Original Article

Establishment of a nomogram for potential prediction of lung metastasis in patients with primary limb bone tumors: a study based on the SEER database

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Background: The prognosis of lung metastasis in primary limb bone tumors represents a pivotal yet challenging aspect of oncological management. Despite advancements in diagnostic modalities, the predictive accuracy for metastatic spread remains suboptimal. This study aims to bridge this gap by leveraging the Surveillance, Epidemiology, and End Results (SEER) database to construct a nomogram that forecasts the risk of lung metastasis, thereby enhancing clinical decision-making processes.

Methods: A retrospective cohort, including 1,822 patients with primary limb bony tumors from 2010 to 2015 in the SEER database, was extracted. Using precise inclusion and exclusion criteria, variables essential for predicting lung metastasis were identified through univariate and multivariate analyses, along with least absolute shrinkage and selection operator (LASSO) regression. These variables provided a solid basis for creating the multivariable nomogram, of which the discriminating power and utility were verified using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis.

Results: The model incorporated seven key predicting variables, including age, histological type, surgery, radiation, chemotherapy, T stage, and N stage. The nomogram emerged as a cohesive whole with good discriminative power. The area under the curve (AUC) was 0.806 in the training cohort and 0.767 in the validation cohort. The calibration curves demonstrated the model's validity by showing a good match between the actual outcomes and the model-predicted probabilities of lung metastasis.

Conclusions: This study showed for the first time the reliability of the predictive model in translating the hard-to-interpret demographic, clinical, and pathologic data into a very usable predictive model. Thus, it represents a significant step toward demystifying the risk of lung metastasis in primary limb bone tumors. It is an invitation for a paradigm shift of oncology, to evidence-based, person-based oncology that is taking a new metric for cancer prognosis.

Keywords: Bone cancer; nomogram; Surveillance, Epidemiology, and End Results database (SEER database); limb; lung metastasis

Submitted Apr 07, 2024. Accepted for publication Jul 19, 2024. Published online Sep 21, 2024.
doi: 10.21037/tcr-24-570
View this article at: https://dx.doi.org/10.21037/tcr-24-570

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Introduction

In the current 21st century, cancer has been on the rise as a major cause of death, both within China and worldwide (1,2). Cancer currently remains one of the major constraints for expanding life expectancy. In the United States, malignancies of bones and joints have become the third leading causes of death related to cancers in individuals under the age of 20 years (3). According to the newest figures, the one-year overall survival rates for a malignant bone tumor are 74% for the age group of 0–14 years and 69% in those aged 15–19 years (4).

Primary limb bone tumors are widespread, due to the prevalence of different cancer types ranging from bone-forming osteosarcoma (5), chondrosarcoma (6), to Ewing's sarcoma (7). Typically, the tumors that adversely affect the long bones of adolescents are quite obvious and would not be initially discovered at the spinal column or pelvic bones sites (8).

The Surveillance, Epidemiology, and End Results (SEER) database, developed by the National Cancer Institute (NCI) of the United States, is a very large cancer registry which records and stores comprehensive information about cancer patients. This repository is designed to capture detailed data of the present epidemiological traits of various tumors, including primary limb bone tumors, and permits comprehensive exploration and analysis of these data. Covering approximately 28% of the United States (US) population (9), the database contains valuable data, including fundamental demographics such as age and gender, as well as specific disease attributes including tumor size and location. Data on survival and death rates are also included and are of utmost importance.

Nomograms solely dominate the territory of clinical prognosticating tools and are the unique pillar of such pragmatic types of tools; they amalgamate statistical data and clinical acumen, which helps to determine the true course of cancer progression (10,11). In general, the establishment of a nomogram is usually based on a development cohort and is validated in a validation cohort to further ensure the model's validity. A handful of nomograms have been established to predict the general prognosis of primary spinal tumors (8,12), and individual nomograms have been created for specific pathological types of tumors, namely, osteosarcoma, chondrosarcoma, and Ewing's sarcoma (13-16), to address concerns metastatic and survival issues. However, there is currently a noticeable lack of a model that can predict the spread to the lung from primary limb tumors. Herein, we raise several queries: Does the specter of lung metastasis have an important impact on the survival rates of patients with primary limb bone tumors? Which factors may affect the course of the diseases? Can we distill these variables into a nomogram which can predict the risk of lung metastasis accurately? The answers to these questions will help doctors to make more evidence-based decisions, to the benefit of a larger number of patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-570/rc).

