Prognostic Factors, Predictive Modeling, and Treatment Patterns in Breast Cancer Patients with Bone Metastasis Receiving First-Line Chemotherapy: A Population-Based Study

Ann. Ital. Chir., 2024 95, 6: 1095–1107
https://doi.org/10.62713/aic.3807

Xin Fu[1], Pengfei Cai[1], Zhengqiang Yan[1], Kangshuai Xu[1], Wei Zhao[1], Jinhua Wang[1]

[1]The Orthopedics Department, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, 321000 Jinhua, Zhejiang, China

AIM: The prognostic factors and a nomogram applicable to breast cancer (BC) patients with bone metastasis (BM) who received first-line chemotherapy have not been extensively studied. This study aimed to identify prognostic factors and construct a prognostic nomogram to predict overall survival (OS) in this population.

METHODS: Data for BC patients with BM undergoing first-line chemotherapy were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2016. A total of 2996 BC patients with BM undergoing first-line chemotherapy were included. Age, tumor size, race, tumor grade, breast cancer subtype, brain metastasis, liver metastasis, lung metastasis, surgical intervention, and marital status were identified as independent prognostic factors in the training cohort. Patients were randomly assigned into a training cohort (n = 2100) and an internal validation cohort (n = 896). Prognostic variables were identified using univariate and multivariate Cox Proportional Hazards (Cox) regression analysis. A nomogram was constructed and validated in both cohorts. The discrimination and accuracy of the nomogram were evaluated using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

RESULTS: The areas under the curves (AUCs) for 1-, 2- and 3-year OS were 0.803 (95% confidence interval (CI): 0.752–0.854), 0.785 (95% CI: 0.756–0.814), and 0.767 (95% CI: 0.701–0.803), respectively, in the training cohort, and 0.793 (95% CI: 0.756–0.830), 0.791 (95% CI: 0.761–0.821), and 0.756 (95% CI: 0.719–0.793), respectively, in the validation cohort. The nomogram demonstrated excellent discrimination, calibration, and clinical utility.

CONCLUSIONS: This study developed and validated a robust survival prediction model for breast cancer patients with bone metastasis receiving first-line chemotherapy. The nomogram demonstrates strong predictive performance and can aid clinicians in formulating individualized treatment strategies, thereby improving patient outcomes.

Keywords: breast cancer; bone metastasis; overall survival; prognosis; nomogram; treatment patterns

Introduction

Breast cancer (BC) is the second leading cause of cancer-related mortality among women worldwide [1]. Despite advances in BC treatment, largely driven by the emergence of endocrine and anti- human epidermal growth factor receptor-2 (HER2) therapies, the burden of metastasis breast cancer (mBC) remains substantial. In developing countries, up to 30% of BC patients present with *de novo* metastases at diagnosis [2, 3]. Studies on BC patients with distant metastasis report a median survival time of 1–3 years [4, 5].

Bone is the most common site for BC metastasis, accounting for 55–70% of mBC cases, with a 5-year survival rate as low as 13% [6, 7]. Notably, patients with bone metastasis (BM) frequently experience skeletal-related events, including severe bone pain, pathological fractures, and spinal cord compression, which significantly impact their quality of life [8]. BM in advanced BC is associated with reduced survival rates and the development of severe complications [9, 10].

Generally, BC with BM is considered incurable, and treatment primarily focuses on prolonging survival, alleviating symptoms, and improving quality of life. According to the 5th ESO-ESMO International Consensus Guidelines for advanced BC, systemic palliative chemotherapy is the recommended first-line treatment for mBC rather than locoregional treatment [11]. A multicenter study involving 22,000 women with mBC from the Epidemiological Strategy and Medical Economics (ESME) cohort reported that 63.2%–70.4% of patients received systemic chemotherapy as first-line or adjuvant therapy [12]. However, survival outcomes remain highly heterogeneous in this patient population.

