Original Article

Nomogram for predicting survival in breast cancer with lung metastasis based on SEER data

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Background: The incidence of breast cancer (BC) has been steadily increasing, highlighting the need for a predictive model to assess the survival prognosis of BC patients. The objective of this research was to formulate a prognostic nomogram framework tailored to forecast survival among individuals diagnosed with BC with lung metastasis (BCLM).

Methods: Our information was sourced from the Surveillance, Epidemiology, and End Results (SEER) database. Individuals who were diagnosed with BC from 2010 to 2015 were selected. The 4,309 collected participants were randomly separated into a training cohort (n=3,231) and a validation cohort (n=1,078). In this study, age, marital status, race, tumor location, laterality, type of primary surgery, surgical margin, tumor grade, tumor (T) stage, node (N) stage, as well as the use of radiotherapy and chemotherapy, were identified as potential prognostic factors. The overall survival (OS) and breast cancer-specific survival (CSS) were defined as the primary endpoints of this study. Univariate and multivariate analyses were conducted to assess the impact of different factors on prognosis. Structured nomograms were developed to improve the prediction of OS and CSS. The concordance index (C-index), receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) were employed to estimate the performance of the nomogram.

Results: The nomograms incorporated age, marital status, race, primary surgery or not, BC subtype, grade, T stage, and the use of chemotherapy or not. The C-index for OS was 0.77, and it was 0.77 in CSS for the training group. The C-indexes for the control group of OS and CSS prediction were 0.78 and 0.78, respectively. ROC curves, calibration plots, and DCA curves displayed excellent predictive validity. The results indicate a median survival time of 1.67 years [95% confidence interval (CI): 1.58–1.83], with a total of 3,640 deaths recorded. Survival time was found to be associated with factors such as age, marital status, race, whether primary site surgery was performed, BC subtype, tumor grade, T stage, and the administration of chemotherapy.

Conclusions: Nomograms were created to predict OS and CSS for individuals diagnosed with BCLM. The nomogram has a reliable and valid prediction power; it could perhaps assist physicians in calculating patients' mortality risk.

Keywords: Nomograms; prognosis; Surveillance, Epidemiology, and End Results program (SEER program); breast neoplasms; lung metastasis

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Introduction

Breast cancer (BC) ranks among the most frequently occurring malignant tumors globally, and it considerably increases morbidity and mortality worldwide (1). Although mortality rates have declined in the recent several years with the development of medical technology, good medical care is not available everywhere. More than 90% of BC-related deaths are associated with metastasis, which mainly occurs in the lungs, bone, liver, and brain (2,3). Isolated mediastinal lymph node metastasis in BC has also been reported (4). Metastatic lung cancer significantly contributes to cancer-related deaths in the United States. Until recent years, the survival outlook over 5 years for individuals with metastatic lung adenocarcinoma has stood at under 5% (5). It is significant to pinpoint the determinants influencing survival in individuals with BC with lung metastasis (BCLM). Wang *et al.* developed a diagnostic and prognostic prediction model for pulmonary metastasis in triple-negative BC (TNBC). The study encompassed 27,048 TNBC patients, identifying age, tumor size, tumor (T)-stage, and node (N)-stage as independent risk factors for those with lung metastasis. Additionally, histological type, marital status, prior surgical history, chemotherapy, and the presence of bone, brain, and lung metastases were determined to be independent prognostic factors for TNBC patients with lung metastasis (6). van Ommen-Nijhof *et al.* conducted a survival prognosis analysis of over 200 oligometastatic BC patients using univariate and multivariate analyses (7). An *et al.* analyzed the relationship between surgical duration and survival time in BC patients using univariate and multivariate analyses (8). Chen *et al.* found that the long non-coding RNAs (lncRNAs) ZNF582-AS1, MALAT1, and AFAP1-AS1 are involved in influencing lymph node metastasis in BC (9). In the aforementioned studies, univariate analysis considered only the relationship between a single variable and the outcome. Although multivariate analysis can provide estimates of the relative risk or impact of each factor on the outcome, it typically relies on certain statistical assumptions (e.g., linear relationships). In practical applications, many relationships among variables may be nonlinear, and violations of these assumptions can diminish the validity of the analysis results. Furthermore, the estimates of relative risk or impact derived from multivariate analysis tend to be abstract, making them challenging for clinicians or decision-makers to interpret and apply directly. Consequently, it is essential to formulate a stratification framework that integrates both the individual's health status and the traits of the cancer. The nomogram is extensively employed as a predictive instrument in the realms of medicine; by combining various predictive and influential factors, the nomogram calculates personalized likelihoods of clinical occurrences. This meets the demand for comprehensive biological and clinical frameworks, thereby facilitating the advancement of personalized medicine. Compared with traditional staging, the accuracy is higher, the prognosis is easier to understand, and the prognosis derived from the nomogram is capable of being seamlessly integrated to aid in clinical medicine strategy-making (10-12). The Surveillance, Epidemiology, and End Results (SEER) database serves as a reputable repository for cancer statistics that documents the morbidity, mortality, and health conditions of a large number of individuals diagnosed with cancer. It is frequently utilized to study the epidemiological characteristics of malignant tumors in various populations (13,14). Since there are few studies on patients with BCLM, the intention of our research was to construct a nomogram to forecast the survival prognosis model in patients with BCLM. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1047/rc).

Highlight box

Key findings

- In this study, a nomogram was constructed to predict the prognosis of patients diagnosed breast cancer (BC) with lung metastasis (BCLM).

What is known and what is new?

- There are few survival prognostic methods for BCLM.
- Through this study, the prognosis of patients with BCLM can be reasonably predicted now.

What is the implication, and what should change now?

- Clinicians can now predict survival outcomes in patients with BCLM more intuitively and easily.

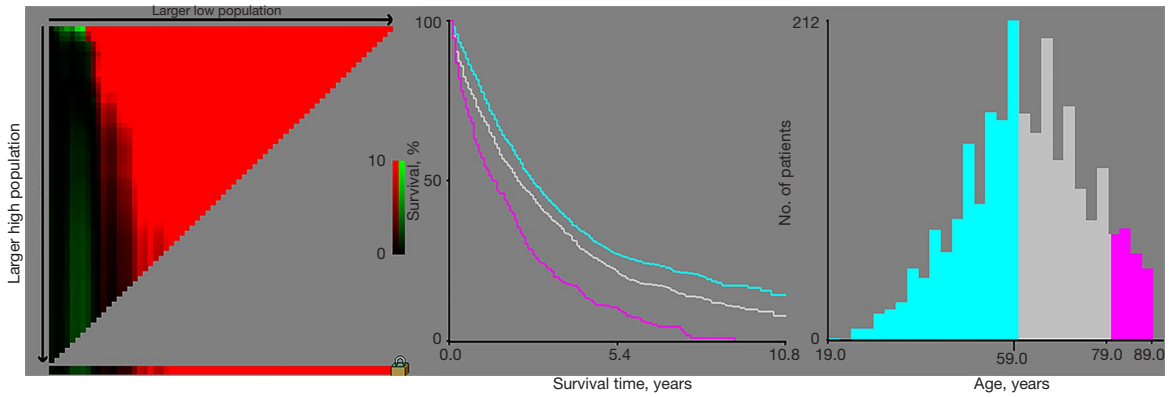

Figure 1 X-tile analysis determined the optimal threshold for the age of diagnosis. The ideal age thresholds based on OS were 59 and 79 years old. Histograms and Kaplan-Meier analyses were constructed using the specified thresholds. The red scale bar represents the percentage of younger individuals, whereas the green scale bar denotes the percentage of older individuals. The curves in the graph correspond to the columns in the histogram: blue lines indicate low-risk age groups, gray lines denote moderate-risk age groups, and purple lines signify high-risk age groups. Blue bar indicates low-risk age groups, gray bar denotes moderate-risk age groups, and purple bar signifies high-risk age groups. OS, overall survival.