Highlight box

Key findings

- The study developed a nomogram for predicting the risk of lung metastasis in patients with primary limb bone tumors, using data from the SEER database. Seven key predicting variables were identified: age, histological type, tumor size, surgery, radiation, chemotherapy, and TNM classification. The nomogram showed good accuracy with an area under the curve of 0.806 in the training cohort and 0.767 in the validation cohort.

What is known and what is new?

- It is known that predicting lung metastasis in patients with primary bone tumors of the limb is challenging due to the complexity of factors involved. Existing models have not specifically addressed this patient population.
- This manuscript introduces a novel predictive tool that translates demographic, clinical, and pathological data into a usable nomogram, improving risk prediction for lung metastasis.

What is the implication, and what should change now?

- The nomogram can enhance clinical decision-making by providing a more accurate risk assessment for lung metastasis in patients with primary limb bone tumors. This tool aids in early detection and timely intervention, potentially improving patient outcomes. Clinicians should integrate this nomogram into their practice to better stratify patients by risk and personalize treatment plans accordingly.

Methods

Data acquisition

The SEER database, maintained by the NCI, is the source of our study. The research cases for the SEER database, which come from 17 registries, ranging between 2000 and 2020, have been updated to correctly reflect the survival and incidence of cancer patients from different population groups. Data extraction was performed using SEER*Stat

software, version 8.4.3 (https://seer.cancer.gov/seerstat/), to ensure that the process and result of our data analysis remained stable and credible. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Cohort definition

The inclusion criteria were as follows: the group consisted of patients with primary tumors of the limb bones diagnosed between 2010 and 2015 using unified diagnostic criteria; a confirmed diagnosis of lung metastasis; and the primary site was restricted to the limbs.

The exclusion criteria were as follows: cases which did not mention the status of surgical intervention, tumor, node, metastasis (TNM) stage and laterality; and failure to provide essential demographic features such as ethnicity.

Clinicopathological variables

Two researchers, X.H. and J.W.G., analyzed the data independently to ensure accuracy. We screened sets of data for further correlation, retrieving demographic details (gender, age, and race) as well as pathological statuses such as lung metastasis, the malignant poly-invasive tumor type, laterality, and tumor size. A coded message was used to indicate the presence of the primary malignant indicator, surgery, radiation, or chemotherapy statuses, and tumor grading according to the TNM stage. These data sources helped us understand the general trends in survival rate metrics, in addition to providing valuable guidance regarding highly correlated metrics. The data used for the analysis are presented in the supplementary material (available at https://cdn.amegroups.cn/static/public/tcr-24-570-1.xlsx) and Table S1.

Statistical analysis

Using the RAND function in Excel to ensure that the basic information between the two groups was the same, we assigned a random number to each case in our dataset. The RAND function generates a random decimal number between 0 and 1. After generating random numbers for all cases, we sorted the entire dataset in ascending order based on the random numbers assigned. Following the sorting, the cohort (containing 1,822 patients) was dichotomized into two groups based on a 3:1 ratio: a training cohort (n=1,364) consisting of the first 75% of cases (those with the smallest random numbers), and the remaining 25% (n=458) were allocated to the validation cohort (which was used to validate the experimental modeling). Chi-squared test was used for categorical outcomes and the Kruskal-Wallis rank sum test was used for continuous outcomes indicating significance level.

Subsequent analyses involved a two-pronged approach: initially, we carried out univariate analysis as well as least absolute shrinkage and selection operator (LASSO) regression on the training cohort to identify significant factors; these then acted as a base for multivariate logistic regression to confirm the prediction factors for inclusion in the nomogram.

This nomogram was subjected to an extensive verification in both cohorts, evaluating not only the areas under receiver operating characteristic (ROC) curve (AUC) (17), but also the AUC metrics, to ascertain its predictive accuracy. Besides the external calibration curves, the model's fit was assessed, and a decision curve analysis (DCA) (18) was performed to evaluate its net benefit and clinical utility. Kaplan-Meier survival curves provided a visual representation of the survival time differences between the two groups. All statistical assessments were conducted using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). A P value of less than 0.05 was considered statistically significant.

Results

Demographic and baseline characteristics

According to the inclusion and exclusion criteria mentioned in the Methods section, we distilled a focused group of 1,822 cases from an initial cohort of 4,849 patients (see *Figure 1* for details of the selection process). Eventually, this cohort was divided into two smaller cohorts, a training cohort of 1,364 cases and a validation cohort of 458 individuals. The statistical analysis did not show a significant difference (P>0.05) between the two groups of patients in several attributes (*Table 1*), for instance, the age, sex, race, and histological type of the given patients. Thus, by using these patients as the training and validation cohorts, we demonstrated their rationality.