Developing a prognostic model tailored for BC patients with BM undergoing first-line chemotherapy is crucial for

Submitted: 15 October 2024 Revised: 29 November 22024 Accepted: 4 December 2024 Published: 20 December 2024
Correspondence to: Wei Zhao, The Orthopedics Department, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, 321000 Jinhua, Zhejiang, China (e-mail: zhaowei66588@163.com); Jinhua Wang, The Orthopedics Department, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, 321000 Jinhua, Zhejiang, China (e-mail: jinhuawang2024@163.com).

clinical decision-making. Such a model could provide individualized survival predictions, assist clinicians in patient counseling, and optimize follow-up strategies. Additionally, these predictions could inform clinical management and encourage further care for patients with specific prognostic characteristics.

Nomogram-based predictive models have gained prominence with the availability of publicly accessible tumor databases. For instance, Liu *et al.* [13] (2017) developed a nomogram to predict survival in patients with non-metastatic BC following preoperative radiation therapy. However, no study has yet developed a prognostic nomogram specifically for BC patients with BM receiving first-line chemotherapy.

The present study aimed to address this gap by retrospectively analyzing data from the Surveillance, Epidemiology, and End Results (SEER) database. This study aimed to identify independent prognostic factors for overall survival (OS) in BC patients with BM undergoing first-line chemotherapy and to establish a visual nomogram to predict survival outcomes. This tool has the potential to facilitate personalized medical decision-making and improve clinical management for this patient population.

Materials and Methods

Patient Selection

This study included patients identified from the Surveillance, Epidemiology, and End Results (SEER) database [14]. Maintained by the National Cancer Institute, the SEER program is the largest publicly available cancer dataset worldwide. Ethical review and informed consent were exempted as the data did not include personally identifiable information. Since the documentation of specific metastatic sites began in 2010, this retrospective study analyzed patients from 2010 to 2016. A total of 2996 BC patients with BM who received chemotherapy were included and randomly divided into a training cohort (n = 2100) and a validation cohort (n = 896) using a 7:3 ratio.

Inclusion criteria for this study were as follows: (a) Patients aged $\geq$18 years; (b) BM patients diagnosed histologically, and patients received first-line chemotherapy [15, 16]. Exclusion criteria included: (a) Patients with missing key clinicopathology variables; (b) Patients with BC not being the first primary malignant tumor; (c) Patients whose survival duration less than one month. Fig. 1 presents a flowchart illustrating the study design.

Data Elements

Prognosis-related variables for all included patients were retrieved using SEER*Stat software version 8.4.4 (Information Management Service, Inc., Calverton, MD, USA) for further analysis. The demographic factors included age, race, sex, marital status, and insurance status, while tumor characteristics encompassed primary site, laterality, histological type, tumor grade, T stage, N stage, and breast cancer subtype. Moreover, the metastatic sites included the presence of brain, liver, or lung metastases, while treatment factors were surgery, radiotherapy, and chemotherapy.

The primary tumor site was classified according to the International Classification of Diseases for Oncology (ICD-O) codes: central portion (C50.1), upper-inner quadrant (C50.2), lower-inner quadrant (C50.3), upper-outer quadrant (C50.4), lower-outer quadrant (C50.5), and others (C50.0, C50.6, C50.8, and C50.9).

Histological types were classified using the International Classification of Diseases, 10th Revision (ICD-10) codes into invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), IDC and ILC, and others. Breast cancer molecular subtypes were stratified based on hormone receptor (HR) status and human epidermal growth factor receptor-2 (HER2) status into Luminal A, Luminal B, HER2+, and Triple-Negative categories. Surgical interventions were classified as breast-conserving surgery (BCS) or mastectomy, based on the approach to the primary tumor site. Overall survival (OS), defined as the time from initial definite diagnosis to death or the last clinical follow-up, was designated as the primary endpoint for this study.

Statistical Analysis

Baseline data were compared between the training and validation cohorts using the Chi-squared (χ^2) test for categorical variables. Continuous variables, including age and tumor size, were categorized using the X-tile program (3.6.1, Yale University, New Haven, CT, USA) [17]. The optimal cut-off values were 50 and 60 years for age and 42 mm and 84 mm for tumor size.

The construction and validation of the nomogram followed a systematic process. Initially, univariate Cox Proportional Hazards (Cox) regression analysis assessed the association between each variable and OS. Variables with a p-value < 0.05 were considered statistically significant. Subsequently, these significant variables were integrated into a multivariate Cox regression analysis to identify independent prognostic factors. Variables with a p-value < 0.05 in the multivariate analysis were selected as the final predictors. Hazard ratios (HR) and 95% confidence interval (CI) were calculated for each independent prognostic factor.