Methods

Patient screening

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were collected from 17 registries within the SEER database, comprising individuals diagnosed with BC from 2010 to 2014. The inclusion criteria were as follows: (I) explicit data contains the following: age, marital status, race, tumor site, laterality, primary surgery or not, surgery distance or not, grade, T stage, N stage, radiation or not, chemotherapy or not; (II) patients diagnosed with lung metastasis; (III) the cancer has a precise left or right primary site; (IV) clarity regarding whether the primary site or the distant site is operated on; and (V) the dates of follow-up, survival duration, and reasons for mortality must be ascertained.

Endpoint definition

The primary endpoints encompassed overall survival (OS) and cancer-specific survival (CSS). OS was determined by assessing the time since diagnosis to the occurrence of death from any reason, whereas CSS was determined by examining the time since diagnosis to the event of death specifically attributed to BC.

Prognostic factors

Xu *et al.* found that nine variables, including age, marital status, tumor grade, human epidermal growth factor receptor 2 (HER2) status, chemotherapy, surgery, bone metastasis, lung metastasis, and brain metastasis, were significantly associated with the OS of BC. Additionally, age, marital status, T-stage, tumor grade, HER2 status, chemotherapy, surgery, bone metastasis, lung metastasis, and brain metastasis were identified as independent risk factors for BC-specific survival time (15). Xie *et al.* found that age, histopathology, tumor grade, marital status, bone metastasis, brain metastasis, liver metastasis, HER2 status, estrogen receptor (ER), progesterone receptor (PR), surgery, neoadjuvant therapy, and chemotherapy are independent factors influencing the prognosis of patients with BCLM (16). As a result, this study encompassed the calculation of various factors including age, marital status, sex, race, tumor site, laterality, primary surgery, surgical distance, breast subtype, grade, T stage, and N stage. Age groups were divided into <59, 59–79, and >79 years. The optimal threshold point was determined using the X-tile program (Yale University, New Haven, CT, USA) (*Figure 1*) (17).

Statistical analysis

Individuals were assigned to a training cohort (n=3,231) and a validation cohort (n=1,078) using a randomized approach for developing nomograms. The Chi-squared test and Fisher's exact test were employed to compare groups. Univariate and multivariate analyses were utilized to examine factors influencing prognosis independently.

The Akaike Information Criterion (AIC) is a benchmark used to assess the intricacy of statistical models and gauge the appropriateness of the data fit. The lower the AIC value, the more suitable the model (18-20). The stepwise regression method was employed to uncover predictive elements, as confirmed by multivariate analysis, with the aim of achieving the minimum AIC value.

Nomogram establishment

Nomograms were constructed using essential predictive indicators. The prognostic utility of nomograms was evaluated utilizing the concordance index (C-index), receiver operating characteristic (ROC) curve, and decision curve analysis (DCA) (21). An area under the curve (AUC) >0.7 and a C-index >0.7 generally indicate a reasonably good predictive model (22-24). The calibration curve was structured to estimate if the projected life expectancy aligns with the recorded survival. According to the total score assigned to individuals, the overall risk was categorized into two classifications. Kaplan-Meier curves and the log-rank test were employed to assess the differences between two distinct risk cohorts. The X-tile program was utilized to determine the cut-off points for the risk scores, thereby identifying the optimal cut-off points for the entire cohort. In univariate analysis, a P value <0.1 was considered indicative of statistical significance, whereas in multivariate analysis, a P<0.05 was indicative of statistical significance. Statistical software R (version 4.2.2, available at http://www.r-project.org/) was utilized for the analysis of the dataset.

Results

Patients' baseline profiles

A total of 4,309 cases were counted. The individuals were allocated into a training cohort (n=3,231) and a validation cohort (n=1,078) through a random assignment for the construction of nomograms. Among all the patients, 1,650 (38.29%), 2,101 (48.76%), and 558 (12.95%) were aged <59, 59–79, and >79 years, respectively. Of the total, 1,801 (41.8%) were married, 1,053 (24.44%) were single, and 1,455 (33.77%) had other marital statuses. Furthermore, 65 (1.51%) were male, whereas 4,244 (98.49%) were female. In terms of race, 781 (18.12%) were Black, 3,150 (73.10%) were White, and 378 (8.77%) belonged to other racial groups. Regarding the tumor location, 30 (0.70%) were in the nipple, 406 (9.42%) in the central portion of the breast, 463 (10.74%) in the upper-inner quadrant, 234 (5.43%) in the lower-inner quadrant, 1,382 (32.07%) in the upper-outer quadrant, 344 (7.98%) in the lower-outer quadrant, 45 (1.04%) in the axillary tail of the breast, and 1,405 (32.61%) in overlapping lesions of the breast. Breast distribution included 2,211 (51.31%) in the left breast and 2,098 (48.69%) in the right breast. In terms of surgical intervention, 1,201 (27.87%) underwent primary site tumor surgery, whereas 3,108 (72.13%) did not. Regarding molecular subtypes, 2,333 (54.14%) were luminal A, 739 (17.15%) luminal B, 440 (10.21%) HER2-enriched, and 797 (18.50%) triple-negative. Tumor grading showed 245 (5.69%) as grade I, 1,691 (39.24%) as grade II, and 2,373 (55.07%) as grade III and IV. Tumor size distribution included 464 (10.77%) as T1, 1,200 (27.85%) as T2, 734 (17.03%) as T3, and 1,911 (44.35%) as T4. Lymph node involvement included 1,041 (24.16%) as N0, 2,127 (49.36%) as N1, 521 (12.09%) as N2, and 620 (14.39%) as N3. Treatment details showed that 518 (12.02%) of the patients received radiation, whereas 3,791 (87.98%) did not. Additionally, 2,409 (55.91%) received chemotherapy, whereas 1,900 (44.09%) did not. Demographics and pathology showed no statistically notable distinctions among individuals in the training cohort and the validation cohort (*Table 1*). The results indicate a median survival time of 1.67 years [95% confidence interval (CI): 1.58–1.83], with a total of 3,640 deaths recorded.