Kaplan-Meier survival analysis

Figure 2A shows that at 12 months, patients with lung

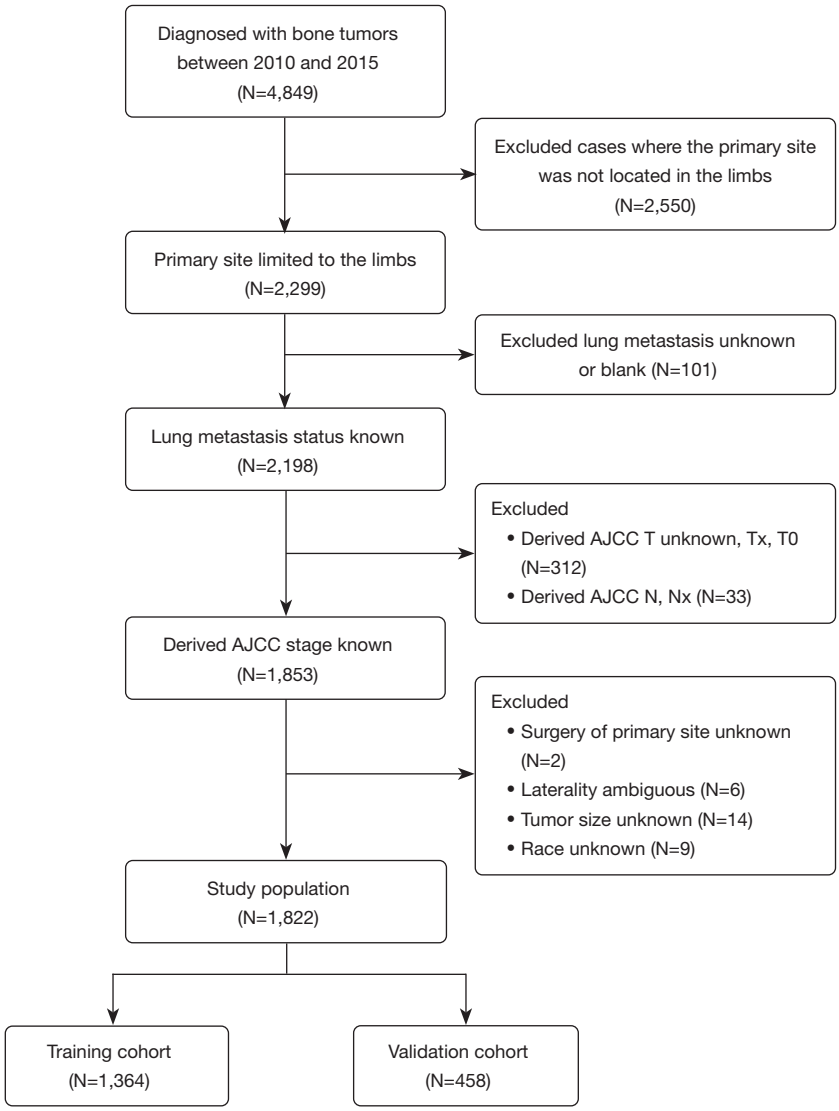

Figure 1 Inclusion and exclusion criteria flowchart. AJCC, American Joint Committee on Cancer.