A visual nomogram was developed using the identified predictors to predict 1-, 2-, and 3-year OS. The performance of the model was validated in the internal validation cohort using the following metrics: (a) Discrimination ability that was measured using receiver operating characteristic (ROC) curve and the area under the curve (AUC); (b) Calibration that was evaluated using calibration curves to compare predicted survival with observed outcomes; (c) Clinical benefits that were assessed using decision curve analysis (DCA) [18].

Additionally, Kaplan-Meier survival analysis was performed, and log-rank tests were used to compare OS across

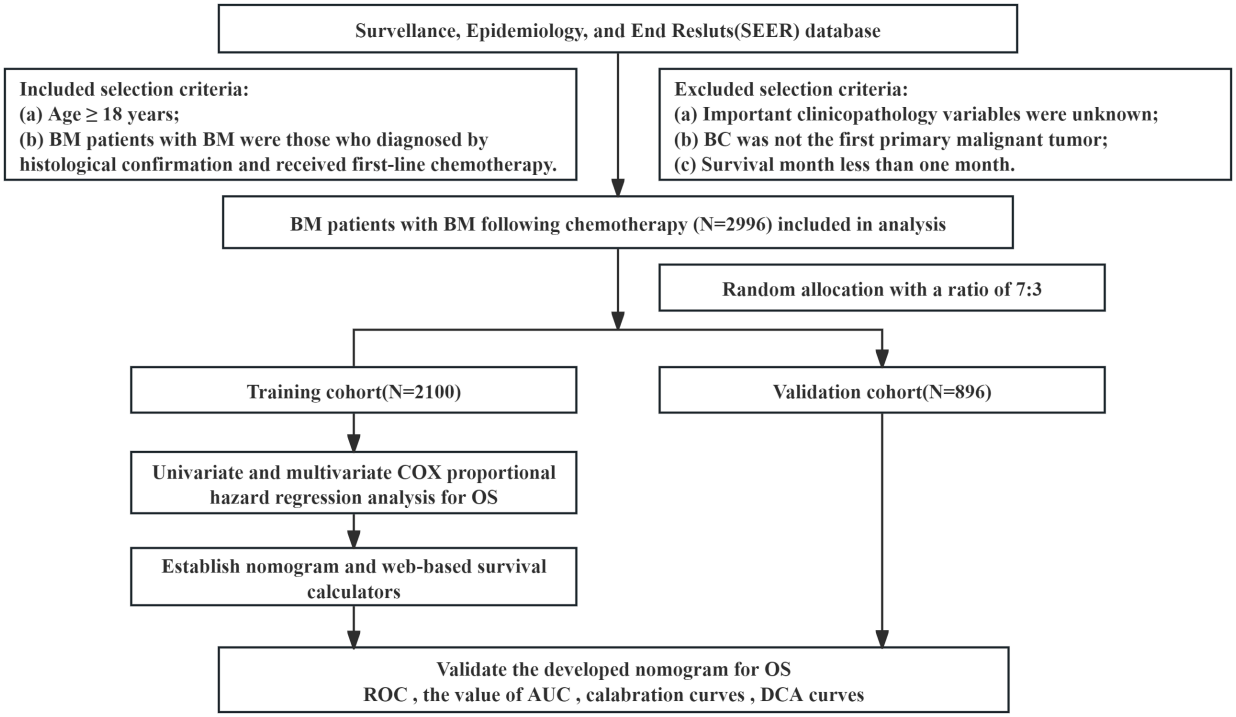

Fig. 1. Patient screening and study design flowchart. BM, bone metastasis; BC, breast cancer; OS, overall survival; Cox, Cox Proportional Hazards; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

different risk subgroups. All statistical analyses were performed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA), and figure plots were generated using R software (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria; available at https://www.r-project.org). X-tile software was used to calculate optimal cut-off values. A p-value < 0.05 was considered statistically significant for all tests.