Univariate analyses revealed significant statistical associations between OS and age (P<0.001, P<0.001), marital status (P<0.001, P<0.001), race (P<0.001, P<0.001), surgery of primary (P<0.001), breast subtype (P<0.001, P=0.19, P<0.001), grade (P=0.002, P<0.001), T stage (P=0.03, P=0.01, P<0.001), utilization of radiation (P<0.001), and application of chemotherapy (P<0.001) (*Table 2*). Similar associations were observed for CSS, where age (P=0.007, P<0.001), marital status (P<0.001, P<0.001), race (P<0.001, P<0.001), surgery of primary (P<0.001), breast subtype (P=0.001, P=0.17, P<0.001), grade (P<0.001, P<0.001), T stage (P=0.01, P=0.003, P<0.001), utilization of radiation (P<0.001), and application of chemotherapy (P<0.001) showed significant statistical connections (*Table 3*). Age (OS: P=0.050, P<0.001; CSS: P=0.27, P<0.001), marital status (OS: P<0.001, P<0.001; CSS: P<0.001, P<0.001), race (OS: P<0.001, P<0.001; CSS: P=0.001, P<0.001), surgery of primary (OS: P<0.001; CSS: P<0.001), grade (OS: P<0.001, P<0.001; CSS: P<0.001, P<0.001), T stage (OS: P=0.044, P=0.051, P<0.001; CSS: P=0.03, P=0.02, P<0.001), and the decision to use chemotherapy (OS: P<0.001; CSS: P<0.001)

Table 1 Demographic and pathological profiles of the study participants

Characteristics	Total (n=4,309)	Training cohort (n=3,231)	Validation cohort (n=1,078)	P value
Age				0.59
<59 years	1,650 (38.29)	1,245 (38.53)	405 (37.57)	
59–79 years	2,101 (48.76)	1,577 (48.81)	524 (48.61)	
>79 years	558 (12.95)	409 (12.66)	149 (13.82)	
Marital status				0.37
Married	1,801 (41.80)	1,364 (42.22)	437 (40.54)	
Single	1,053 (24.44)	773 (23.92)	280 (25.97)	
Other	1,455 (33.77)	1,094 (33.86)	361 (33.49)	
Sex				0.17
Female	4,244 (98.49)	3,177 (98.33)	1,067 (98.98)	
Male	65 (1.51)	54 (1.67)	11 (1.02)	
Race				0.79
Black	781 (18.12)	589 (18.23)	192 (17.81)	
White	3,150 (73.10)	2,354 (72.86)	796 (73.84)	
Other	378 (8.77)	288 (8.91)	90 (8.35)	
Tumor site				0.38
Nipple	30 (0.70)	27 (0.84)	3 (0.28)	
The central portion of the breast	406 (9.42)	308 (9.53)	98 (9.09)	
Upper-inner quadrant of the breast	463 (10.74)	340 (10.52)	123 (11.41)	
Lower-inner quadrant of the breast	234 (5.43)	176 (5.45)	58 (5.38)	
Upper-outer quadrant of the breast	1,382 (32.07)	1,038 (32.13)	344 (31.91)	
Lower-outer quadrant of the breast	344 (7.98)	270 (8.36)	74 (6.86)	
The axillary tail of the breast	45 (1.04)	33 (1.02)	12 (1.11)	
Overlapping lesion of the breast	1,405 (32.61)	1,039 (32.16)	366 (33.95)	
Laterality				0.31
Left	2,211 (51.31)	1,643 (50.85)	568 (52.69)	
Right	2,098 (48.69)	1,588 (49.15)	510 (47.31)	
Surgery of primary				0.06
No surgery	3,108 (72.13)	2,306 (71.37)	802 (74.40)	
Surgery	1,201 (27.87)	925 (28.63)	276 (25.60)	
Breast subtype				0.60
Luminal A	2,333 (54.14)	1,745 (54.01)	588 (54.55)	
Luminal B	739 (17.15)	548 (16.96)	191 (17.72)	
HER2-enriched	440 (10.21)	326 (10.09)	114 (10.58)	
Triple-negative	797 (18.50)	612 (18.94)	185 (17.16)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=4,309)	Training cohort (n=3,231)	Validation cohort (n=1,078)	P value
Grade				0.45
Grade I	245 (5.69)	180 (5.57)	65 (6.03)	
Grade II	1,691 (39.24)	1,254 (38.81)	437 (40.54)	
Grade III + IV	2,373 (55.07)	1,797 (55.62)	576 (53.43)	
T stage				0.72
T1	464 (10.77)	340 (10.52)	124 (11.50)	
T2	1,200 (27.85)	911 (28.20)	289 (26.81)	
T3	734 (17.03)	548 (16.96)	186 (17.25)	
T4	1,911 (44.35)	1,432 (44.32)	479 (44.43)	
N stage				0.54
N0	1,041 (24.16)	790 (24.45)	251 (23.28)	
N1	2,127 (49.36)	1,602 (49.58)	525 (48.7)	
N2	521 (12.09)	387 (11.98)	134 (12.43)	
N3	620 (14.39)	452 (13.99)	168 (15.58)	
Radiation				0.99
No	3,791 (87.98)	2,842 (87.96)	949 (88.03)	
Yes	518 (12.02)	389 (12.04)	129 (11.97)	
Chemotherapy				0.35
No	1,900 (44.09)	1,411 (43.67)	489 (45.36)	
Yes	2,409 (55.91)	1,820 (56.33)	589 (54.64)	

Data are presented as n (%).

were significantly and statistically related to OS as well as CSS according to the results of multivariate Cox analysis (*Tables 2*,*3*).

Construction and certification of the nomogram

Factors autonomously prognostic were discerned employing a backward stepwise methodology with AIC, with the objective of mitigating data redundancy. Nomograms contained age, marital status, race, primary site surgery or not, breast subtype, grade, T stage, and whether to use chemotherapy (*Figure 2*). Each variable was assigned specific points in the nomogram (*Table 4*). The C-index was 0.77 (95% CI: 0.76–0.78) in OS and 0.77 (95% CI: 0.76–0.78) in CSS for the training set, and 0.78 (95% CI: 0.76–0.8) in OS and 0.78 (95% CI: 0.76–0.8) in CSS in the validation set. Within this training set, the nomogram of OS demonstrated 3- and 5-year AUC values of 0.734 and 0.727, respectively, whereas for CSS, the values were 0.733 and 0.728, respectively (*Figure 3*). The plots illustrating the alignment of predicted and observed outcomes at 3- and 5-year intervals for OS and CSS demonstrated a favorable concordance (*Figures 4*,*5*). The DCA demonstrated that the nomogram exhibited superior predictive capability (*Figures 6*,*7*). In the entirety of the study population, Kaplan-Meier curves revealed that the cohort classified as low-risk demonstrated superior survival outcomes in both OS and CSS when contrasted with the high-risk cohort (*Figure 8*). In the OS cohort, the low-risk cohort demonstrated a higher 5-year OS rate (31.4%) than the high-risk cohort (9.58%, P<0.001). In the CSS cohort, the 5-year CSS rate in the low-risk cohort (35.1%) surpassed that in the high-risk cohort (11.63%, P<0.001).

Discussion

We established a nomogram to evaluate OS and CSS among individuals with BCLM. The C-index and AUC values

Table 2 Univariate and multivariate analyses were conducted to evaluate overall survival within the training set