Table 1 Distribution of demographic and clinical information

Characteristics	Total	Training cohort	Validation cohort	P value*
N	1,822 (100.0)	1,364 (74.9)	458 (25.1)	
Age (years)				0.06
<25	894 (49.07)	676 (49.56)	218 (47.60)	
25–49	416 (22.83)	310 (22.73)	106 (23.14)	
50–74	403 (22.12)	287 (21.04)	116 (25.33)	
>74	109 (5.98)	91 (6.67)	18 (3.93)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	Training cohort	Validation cohort	P value*
Sex				0.75
Male	1,046 (57.41)	786 (57.62)	260 (56.77)	
Female	776 (42.59)	578 (42.38)	198 (43.23)	
Race				0.90
White	1,465 (80.41)	1,094 (80.21)	371 (81.00)	
Black	201 (11.03)	151 (11.07)	50 (10.92)	
Others	156 (8.56)	119 (8.72)	37 (8.08)	
Lung metastasis				0.76
No	1,608 (88.25)	1,202 (88.12)	406 (88.65)	
Yes	214 (11.75)	162 (11.88)	52 (11.35)	
Histological type				0.65
Osteosarcoma	890 (48.85)	673 (49.34)	217 (47.38)	
Chondrosarcoma	508 (27.88)	381 (27.93)	127 (27.73)	
Ewing sarcoma	211 (11.58)	158 (11.58)	53 (11.57)	
Others	213 (11.69)	152 (11.14)	61 (13.32)	
Laterality				0.57
Right	874 (47.97)	649 (47.58)	225 (49.13)	
Left	948 (52.03)	715 (52.42)	233 (50.87)	
First malignant primary indicator				0.56
Yes	1,663 (91.27)	1,248 (91.50)	415 (90.61)	
No	159 (8.73)	116 (8.50)	43 (9.39)	
Surgery				0.28
Yes	1,628 (89.35)	1,225 (89.81)	403 (87.99)	
No	194 (10.65)	139 (10.19)	55 (12.01)	
Radiation				0.34
No	1,642 (90.12)	1,224 (89.74)	418 (91.27)	
Yes	180 (9.88)	140 (10.26)	40 (8.73)	
Chemotherapy				0.89
Yes	1,117 (61.31)	835 (61.22)	282 (61.57)	
No	705 (38.69)	529 (38.78)	176 (38.43)	
Total number of tumors				0.83
1	1,566 (85.95)	1,171 (85.85)	395 (86.24)	
>1	256 (14.05)	193 (14.15)	63 (13.76)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	Training cohort	Validation cohort	P value*
T				0.14
T1	846 (46.43)	643 (47.14)	203 (44.32)	
T2	936 (51.37)	696 (51.03)	240 (52.40)	
T3	40 (2.20)	25 (1.83)	15 (3.28)	
N				0.51
N0	1,774 (97.37)	1,330 (97.51)	444 (96.94)	
N1	48 (2.63)	34 (2.49)	14 (3.06)	
M				0.86
M0	1,563 (85.78)	1,169 (85.70)	394 (86.03)	
M1	259 (14.22)	195 (14.30)	64 (13.97)	
Tumor size (mm)				0.84
≤68	616 (33.81)	462 (33.87)	154 (33.62)	
>68, ≤110	617 (33.86)	457 (33.50)	160 (34.93)	
>110	589 (32.33)	445 (32.62)	144 (31.44)	

Data are presented as n (%). *, if it is a continuous variable, it is obtained by the Kruskal-Wallis rank sum test; if it is a count variable with expected count less than 10, it is obtained by the Fisher's exact test.