Results

Patient Baseline Characteristics

A total of 2996 BC patients with BM receiving first-line chemotherapy were included in this study. These patients were divided into a training cohort (n = 2100) and a validation cohort (n = 896) at a 7:3 ratio. In the training cohort, a significant majority of the patients were female (n = 2075, 98.8%) compared to male patients (n = 25, 1.2%). Based on the age optimal cut-off values determined by the X-tile program, patients were categorized into three age groups: <50 years (n = 656, 31.2%), 50–60 years (n = 719, 34.2%), and >60 years (n = 725, 34.5%). In terms of racial distribution, the majority were White (n = 1547, 73.7%). Additional metastatic sites were observed in some patients, including brain metastasis (n = 131, 6.2%), liver metastasis (n = 585, 27.9%), and lung metastasis (n = 523, 24.9%). More than a third of the patients received surgery and radiotherapy as part of their treatment, with mastectomy being the predominant surgical approach. Detailed clinicopathological characteristics of patients are summarized in Table 1.

Independent Prognostic Factors for BC Patients with BM Undergoing Chemotherapy

Univariate analysis identified several variables significantly associated with OS, including age, tumor size, race, tumor grade, breast cancer subtype, T stage, histological type, liver metastasis, lung metastasis, brain metastasis, surgery, radiotherapy, and marital status. These variables were subsequently included in a multivariate Cox regression analysis. The results revealed that age, race, tumor size, tumor grade, breast cancer subtype, brain metastasis, liver metastasis, lung metastasis, surgery, and marital status were independent prognostic factors for OS in BC patients with BM receiving chemotherapy (all $p < 0.05$, Table 2).

A nomogram was constructed to predict 1-, 2-, and 3-year OS for this population (Fig. 2). Each condition of the prognostic variables was assigned a score on a graduated scale, allowing the calculation of total points to estimate individual survival possibilities at specific points. Among the variables, the breast cancer subtype emerged as the most influential prognostic factor in BC patients with BM, with triple-negative breast cancer carrying the highest risk (maximum score of 100 points). The Luminal A and HER2+ subtypes followed this, while the Luminal B subtype presented the lowest risk. Additionally, our study revealed that marital status had the least significant impact on prognosis.

Table 1. Baseline data of BC patients with BM receiving first-line chemotherapy.

Variables	Initial cohort (2996 cases)	Training cohort (2100 cases)	Internal validation cohort (896 cases)	χ^2	*p*-value
Age (years)				1.109	0.574
<50	945 (31.5%)	656 (31.2%)	289 (32.3%)		
50–60	1008 (33.6%)	719 (34.2%)	289 (32.3%)		
>60	1043 (34.8%)	725 (34.5%)	318 (35.5%)		
Tumor size				1.842	0.398
<42	1466 (48.9%)	1038 (49.4%)	428 (47.8%)		
42–84	1103 (36.8%)	757 (36.0%)	346 (38.6%)		
>84	427 (14.3%)	305 (14.5%)	122 (13.6%)		
Race				3.586	0.166
Black	525 (17.5%)	362 (17.2%)	163 (18.2%)		
Other[a]	254 (8.5%)	191 (9.1%)	63 (7.0%)		
White	2217 (74.0%)	1547 (73.7%)	670 (74.8%)		
Sex				2.974	0.085
Female	2953 (98.6%)	2075 (98.8%)	878 (98.0%)		
Male	43 (1.4%)	25 (1.2%)	18 (2.0%)		
Primary site				6.024	0.304
Central portion	200 (6.7%)	142 (6.8%)	58 (6.5%)		
Lower-inner quadrant	123 (4.1%)	89 (4.2%)	34 (3.8%)		
Lower-outer quadrant	172 (5.7%)	124 (5.9%)	48 (5.4%)		
Upper-inner quadrant	216 (7.2%)	147 (7.0%)	69 (7.7%)		
Upper-outer quadrant	808 (27.0%)	542 (25.8%)	266 (29.7%)		
Others	1477 (49.3%)	1056 (50.3%)	421 (47.0%)		
Laterality				1.261	0.262
Left	1535 (51.2%)	1090 (51.9%)	445 (49.7%)		
Right	1461 4(8.8%)	1010 (48.1%)	451 (50.3%)		
Histological type				0.069	0.995
IDC	2386 (79.6%)	1675 (79.8%)	711 (79.4%)		
IDC and ILC	139 (4.6%)	97 (4.6%)	42 (4.7%)		
ILC	238 (7.9%)	166 (7.9%)	72 (8.0%)		
Others	233 (7.8%)	162 (7.7%)	71 (7.9%)		
Tumor grade				1.476	0.688
Grade I	194 (6.5%)	141 (6.7%)	53 (5.9%)		
Grade II	1274 (42.5%)	880 (41.9%)	394 (44.0%)		
Grade III	1512 (50.5%)	1068 (50.9%)	444 (49.6%)		
Grade IV	16 (0.5%)	11 (0.5%)	5 (0.6%)		
Breast subtype				4.226	0.238
Luminal A	1613 (53.8%)	1107 (52.7%)	506 (56.5%)		
Luminal B	696 (23.2%)	494 (23.5%)	202 (22.5%)		
HER2+	279 (9.3%)	200 (9.5%)	79 (8.8%)		
Triple-negative	408 (13.6%)	299 (14.2%)	109 (12.2%)		
T stage				0.942	0.815
T1	360 (12.0%)	248 (11.8%)	112 (12.5%)		
T2	1073 (35.8%)	760 (36.2%)	313 (34.9%)		
T3	612 (20.4%)	433 (20.6%)	179 (20.0%)		
T4	951 (31.7%)	659 (31.4%)	292 (32.6%)		
N stage				2.582	0.461
N0	535 (17.9%)	375 (17.9%)	160 (17.9%)		
N1	1480 (49.4%)	1055 (50.2%)	425 (47.4%)		
N2	454 (15.2%)	312 (14.9%)	142 (15.8%)		
N3	527 (17.6%)	358 (17.0%)	169 (18.9%)		
Surgery				1.856	0.395
BCS	343 (11.4%)	251 (12.0%)	92 (10.3%)		
Mastectomy	919 (30.7%)	644 (30.7%)	275 (30.7%)		
None	1734 (57.9%)	1205 (57.4%)	529 (59.0%)		