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
<59 years	Reference group		Reference group	
59–79 years	1.17 (1.07–1.27)	<0.001	1.09 (1–1.19)	0.050
>79 years	1.95 (1.73–2.19)	<0.001	1.61 (1.41–1.84)	<0.001
Marital status				
Married	Reference group		Reference group	
Single	1.34 (1.21–1.47)	<0.001	1.22 (1.11–1.35)	<0.001
Other	1.41 (1.3–1.54)	<0.001	1.19 (1.09–1.3)	<0.001
Sex				
Female	Reference group		–	–
Male	1.03 (0.77–1.37)	0.87	–	–
Race				
Black	Reference group		Reference group	
White	0.79 (0.71–0.87)	<0.001	0.82 (0.74–0.9)	<0.001
Other	0.6 (0.51–0.7)	<0.001	0.65 (0.55–0.76)	<0.001
Tumor site				
Nipple	Reference group		–	–
The central portion of the breast	0.95 (0.62–1.46)	0.83	–	–
Upper-inner quadrant of the breast	1.01 (0.66–1.54)	0.97	–	–
Lower-inner quadrant of the breast	1.08 (0.7–1.68)	0.72	–	–
Upper-outer quadrant of the breast	1.01 (0.67–1.52)	0.98	–	–
Lower-outer quadrant of the breast	0.9 (0.59–1.39)	0.64	–	–
The axillary tail of the breast	0.72 (0.41–1.26)	0.25	–	–
Overlapping lesion of the breast	1.09 (0.72–1.66)	0.67	–	–
Laterality				
Left	Reference group		–	–
Right	1.01 (0.93–1.09)	0.85	–	–
Surgery of primary				
No surgery	Reference group		Reference group	
Surgery	0.64 (0.59–0.7)	<0.001	0.59 (0.54–0.65)	<0.001
Breast subtype				
Luminal A	Reference group		Reference group	
Luminal B	0.8 (0.72–0.9)	<0.001	0.94 (0.84–1.06)	0.32
HER2-enriched	0.91 (0.8–1.05)	0.19	1.16 (1–1.34)	0.04
Triple-negative	1.86 (1.68–2.05)	<0.001	2.32 (2.07–2.6)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Grade				
Grade I	Reference group		Reference group	
Grade II	1.33 (1.11–1.59)	0.002	1.39 (1.16–1.66)	<0.001
Grade III + IV	1.59 (1.33–1.89)	<0.001	1.68 (1.4–2.02)	<0.001
T stage				
T1	Reference group		Reference group	
T2	1.17 (1.01–1.34)	0.03	1.16 (1–1.34)	0.044
T3	1.22 (1.05–1.42)	0.01	1.17 (1–1.36)	0.051
T4	1.43 (1.25–1.64)	<0.001	1.43 (1.24–1.65)	<0.001
N stage				
N0	Reference group		Reference group	
N1	1.01 (0.92–1.11)	0.87	0.99 (0.9–1.1)	0.92
N2	0.89 (0.78–1.02)	0.10	1 (0.87–1.15)	0.98
N3	1.02 (0.9–1.15)	0.81	0.97 (0.85–1.1)	0.62
Radiation				
No	Reference group		Reference group	
Yes	0.69 (0.61–0.78)	<0.001	0.97 (0.85–1.11)	0.64
Chemotherapy				
No	Reference group		Reference group	
Yes	0.62 (0.58–0.67)	<0.001	0.6 (0.55–0.65)	<0.001

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

demonstrated a consistent performance of the nomograms in each of the training and validation sets. The graphical representations of calibration further illustrated the accuracy in predicting OS and CSS. In the context of ROC curve analysis and DCA, we believe that the nomogram has a very strong and accurate ability to predict patient prognosis and survival. This nomogram is invaluable for clinical analysis and prognostic evaluation in BCLM patients, assisting in the development of further individualized treatment plans.

The nomogram consists of several independent general clinical factors. Our study found that age, marital status, race, primary site surgery or not, BC subtype, grade, T stage, and use of chemotherapy can affect the prediction of individuals.

Certain factors are involved in the progression and metastasis of malignant tumors (25). Johnson *et al.* found that younger age is a prognostic risk factor for BC (26), which is consistent with our findings. Younger bodies are generally healthier and better able to withstand the effects of treatments, including surgery, chemotherapy, radiation, targeted therapy, and immunotherapy. Younger people may be more conscious about BC screening; therefore, the cancer is more inclined to be found at an earlier stage and receive better treatment.

Study has shown that single patients have shorter survival and worse outcomes than married patients (27). Our study also showed that in BCLM, unmarried individuals encountered elevated mortality rates in contrast to their married counterparts. The association between marital status and cancer survival may be affected by several factors, including socioeconomic status, family support, mental health, and lifestyle. Married patients may be more likely

Table 3 Univariate and multivariate analyses were conducted to evaluate cancer-specific survival within the training set

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
<59 years	Reference group		Reference group	
59–79 years	1.12 (1.03–1.23)	0.007	1.05 (0.96–1.15)	0.27
>79 years	1.73 (1.52–1.96)	<0.001	1.44 (1.25–1.67)	<0.001
Marital status				
Married	Reference group		Reference group	
Single	1.33 (1.2–1.47)	<0.001	1.21 (1.09–1.34)	<0.001
Other	1.38 (1.26–1.52)	<0.001	1.2 (1.09–1.32)	<0.001
Sex				
Female	Reference group		–	–
Male	1.04 (0.77–1.41)	0.80	–	–
Race				
Black	Reference group		Reference group	
White	0.79 (0.71–0.87)	<0.001	0.83 (0.75–0.92)	0.001
Other	0.58 (0.49–0.69)	<0.001	0.63 (0.53–0.75)	<0.001
Tumor site				
Nipple	Reference group		–	–
The central portion of the breast	0.93 (0.59–1.47)	0.76	–	–
Upper-inner quadrant of the breast	1.04 (0.66–1.64)	0.87	–	–
Lower-inner quadrant of the breast	1.14 (0.71–1.82)	0.58	–	–
Upper-outer quadrant of the breast	1.04 (0.67–1.62)	0.87	–	–
Lower-outer quadrant of the breast	0.97 (0.61–1.53)	0.89	–	–
The axillary tail of the breast	0.69 (0.38–1.28)	0.24	–	–
Overlapping lesion of the breast	1.16 (0.75–1.81)	0.50	–	–
Laterality				
Left	Reference group		–	–
Right	1.02 (0.94–1.1)	0.69	–	–
Surgery of primary				
No surgery	Reference group		Reference group	
Surgery	0.63 (0.58–0.69)	<0.001	0.57 (0.52–0.64)	<0.001
Breast subtype				
Luminal A	Reference group		Reference group	
Luminal B	0.82 (0.73–0.92)	0.001	0.94 (0.83–1.06)	0.29
HER2-enriched	0.9 (0.78–1.04)	0.17	1.09 (0.94–1.27)	0.26
Triple-negative	1.92 (1.74–2.13)	<0.001	2.3 (2.05–2.59)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Grade				
Grade I	Reference group		Reference group	
Grade II	1.43 (1.17–1.74)	<0.001	1.46 (1.2–1.78)	<0.001
Grade III + IV	1.81 (1.49–2.19)	<0.001	1.88 (1.53–2.3)	<0.001
T stage				
T1	Reference group		Reference group	
T2	1.22 (1.05–1.41)	0.01	1.19 (1.02–1.39)	0.03
T3	1.29 (1.09–1.51)	0.003	1.22 (1.03–1.44)	0.02
T4	1.56 (1.35–1.8)	<0.001	1.53 (1.32–1.78)	<0.001
N stage				
N0	Reference group		Reference group	
N1	1.05 (0.95–1.16)	0.36	1.01 (0.91–1.12)	0.83
N2	0.9 (0.78–1.04)	0.14	0.98 (0.84–1.13)	0.76
N3	1.07 (0.93–1.22)	0.35	0.98 (0.85–1.12)	0.76
Radiation				
No	Reference group		Reference group	
Yes	0.72 (0.63–0.81)	<0.001	1 (0.87–1.15)	0.98
Chemotherapy				
No	Reference group		Reference group	
Yes	0.65 (0.6–0.7)	<0.001	0.61 (0.55–0.66)	<0.001

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

to receive family support and care, which can be beneficial in coping with the challenges of cancer treatment and recovery. In addition, marital status could be associated with lifestyle elements, including diet, exercise, and smoking cessation, which can all affect survival rates for cancer patients.