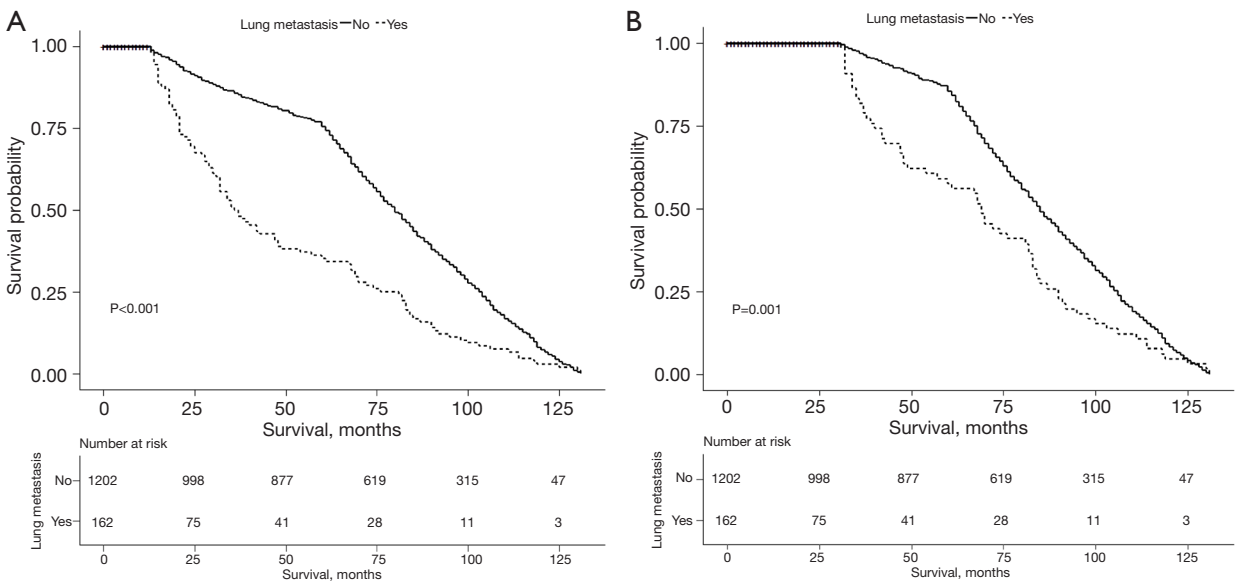

Figure 2 Kaplan-Meier curves. (A) At the 12-month follow-up, patients with pulmonary metastases have a lower survival probability compared to patients with primary limb bone tumors without observed lung metastases (P<0.001). (B) At the 30-month follow-up, the survival probability for patients with lung metastases remains lower than that for patients with primary limb bone tumors without pulmonary involvement (P=0.001). The risk table shows the number of patients at risk at different time points, with data sourced from the same dataset.

Table 2 Univariate analysis identifying factors associated with pulmonary metastasis (N=1,364)

Variable	Univariate analysis	
	OR (95% CI)	P value
Age (years)		
<25	1	
25–49	0.34 (0.20, 0.57)	<0.001
50–74	0.57 (0.36, 0.89)	0.01
>74	0.92 (0.49, 1.71)	0.78
Sex		
Male	1	
Female	0.78 (0.55, 1.09)	0.14
Race		
White	1	
Black	0.86 (0.49, 1.48)	0.58
Others	0.89 (0.48, 1.62)	0.69
Histological type		
Osteosarcoma	1	
Chondrosarcoma	0.29 (0.17, 0.48)	<0.001
Ewing sarcoma	0.99 (0.61, 1.61)	0.97
Others	0.65 (0.37, 1.14)	0.13
Laterality		
Right	1	
Left	0.80 (0.58, 1.11)	0.19
Tumor size (mm)		
≤68	1	
>68, ≤110	1.97 (1.24, 3.14)	0.004
>110	3.01 (1.93, 4.70)	<0.001
First malignant primary indicator		
Yes	1	
No	1.11 (0.63, 1.96)	0.71
Surgery		
Yes	1	
No	5.36 (3.60, 7.98)	<0.001
Radiation		
No	1	
Yes	3.94 (2.62, 5.93)	<0.001
Chemotherapy		
Yes	1	
No	0.15 (0.09, 0.25)	<0.001
Total number of tumors		
1	1	
>1	0.63 (0.37, 1.09)	0.10
T		
T1	1	
T2	2.56 (1.77, 3.72)	<0.001
T3	10.96 (4.69, 25.60)	<0.001
N		
N0	1	
N1	11.95 (5.91, 24.18)	<0.001
M		
M0	1	
M1	inf. (0.00, inf)	0.98

CI, confidence interval; OR, odds ratio.

metastases had a significantly lower survival probability compared to those without (P<0.001). At 30 months, this trend continued, as shown in *Figure 2B*, with survival probabilities remaining lower for those with lung metastases (P=0.001). These Kaplan-Meier curves highlight the negative impact of lung metastasis on survival outcomes.

Prognostic factor identification

In the training cohort, univariate analysis and LASSO regression analysis were conducted to identify factors significantly affecting lung metastasis. Both analyses utilized 14 factors, ultimately identifying eight significant factors (P<0.05): age, histological type, tumor size, surgery, radiation, chemotherapy, T stage, and N stage (*Table 2*, *Figure 3*). These eight factors were then subjected to multivariate logistic regression analysis (detailed in *Table 3*). The results indicated that seven factors—age, histological type, surgery, radiation, chemotherapy, T stage, and N stage—were independent predictors of lung metastasis.