Table 1. Continued.

Variables	Initial cohort (2996 cases)	Training cohort (2100 cases)	Internal validation cohort (896 cases)	χ^2	*p*-value
Radiotherapy				0.490	0.484
No	1703 (56.8%)	1185 (56.4%)	518 (57.8%)		
Yes	1293 (43.2%)	915 (43.6%)	378 (42.2%)		
Brain metastasis				0.048	0.826
No	2811 (93.8%)	1969 (93.8%)	842 (94.0%)		
Yes	185 (6.2%)	131 (6.2%)	54 (6.0%)		
Liver metastasis				0.026	0.871
No	2164 (72.2%)	1515 (72.1%)	649 (72.4%)		
Yes	832 (27.8%)	585 (27.9%)	247 (27.6%)		
Lung metastasis				0.072	0.788
No	2254 (75.2%)	1577 (75.1%)	677 (75.6%)		
Yes	742 (24.8%)	523 (24.9%)	219 (24.4%)		
Insurance status				0.280	0.597
Insured	2877 (96.0%)	2014 (95.9%)	863 (96.3%)		
Uninsured	119 (4.0%)	86 (4.1%)	33 (3.7%)		
Marital status				1.601	0.206
Married	1561 (52.1%)	1110 (52.9%)	451 (50.3%)		
Unmarried	1435 (47.9%)	990 (47.1%)	445 (49.7%)		

Data notes: [a]Includes: American Indian, Native Alaskan, and Asian, Pacific Islander; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor-2.

Construction and Validation of the Nomogram

The nomogram underwent internal validation using bootstrap resampling and subsequently cross-validated with the validation cohort. The predictive performance of the nomogram is summarized in Table 3. Significant predictive accuracy was observed at all time points (all $p < 0.05$). ROC curves showed that the AUC values for the nomogram at 1-, 2-, and 3-year OS were 0.803, 0.785, and 0.767, respectively, in the training cohort (Fig. 3A) and 0.793, 0.791, and 0.756, respectively, in the validation cohort (Fig. 3E). Additionally, the nomogram outperformed individual prognostic factors, exhibiting the highest AUC values in the training cohort (Fig. 3B–D) and the validation cohort, demonstrating the strongest predictive ability (Fig. 3F–H). Calibration curves confirmed excellent consistency between predicted and observed survival probabilities for BC patients with BM undergoing chemotherapy (Fig. 4A,C). The DCA also demonstrated the clinical utility of the nomogram in survival prediction (Fig. 4B,D). A risk stratification system was developed based on the nomogram scores, dividing patients into high-risk (508–644 points), intermediate-risk (432–507 points), and low-risk (312–431 points) groups. Kaplan-Meier survival curves and survival status analysis revealed that patients in the high-risk group had significantly poorer OS compared to those in the intermediate- and low-risk groups (Fig. 5).