Our study shows that the survival rate of BCLM is lower in people of African descent, and this was also shown by Wang *et al.* (28). Black BC patients may face fewer treatment options and lower treatment compliance. This may be related to economic factors, access to healthcare, cultural factors, and social support. Sometimes, a lack of appropriate treatment or an inability to afford treatment can affect a patient's survival rate. BC has a variety of molecular subtypes, some of which have different sensitivity to treatment. Studies have shown that BC in Black women may be predisposed to more aggressive subtypes (29,30), which may have an impact on treatment response and survival.

There may be several reasons why patients with BCLM who have surgery at the primary site have a better survival rate. Surgery can help to control primary BC by reducing its growth and spread in the breast region, thereby reducing metastasis to the lungs. By removing the primary site, the likelihood that the carcinoma will metastasize to distant sites is reduced. Surgery can reduce the tumor load in the body, which may help to slow or stop the progression of metastases in the lungs. Research has demonstrated that in cases of late-stage TNBC, surgical treatment of the primary tumor significantly improves survival in patients with single distant metastases (31). By lowering the number of cancer cells in the body, it may be possible to reduce the impact on additional bodily areas.

TNBC refers to a type of cancer that is not expressed in

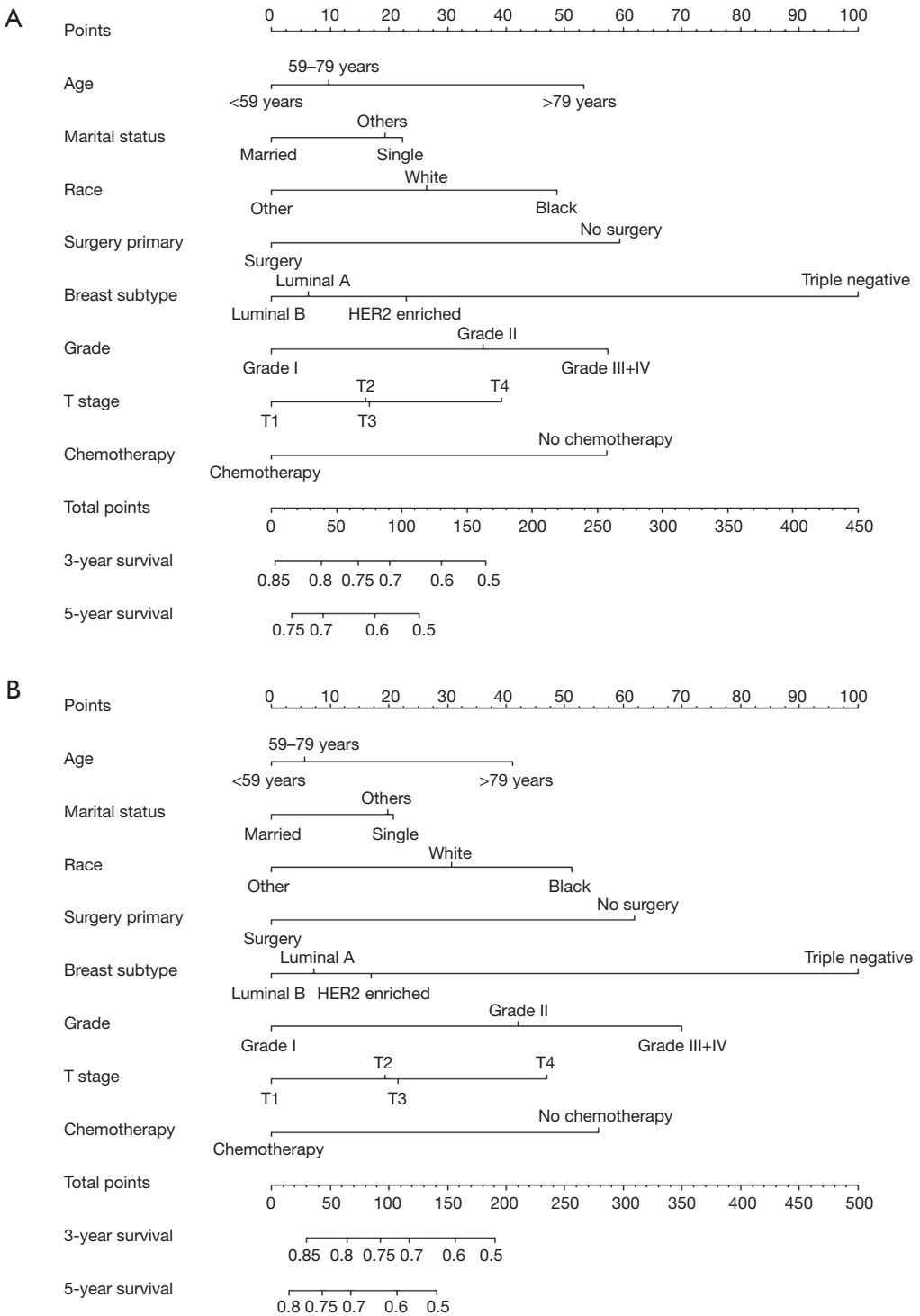

Figure 2 Nomograms for projecting OS (A) and CSS (B) at 3 and 5 years in individuals diagnosed with BCLM. Connect each factor to its corresponding point on the axis with a vertical line to establish the points for each factor. Predicted survival is then calculated by tracing the vertical line that extends from the accumulated points on the scale to intersect with either the OS or CSS axis. BCLM, breast cancer with lung metastasis; CSS, cancer-specific survival; HER2, human epidermal growth factor receptor 2; OS, overall survival.

Table 4 Elaborate the scoring of predictive variables in the nomograms for OS and CSS

Characteristics	OS nomogram	CSS nomogram
Age		
<59 years	0	0
59–79 years	9.72	5.72
>79 years	53.27	41.04
Marital status		
Married	0	0
Single	22.43	20.7
Other	19.36	19.87
Race		
Black	48.71	51.26
White	26.49	30.65
Other	0	0
Surgery of primary		
No surgery	59.36	61.97
Surgery	0	0
Breast subtype		
Luminal A	6.34	7.2
Luminal B	0	0
HER2-enriched	23.02	17.06
Triple-negative	100	100
Grade		
Grade I	0	0
Grade II	36.12	42.05
Grade III + IV	57.38	69.9
T stage		
T1	0	0
T2	16.04	19.38
T3	16.76	21.5
T4	39.18	46.96
Chemotherapy		
No	57.11	55.74
Yes	0	0

CSS, cancer-specific survival; HER2, human epidermal growth factor receptor 2; OS, overall survival.

the ER, PR, and HER2 receptors. This type of cancer limits the applicability of some current treatment options and is generally not sensitive enough to hormone therapy and targeted therapies (32). As a result, patients have relatively few treatment options, which can lead to a relatively poor prognosis. HER2 BC overexpresses HER2, a type of mammary carcinoma that is relatively more aggressive, but the prospects for treatment in these patients have improved due to the availability of drugs targeting HER2, such as herceptin, tyrosine kinase inhibitors, monoclonal antibodies, and antibody-drug conjugates such as DS-8201 (33). Patients with luminal A subtype of BC typically experience a more favorable prognosis compared to those with luminal B subtype, and the favorable outcome of individuals with luminal B type observed within this investigation may be due to the fact that patients with luminal B type have received a more aggressive treatment regimen such as chemotherapy combined with endocrine therapy.

The grade of BC is usually determined by evaluating the cytological and histological characteristics of the tissue sample, including the level of differentiation among the tumor cells, the atypia of the nucleus, and the proliferative activity of the tumor cells. High-grade (grade III and grade IV) BCs usually exhibit the following characteristics: higher cell atypia: cells have a higher degree of abnormalities in morphology and structure; poor cell differentiation: tumor cells are less differentiated than normal breast cells; high proliferative activity: tumor cells proliferate and spread faster (34). These features are often associated with more aggressive tumors, which may lead to a poorer prognosis.