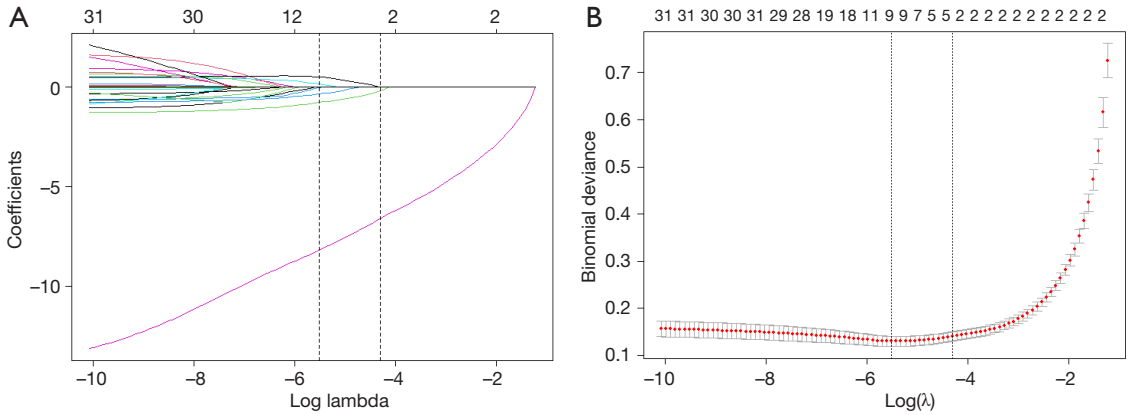

Figure 3 Utilizing the LASSO for logistic regression in feature selection. (A) The graph illustrates the binomial deviance plotted against the logarithm of lambda [log(λ)]. Vertical black lines indicate the position of optimal λ, determined by the minimal criterion and its standard error. (B) Depicts the trajectories of LASSO coefficients for 14 clinical variables, showcasing how these coefficients vary with log(λ). LASSO, least absolute shrinkage and selection operator.

Table 3 Multivariate logistic regression analysis of factors associated with pulmonary metastasis in the training cohort

Variable	Multivariate analysis	
	OR (95% CI)	P value
Age (years)		
<25	1	
25–49	0.58 (0.35, 0.96)	0.03
50–74	1.17 (0.69, 1.96)	0.56
>74	2.25 (0.96, 5.26)	0.06
Histological type		
Osteosarcoma	1	
Chondrosarcoma	0.90 (0.47, 1.72)	0.75
Ewing sarcoma	0.41 (0.24, 0.70)	0.001
Others	0.81 (0.44, 1.50)	0.50
Tumor size (mm)		
≤68	1	
>68, ≤110	1.02 (0.54, 1.90)	0.96
>110	1.36 (0.68, 2.74)	0.39
Surgery		
Yes	1	
No	4.68 (3.02, 7.26)	<0.001
Radiation		
No	1	
Yes	2.06 (1.25, 3.40)	0.005
Chemotherapy		
Yes	1	
No	0.15 (0.08, 0.28)	<0.001
T		
T1	1	
T2	1.66 (0.93, 2.95)	0.09
T3	4.97 (2.01, 12.25)	0.001
N		
N0	1	
N1	4.98 (2.49, 9.94)	<0.001

CI, confidence interval; OR, odds ratio.

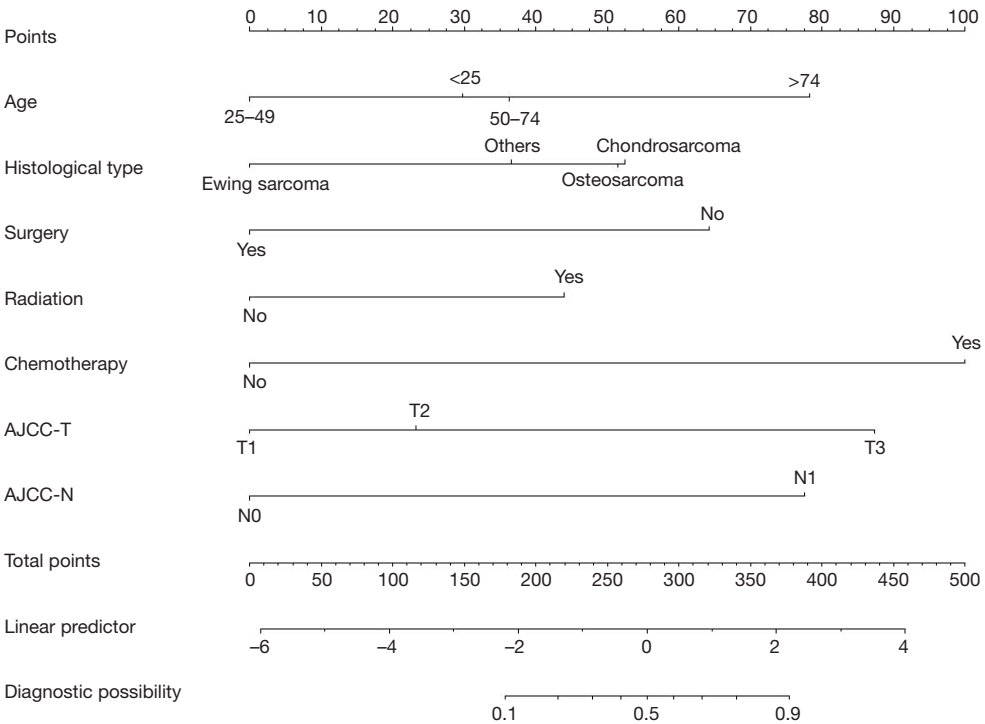

Figure 4 The nomogram to predict the risk of lung metastasis in patients with primary bone tumors of the limb. Age in the nomogram is in years. AJCC, American Joint Committee on Cancer.