Discussion

Previous studies have consistently demonstrated that the bone is the most common metastatic site in BC patients [19, 20]. The prognosis for BC patients presenting with BM at initial diagnosis is particularly poor. A recent retrospective study by Tripathy *et al*. [21] reported that 89.7% of *de novo* mBC patients with HER2-positive disease received first-line chemotherapy. However, a reliable clinical model tailored to BC patients with BM receiving chemotherapy has not been established. To address this gap, we conducted a real-world study to develop and validate a survival prediction model for this population to guide prognosis and clinical management.

In this study, ten variables were identified as independent prognostic factors for OS in BC patients with BM undergoing chemotherapy. Among these prognostic factors, breast cancer subtype emerged as the most significant factor, followed by tumor grade, liver metastasis, brain metastasis, and surgery, which displayed moderate impacts. Age, race, tumor size, lung metastasis, and marital status also contributed but had relatively modest influences. A visual prognostic nomogram incorporating these variables was constructed and validated in the training and validation cohorts. This nomogram exhibited robustness, accuracy, reliability, and practical utility in patient counseling and risk-adapted clinical-decision making. Notably, the parameters included in the nomogram are routinely accessible in clinical practice.

Table 2. Cox regression analysis of BC patients with BM receiving first-line chemotherapy.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age				
<50	Reference		Reference	
50–60	1.410 (1.210–1.643)	<0.001	1.237 (1.058–1.445)	0.007
>60	1.622 (1.410–1.884)	<0.001	1.514 (1.300–1.765)	<0.001
Tumor size				
<42	Reference		Reference	
42–84	1.150 (1.007–1.314)	0.040	1.022 (0.858–1.219)	0.804
>84	1.789 (1.517–2.109)	<0.001	1.396 (1.128–1.729)	0.002
Race				
Black	Reference		Reference	
Other[a]	0.693 (0.544–0.883)	0.003	0.729 (0.569–0.934)	0.012
White	0.696 (0.600–0.808)	<0.001	0.789 (0.677–0.920)	0.002
Sex				
Female	Reference			
Male	1.252 (0.709–2.212)	0.439		
Primary site				
Central portion	Reference			
Lower-inner quadrant	1.239 (0.869–1.766)	0.237		
Lower-outer quadrant	0.862 (0.604–1.232)	0.415		
Upper-inner quadrant	1.122 (0.878–1.435)	0.357		
Upper-outer quadrant	1.011 (0.731–1.398)	0.948		
Others	1.101 (0.850–1.417)	0.467		
Laterality				
Left	Reference			
Right	1.049 (0.931–1.182)	0.431		
Tumor grade				
Grade I	Reference		Reference	
Grade II	1.254 (0.942–1.669)	0.121	1.326 (0.992–1.774)	0.057
Grade III	1.808 (1.366–2.395)	<0.001	1.685 (1.254–2.265)	0.001
Grade IV	4.441 (2.318–8.509)	<0.001	2.304 (1.186–4.479)	0.014
Histological type				
IDC	Reference		Reference	
IDC and ILC	0.958 (0.722–1.271)	0.768	1.264 (0.947–1.687)	0.112
ILC	0.866 (0.687–1.092)	0.223	1.067 (0.832–1.367)	0.609
Others	1.264 (1.023–1.563)	0.030	1.141 (0.921–1.414)	0.229
T stage				
T1	Reference		Reference	
T2	0.991 (0.802–1.224)	0.933	1.114 (0.895–1.386)	0.333
T3	1.364 (1.091–1.704)	0.006	1.199 (0.907–1.585)	0.203
T4	1.466 (1.189–1.809)	<0.001	1.076 (0.839–1.380)	0.565
N stage				
N0	Reference			
N1	0.999 (0.847–1.176)	0.986		
N2	0.972 (0.790–1.197)	0.789		
N3	1.074 (0.889–1.322)	0.423		
Breast cancer subtype				
Luminal A	Reference		Reference	
Luminal B	0.807 (0.687–0.948)	0.009	0.641 (0.541–0.759)	<0.001
HER2+	1.009 (0.811–1.255)	0.935	0.668 (0.530–0.841)	0.001
Triple-negative	2.959 (2.529–3.450)	<0.001	2.516 (2.125–2.978)	<0.001
Brain metastasis				
No	Reference		Reference	
Yes	2.266 (1.837–2.796)	<0.001	1.676 (1.337–2.102)	<0.001