The prognosis deteriorates as the tumor size increases. The larger the primary tumor, the more it indicates that the tumor has been in the breast for a longer time or has developed to a relatively advanced stage.

Research has shown that dose-dense chemotherapy is associated with a more favorable prognosis, indicating its potential preference as a treatment for BC patients; especially for women with lymph node infiltration (35), longer time to adjuvant chemotherapy is probably related to worse survival among patients with BC (36). Research has indicated that supplementary chemotherapy markedly enhances the rates of OS and freedom from distant disease in a broad population (37). Our study shows that patients with BCLM who receive chemotherapy have a better prognosis. Chemotherapy is able to help control

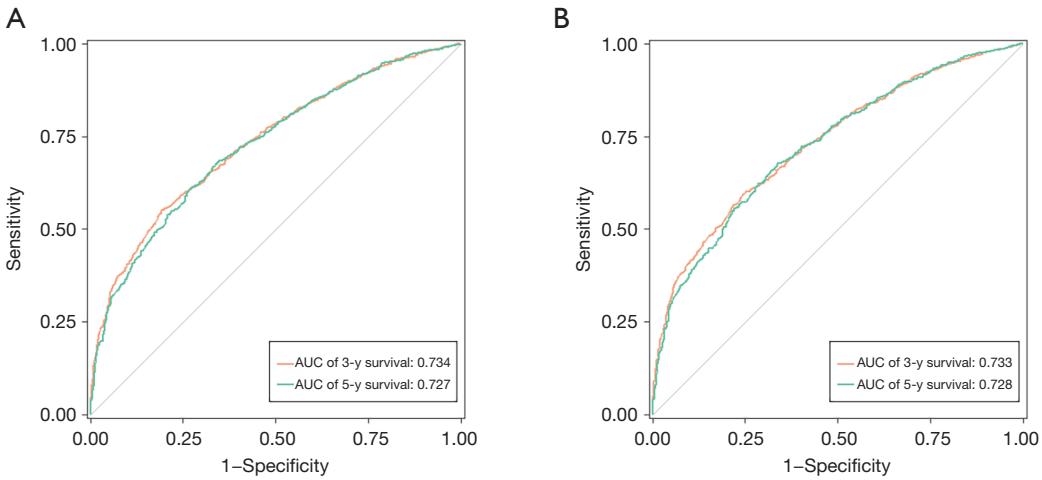

Figure 3 The ROC curves were generated for 3- and 5-year OS (A) and CSS (B) within the training cohort. AUC, area under the curve; CSS, cancer-specific survival; OS, overall survival; ROC, receiver operating characteristic; y, year.

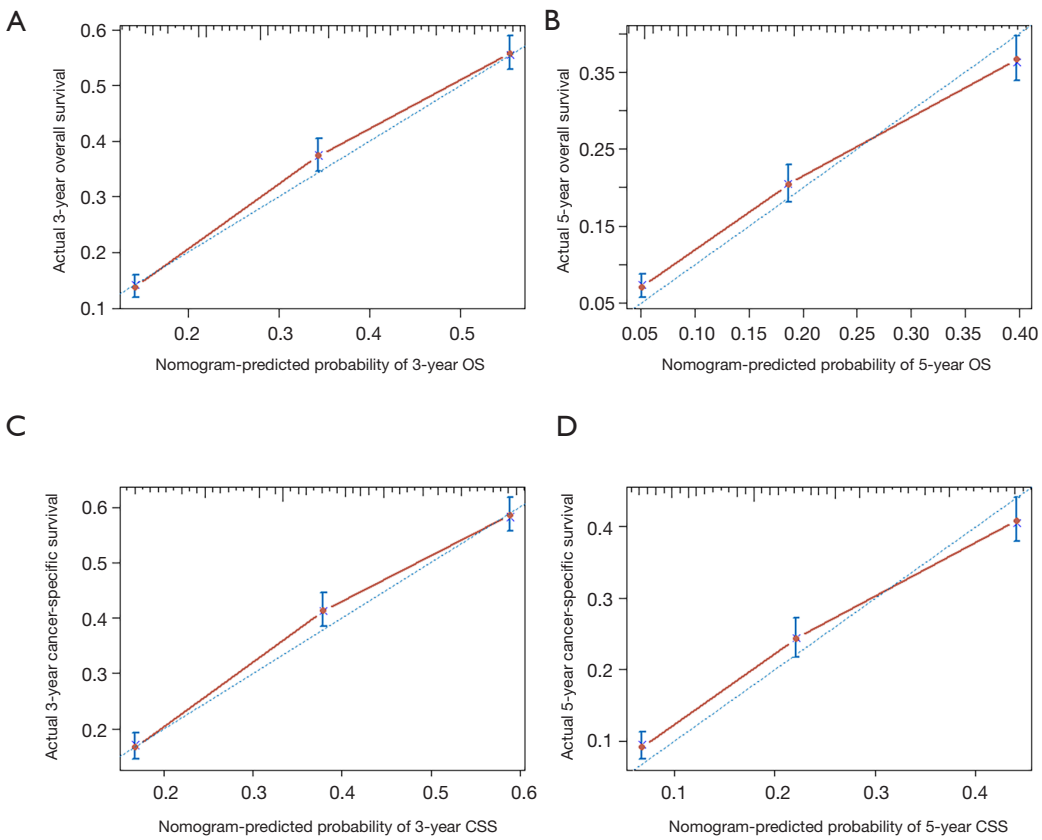

Figure 4 Calibration plot in the training set. Nomogram calibration curves are provided for 3-year (A) and 5-year (B) OS, as well as for 3-year (C) and 5-year (D) CSS. The cohort was stratified into triads, with consistent specimens for internal verification. The dotted lines represent a strong correlation between authentic survival outcomes (y-axis) and nomogram forecasts (x-axis). The more closely the dashed line aligns with the plotted values, the greater the precision of the forecasts. CSS, cancer-specific survival; OS, overall survival.