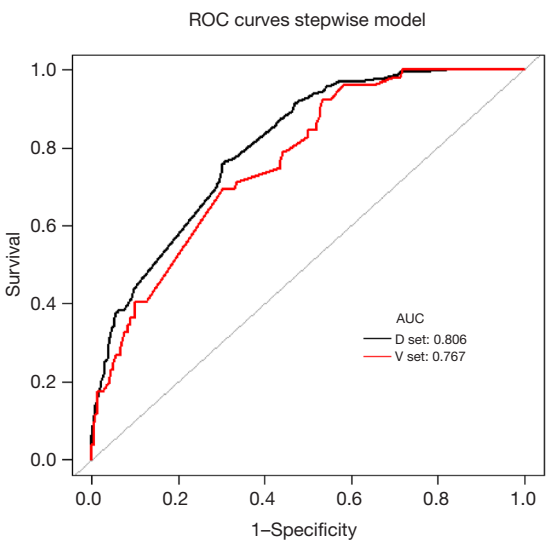

Figure 5 ROC curves in the training and validation cohorts used to validate the nomogram. D means development cohort and V means validation cohort. ROC, receiver operating characteristic; AUC, area under the curve.

Nomogram development and external validation

Using the seven factors selected by multivariate logistic regression, we constructed a nomogram to predict the risk of lung metastasis (*Figure 4*). Every predictor was assigned an individualized score, which was then amalgamated into a composite score to forecast the likelihood of lung metastasis. We plotted the ROC curve, which unveiled an AUC of 0.806 [95% confidence interval (CI): 0.7754–0.8375] for the training cohort and 0.767 (95% CI: 0.7067–0.8279) for the validation (*Figure 5*). There was no significant difference in AUC between the training and validation groups.

External calibration curves further demonstrated the nomogram's repeatability in predicting probabilities of lung metastasis, with a logistic calibration curve approaching the ideal (*Figure 6*). This consistency between the training and validation cohorts accentuates the model's stability.

Clinical utility

Based on the training cohorts' data, the DCA assessed the

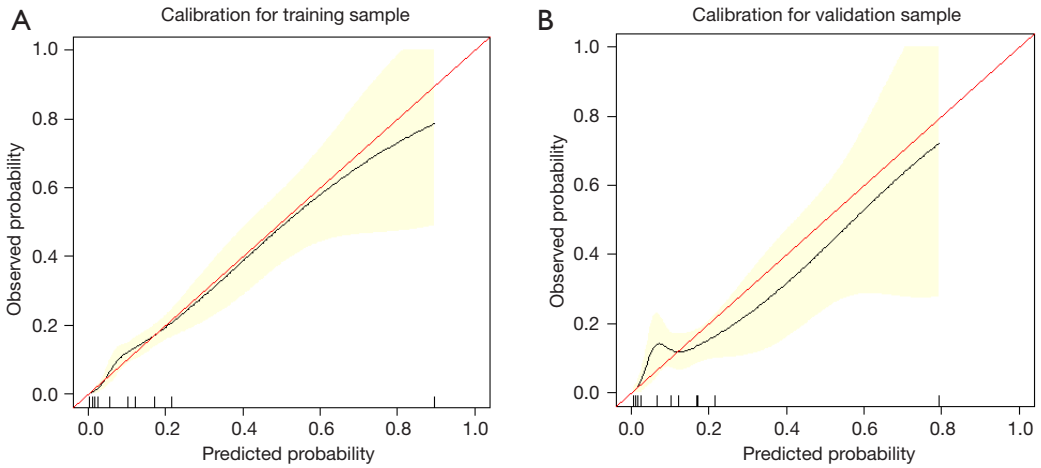

Figure 6 The external calibration curves for the nomogram predicting the probability of lung metastasis. (A) Calibration for training sample. The red line represents perfect prediction. The black line shows the model's performance on the training dataset with the shaded area indicating the 95% CI. (B) Calibration for validation sample. The red line represents perfect prediction. The black line shows the model's performance on the validation dataset with the shaded area indicating the 95% CI. CI, confidence interval.