Table 2. Continued.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Liver metastasis				
No	Reference		Reference	
Yes	2.157 (1.905–2.443)	<0.001	2.100 (1.835–2.404)	<0.001
Lung metastasis				
No	Reference		Reference	
Yes	1.896 (1.669–2.155)	<0.001	1.396 (1.215–1.604)	<0.001
Surgery				
BCS	Reference		Reference	
Mastectomy	1.376 (1.094–1.731)	0.006	1.213 (0.957–1.539)	0.111
No	2.401 (1.936–2.977)	<0.001	1.993 (1.585–2.505)	<0.001
Radiotherapy				
No	Reference		Reference	
Yes	0.882 (0.783–0.995)	0.041	1.053 (0.926–1.197)	0.434
Insurance status				
Insured	Reference			
Uninsured	1.131 (0.851–1.502)	0.396		
Marital status				
Married	Reference		Reference	
Unmarried	1.248 (1.108–1.406)	<0.001	1.202 (1.063–1.358)	0.003

Data notes: [a]Includes: American Indian, Native Alaskan and Asian, Pacific Islander; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BCS, breast-conserving surgery.

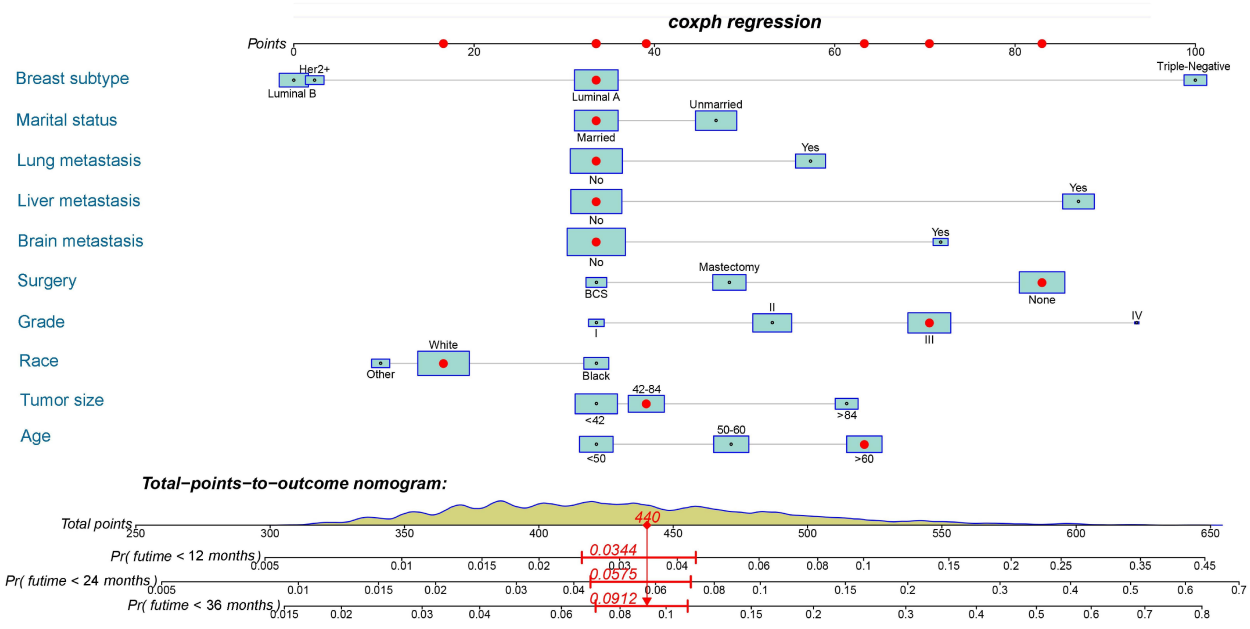

Fig. 2. Nomograms for predicting 1-, 2-, and 3-year OS in BC patients with BM receiving chemotherapy. The nomogram visually represents independent risk factors and their respective