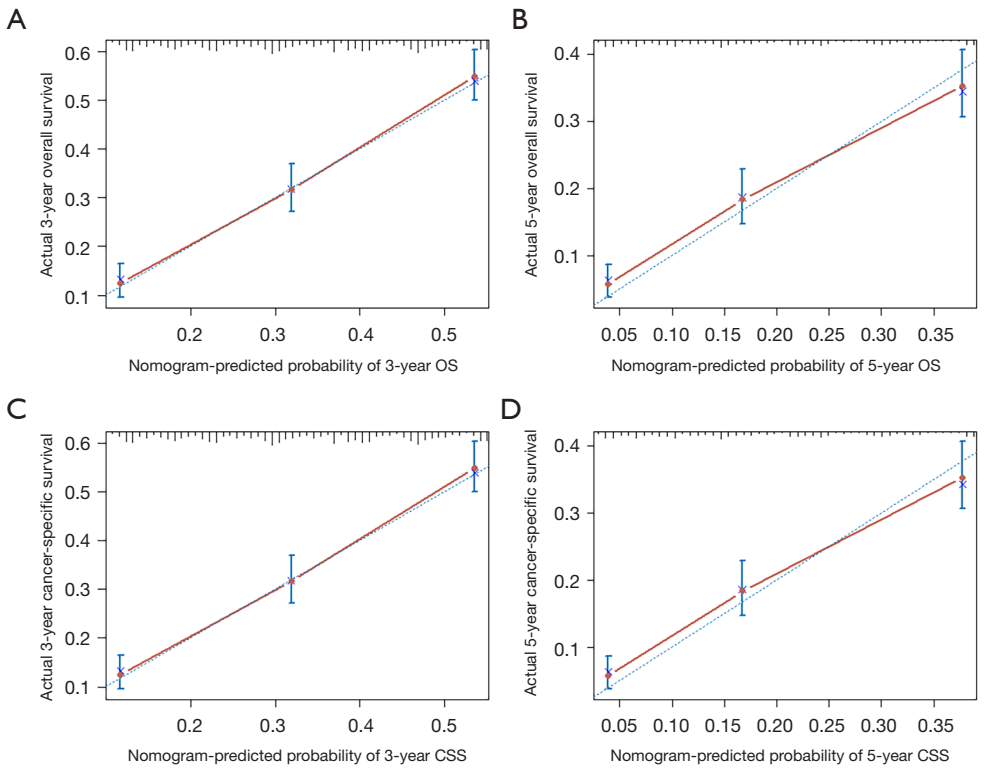

Figure 5 Calibration plots were generated in the validation set. Nomogram calibration curves were constructed for 3-year (A) and 5-year (B) OS, as well as for 3-year (C) and 5-year (D) CSS. The sample was stratified into three groups with equal numbers of participants for external verification. Dashed lines denote optimal alignment between observed survival outcomes (y-axis) and nomogram predictions (x-axis). Proximity of the dashed line to data points indicates elevated forecast precision. CSS, cancer-specific survival; OS, overall survival.

the proliferation and spread of cancer cells, slow the deterioration of the disease, and extend the life expectancy of individuals.

Wang *et al.* found that marital status, previous surgery, and chemotherapy are confirmed to constitute autonomous predictors of prognosis for TNBC patients with BCLM (6). Wang *et al.* also discovered associations between the forecast of individuals with BCLM and factors such as age, marital status, race, grade, American Joint Committee on Cancer (AJCC) T stage, subtype, surgery, and chemotherapy, but not with radiotherapy (38). Chen *et al.* documented that factors such as age, race, marital status, pathological grade, molecular subtype, site of extrapulmonary metastasis, as well as whether surgery and chemotherapy were performed, influenced the outcomes of individuals with BCLM (39). Xiao *et al.* showed that the mortality from all causes and mortality specifically from BC in BCLM were related to molecular subtypes, age, sex, race, marital status, number of distant metastases, and pathological grade (40). These previous findings are generally consistent with this study.

Lymph node staging did not impact the prediction of BC patients experiencing lung metastasis, which may be related to the special condition of lung metastasis. In the case of lung metastasis from BC, it is usually the lungs that have metastases, and the condition of the lymph nodes may have relatively little impact on the development and prognosis of lung metastasis. Lung metastases are usually spread directly from BC cells through the bloodstream to the lungs, rather than through the lymphatic system. Therefore, lymph node involvement often has a limited impact on the treatment and prognosis of lung metastasis. As a consequence, the lymph node stage may not be the main predictor of prognosis of patients with BCLM. Radiation therapy does not directly affect the prognosis of patients with BCLM, possibly because when BC metastases to the lungs, it is usually extensive, meaning that the tumor has metastasized to other areas of the body. In cases of widespread metastasis, radiotherapy targeting a small number of metastases may

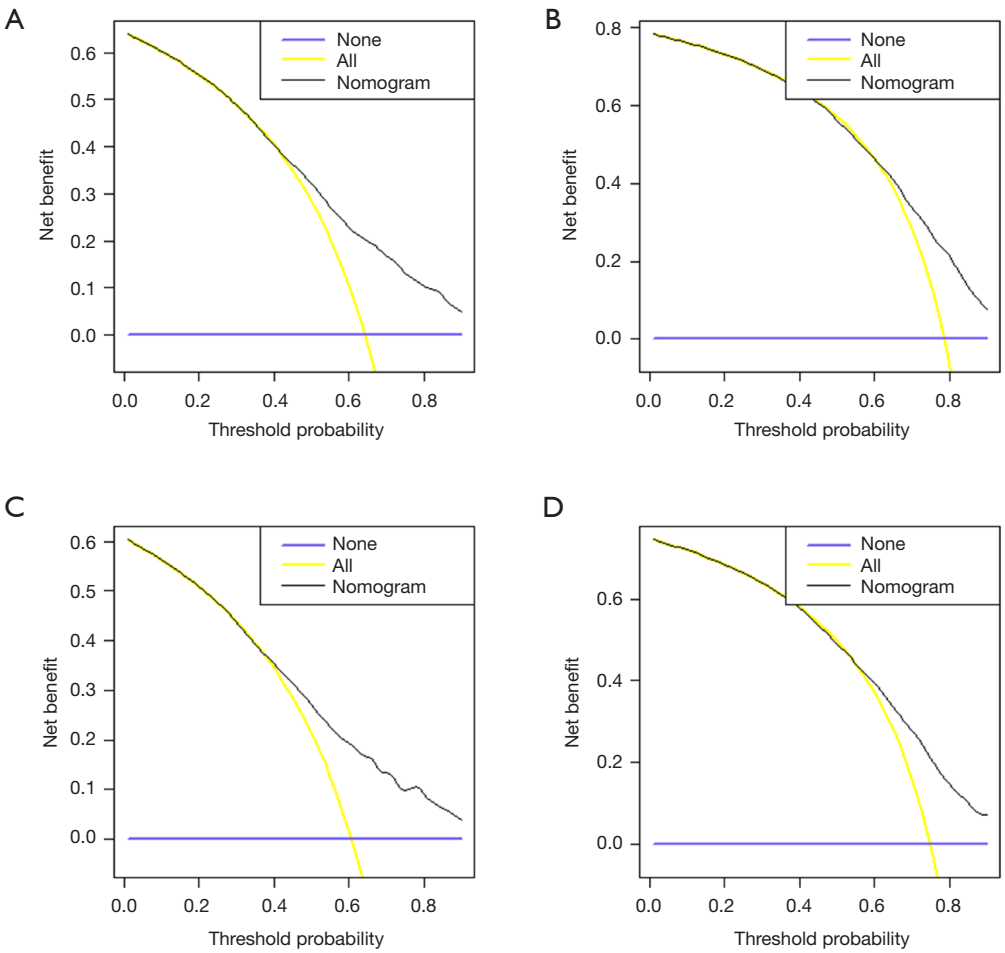

Figure 6 DCA depicting the nomogram's performance within the training dataset. The decision curves illustrate 3-year (A) and 5-year (B) OS, as well as for 3-year (C) and 5-year (D) CSS. The x-axis denotes different probability thresholds, while the y-axis depicts net proceeds derived from the true positive rate minus the false positive rate. When a line extends horizontally across the chart, it signifies that there were no occurrences of patient mortality, and the yellow line suggests that beneath a particular threshold, all individuals will have succumbed. The black line is on behalf of the net proceeds from employing the nomogram. CSS, cancer-specific survival; DCA, decision curve analysis; OS, overall survival.

not be able to fully control the disease. Radiotherapy is recommended for the treatment of lymph node metastasis and palliative care of bone metastasis in BC, but is less effective in patients with lung metastasis (41). Although radiotherapy targeting lung metastases may slow down the advancement of the illness, alleviate symptoms, and enhance overall quality of life to some extent, it may have limited effect on OS extension in patients with BCLM. In addition, Wang *et al.* discovered that the survival of BCLM individuals was not associated with radiotherapy (42). Zhang *et al.* even revealed that local radiotherapy can promote lung metastasis of BC in mice to a certain extent (43).

