our results found that the prognosis was better in ADC than in other subtypes of NSCLC, which was in line with earlier findings (22,23). Nevertheless, histology surprisingly did not remain significant statistically in the multivariate analysis. It has been reported that the survival benefit for ADC is only observed in recent decades, indicating the increasing impact of molecular targeted therapy in ADC patients (35). Unfortunately, recent studies demonstrated that LM was a negative prognostic factor in NSCLC patients receiving EGFR-TKIs therapy. Compared to NSCLC patients with an absence of LM, the treatment response was dramatically poorer in those with the presence of LM (10,11). Therefore, the discrepancy in our study could be attributed to the liver resistance to the molecular target therapy.

As shown in the nomogram, chemotherapy contributed the most to OS. In our study, the patients who received chemotherapy had a much better prognosis than those without chemotherapy (7 *vs.* 2 months, $P < 0.001$). Similarly, prior studies suggested that chemotherapy made a large contribution to the survival outcomes for NSCLC patients

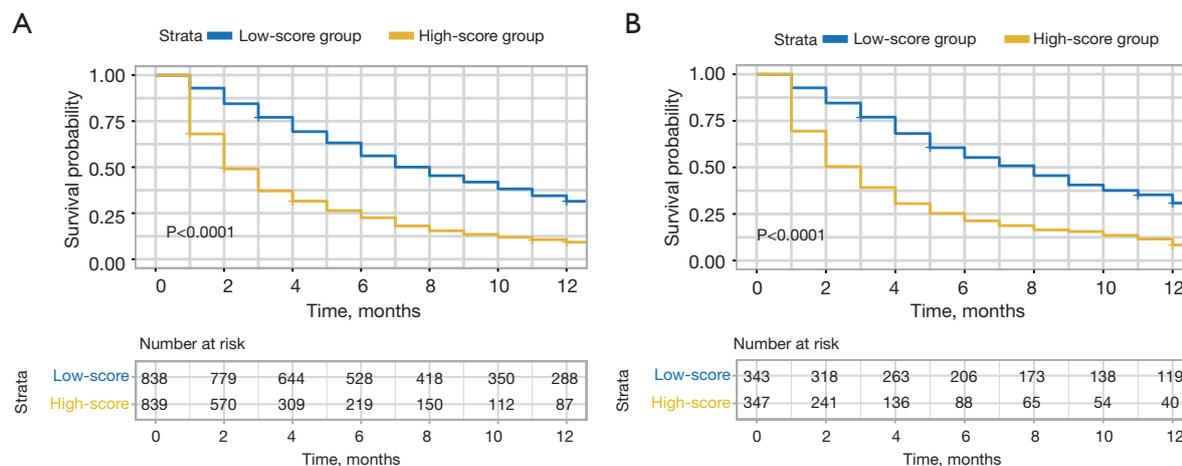


Figure 4 Kaplan-Meier survival analysis according to high-score and low-score groups in the training set (A) and validation set (B).

with brain or bone metastasis (24,25,36-38). Moreover, given that LM was significantly related to dismal prognosis in patients who had targeted therapy and immunotherapy (10-12,14-16), chemotherapy still plays an essential role in the setting of LM. The significance of local treatment in patients with metastatic NSCLC remains controversial. The current study revealed a survival benefit in patients with surgically treated NSCLC with LM. Of patients who received resection of the primary tumor, 71% were treated with chemotherapy, and 33% were treated with radiotherapy, indicating that local resection was only a part of the multimodal therapy in most cases. David and colleagues also reported that the median OS time was significantly increased with surgical procedures in NSCLC patients with metastasis (39). Besides, they also stated that surgery might be considered part of multimodality therapy, given the crucial role of systemic therapies. Of note, not all patients can benefit from surgery. Various individual and tumor-related risk factors should be taken into consideration when surgical treatment is performed in a multidisciplinary setting (40-42). Interestingly, our study found that radiotherapy, as another option of local treatment strategies, was not able to independently predict the OS in NSCLC patients with LM ($P=0.403$). Our data indicated that radiotherapy alone might have a modest impact on prognosis. However, it should be noted that the prognosis of NSCLC patients with LM is unfortunately dismal, with a median OS of only 5 months. Due to a relatively long course of treatment, there might not be much of a chance to prove the value of radiotherapy in long-term prediction. Hence, Wallace and colleagues

suggested that shorter courses of radiotherapy should be considered in patients with limited prognosis (43). Further, preclinical studies reported that radiotherapy-induced T-cell infiltration increased tumor antigen release, which led to an enhancement of antitumor immune response (44-46). As a result, Corrao and colleagues implied that the survival outcomes in NSCLC patients with LM might be improved when radiotherapy is combined with immunotherapy (47). Besides, for patients with severe pain or complications, radiotherapy may still be an option for palliative care.

Unlike bone or brain metastasis, limited data exist to look at LM of NSCLC. To date, this is the first study to establish a prediction model focusing on the OS of NSCLC patients with LM. As all factors in our nomogram can be readily obtained, it might be applicable in both developed and low or middle-income countries. This user-friendly tool will allow physicians to identify the subgroup of patients requiring closer attention. For example, EGFR-TKIs remain the standard first-line therapy for EGFR-mutated NSCLC patients with LM. Still, more extensive treatment like chemotherapy would be suggested for the high-risk subgroup with EFGR mutant recognized by our nomogram. Further, more palliative care and a shorter follow-up period might be considered for the high-risk subgroup. Similarly, hospice referral could be recommended for patients with limited life expectancy.

Nevertheless, limitations should be admitted in this study. First, there was an inevitable selection bias resulting from its retrospective nature. Second, the SEER database was unavailable for detailed treatment information, such as chemotherapy regimens, radiation doses, targeted

therapy, and immunotherapy. Similarly, genomic data, other metastatic sites, including adrenal metastasis, and performance status cannot be obtained. Third, our nomogram was only validated internally with a relatively small cohort, and an independent external cohort with a larger sample size is still required for future application. Finally, given that all enrolled records were from the United States, the perspective of global data is warranted to apply our model to the Asian population and patients worldwide.

Conclusions

In summary, we developed and validated a practical nomogram to predict the OS of NSCLC patients with LM. The predictive model can be used to assist clinicians in deciding personalized treatment strategies.

Acknowledgments

Funding: This work was supported by the Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University, funded by the Natural Science Foundation of Hunan Province (grant No. 2023JJ40837).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-899/rc>

Peer Review File: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-899/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-899/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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Cite this article as: Xu T, Liu X, Liu C, Chen Z, Ma F, Fan D. Development and validation of a nomogram for predicting the overall survival in non-small cell lung cancer patients with liver metastasis. *Transl Cancer Res* 2023;12(11):3061-3073. doi: 10.21037/tcr-23-899