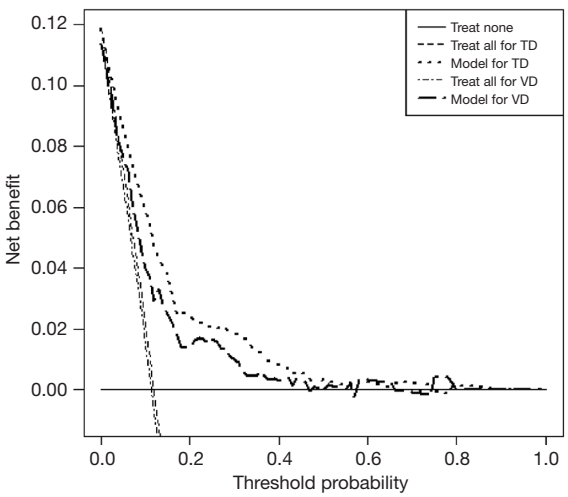

Figure 7 The DCA for the nomogram predicting the probability of lung metastasis. "Treat none" and "Treat all" curves are shown for both training (TD) and validation (VD) datasets. The solid and dashed lines represent the model's performance for training and validation datasets, respectively. The x-axis represents the threshold probability, and the y-axis represents the net benefit. DCA, decision curve analysis.

nomogram's practical applicability and underscored its substantial clinical benefit. As shown in *Figure* 7, the model decision curve for the training dataset (model for TD) demonstrated a higher net benefit across various threshold probabilities compared to the "Treat none" and "Treat all" decisions. This indicated that the model performed well on the training dataset. Similarly, the model decision curve for the validation dataset (model for VD) also exhibited a higher net benefit, confirming the model's reliability and generalizability on an independent dataset (*Figure* 7).

Discussion

We endeavored to create a nomogram to show the risk of lung metastasis derived from data of the SEER database which have not been previously reported. The calculations and the analysis will be conducted among patients with primary bone limb tumor.

The Kaplan-Meier curves (*Figure 2*) illustrate that lung metastasis significantly reduces survival probabilities at both 12 and 30 months (P<0.001 and P=0.001, respectively). This underscores the severe impact of lung metastasis on patient survival, emphasizing the need for early prediction and intervention. The nomogram we developed can aid in this by accurately predicting lung metastasis risk, thereby improving clinical decision-making and patient outcomes. The prediction model contains seven different factors including age, histopathological type, surgery, radiation therapy, chemotherapy, T stage, and N stage. Interestingly, we observed a paradoxical fact: patients who accept chemotherapy or radiation therapy may have an increased risk of lung metastasis. In Zhang *et al.*'s study (19),

although this phenomenon was not discussed separately, the nomogram showed similar results, indicating that radiotherapy increased the probability of pancreatic cancer bone metastasis. This phenomenon may suggest a more aggressive disease phenotype or a selection bias towards non-adjuvant therapies in early-stage tumors, warranting further investigation.

The AUC values reflect a reliable prognostic tool for clinical use, supporting the predictive accuracy of our model. The external calibration curves demonstrate the repeatability of our model, indicating that this nomogram can improve patient outcomes and overall health.

The clinical effectiveness of our nomogram, as shown by the DCA, demonstrates that using it provides more benefit than a treat-all or treat-none approach. Due to the radioactive or invasive nature of computed tomography (CT) and needle biopsy, these methods are not usually used for routine screening of lung metastasis. Lung metastases are typically found by chest CT scanning; however, in previous studies, up to 36% of lung metastases were not detected by CT (20-22). Therefore, our predictive model shows good clinical benefit. This predictive tool will aid in the early detection of metastatic disease, facilitating timely and targeted interventions.

Our study had some limitations. It would undoubtedly be more reliable to verify the results using data from another independent medical institution and the reliance on a single database may have introduced biases as a result of the dataset's demographic and geographic constraints. Moreover, future research has the potential for enhancement due to the deficiency of genomic characteristics in the SEER database.

Conclusions

This study developed a robust nomogram using SEER database data to predict lung metastasis in primary limb bone tumor patients. Incorporating seven key variables, the model demonstrated strong predictive accuracy with AUC values of 0.806 and 0.767 in the training and validation cohorts, respectively. This tool enhances clinical decision-making, enabling timely and personalized interventions. Although further validation in diverse settings is needed due to the SEER database's limitations, this nomogram marks a significant advancement in personalized oncology, improving risk stratification and patient outcomes.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-570/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-570/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-570/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: Huang X, Guo JW, Han F, Zhang DW. Establishment of a nomogram for potential prediction of lung metastasis in patients with primary limb bone tumors: a study based on the SEER database. Transl Cancer Res 2024;13(9):4763-4774. doi: 10.21037/tcr-24-570