In oncology and medicine, nomograms are frequently used as prognostic devices. Through the integration of diverse predictive and determining factors, the nomogram formulates individualized likelihoods of clinical outcomes, addressing the need for a prognostic model and fulfilling our quest for tailored medical approaches (44,45). Wu *et al.* used nomograms for predicting the outcome of low-grade endometrial stromal sarcoma (46). A study found that nomograms outperformed AJCC staging in prognosticating individuals' survival diagnosed with small cell lung cancer (47). Therefore, the nomograms exhibit excellent precision in forecasting survival for malignant tumors.

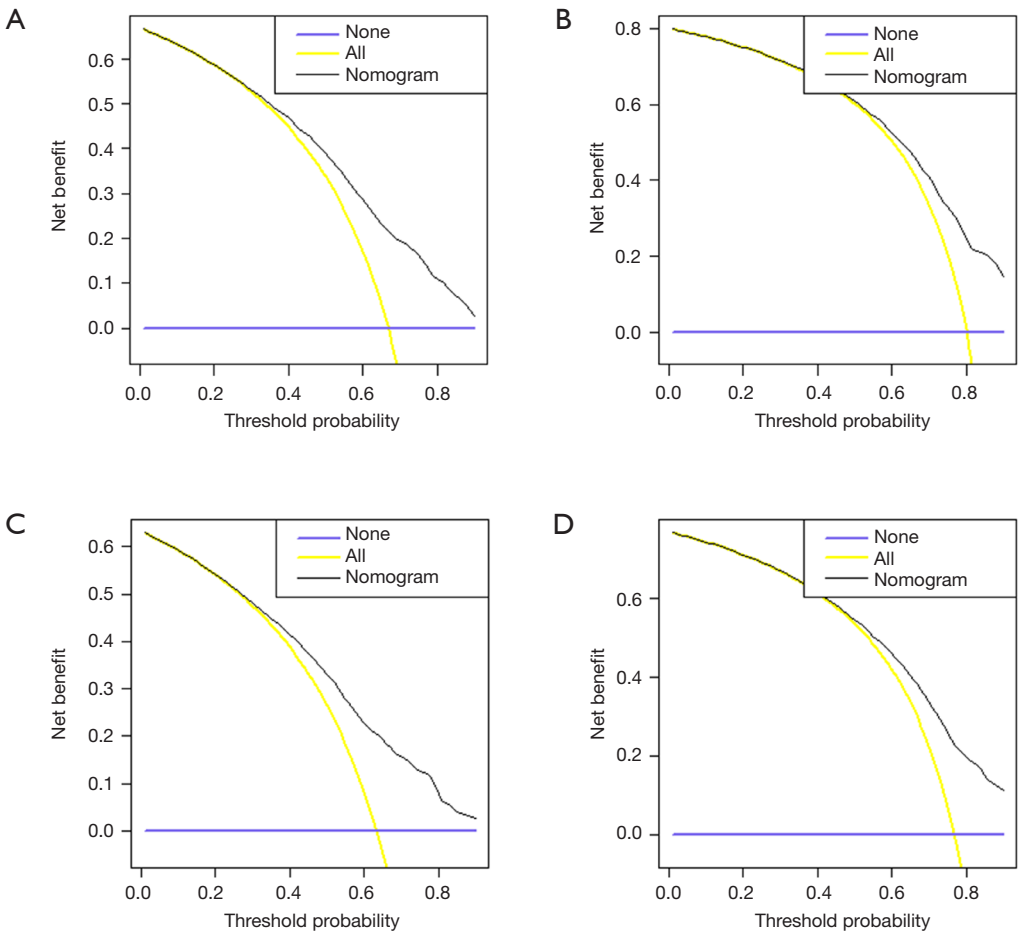

Figure 7 DCA for the nomogram were generated in the validation group, illustrating decision curves for 3-year (A) and 5-year (B) OS, as well as for 3-year (C) and 5-year (D) CSS. Threshold probabilities are represented by the x-axis, while the y-axis demonstrates the net benefit counted by subtracting the false positives rate from the true positives rate. A level line adjacent to the x-axis signifies no patient mortality, whereas a yellow line indicates each individual is predicted to decease below a specific level. The black line illustrates the net benefit obtained from utilizing the nomogram. CSS, cancer-specific survival; DCA, decision curve analysis; OS, overall survival.

Here are the steps to apply our nomograms. First, connect each clinicopathological feature to the "points" line with vertical lines. Each "point" is then aggregated into the "total points", and a vertical marker is drawn extending the "total points" to the "OS" and "CSS" rows. In this way, we can predict survival.

Our research has the following advantages: the SEER database has a long data collection time, a large number of cases, and avoids selection bias. The nomograms transform intricate regression data into a visual graph, enhancing the readability and convenience of evaluating BCLM patient predictions. Rapid calculations through a user-friendly digital interface, coupled with improved accuracy, make nomograms easier to understand than traditional staging.

There are still some limitations to our research. In the framework of a retrospective study, the nomogram still requires validation through prospective studies. The detailed operation of the tumor at the primary site, vascular and nerve infiltration, tumor margin after surgery, the site of lymph node metastasis, and the metastatic tumor size could not be classified and expanded. With the improvement of the database, these problems will receive more attention in the future. Despite these limitations, the nomograms we built still have very good predictive value.

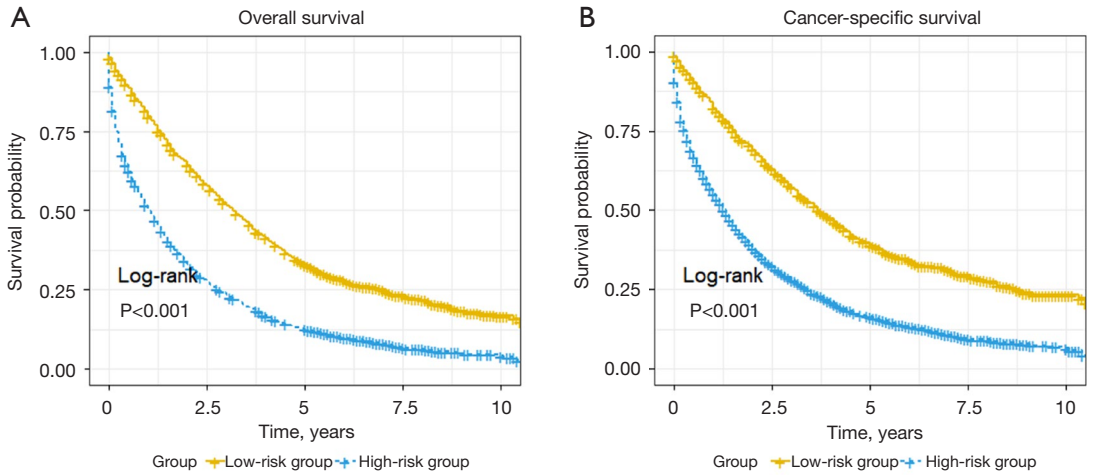

Figure 8 Kaplan-Meier curves illustrating OS and CSS for high- and low-risk patients. CSS, cancer-specific survival; OS, overall survival.

Conclusions

We formulated nomograms for forecasting OS as well as CSS in individuals diagnosed with BCLM. The nomogram has a reliable and valid prediction power; it could perhaps assist physicians in calculating patients' mortality risk. Nevertheless, future clinical studies are needed.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1047/rc

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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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