scores on a points scale. The total score was calculated by summing the individual scores and is then used to estimate the patient's survival probability over 1, 2, and 3 years.

This study differs from previous research in several key aspects. For instance, Xiong *et al*. [22] investigated 634 mBC patients diagnosed from 2004 to 2011, with 36.9% having bone or soft tissue metastases. However, their study was not specifically designed for BC patients with BM who received chemotherapy, and significant variables such as age, tumor grade, race, insurance status, and marital status were not included. Our findings align with evidence suggest-

Table 3. The cut-off values, AUC (95% confidence interval (CI)), and *p*-values for ROC curves.

Cohort	Time point	Cut-off	AUC (95% CI)	*p*-value
Training cohort	12-month	0.225	0.803 (0.752–0.854)	0.031
	24-month	0.214	0.785 (0.756–0.814)	0.042
	36-month	0.211	0.767 (0.701–0.803)	0.029
Validation cohort	12-month	0.216	0.793 (0.756–0.830)	0.012
	24-month	0.212	0.791 (0.761–0.821)	0.033
	36-month	0.208	0.756 (0.719–0.793)	0.022

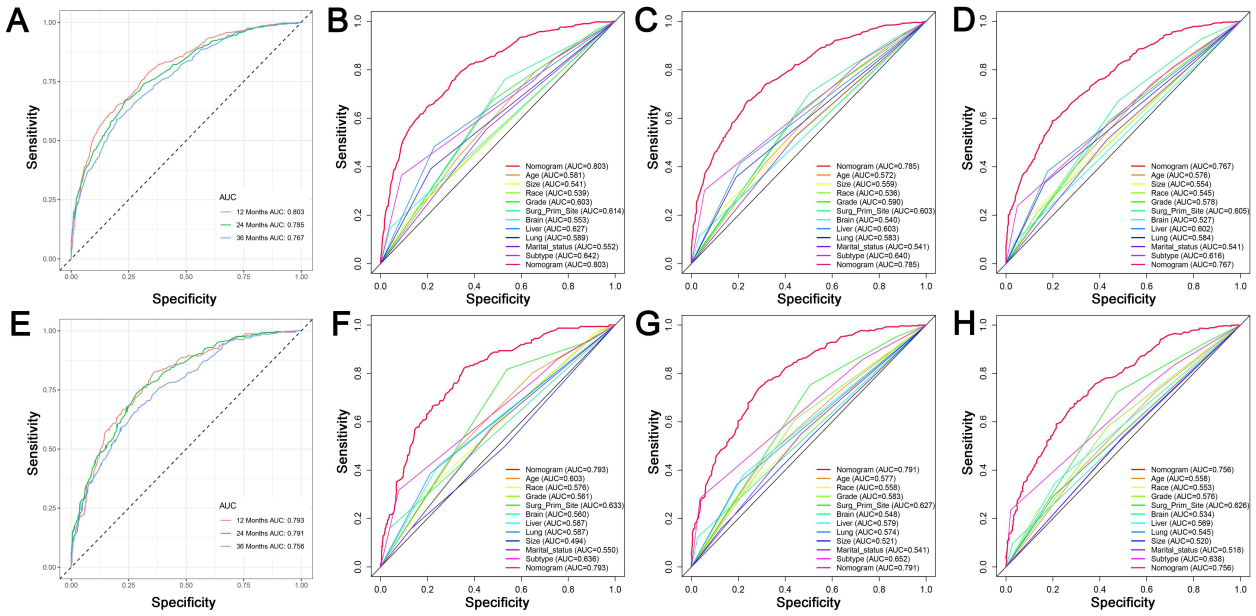

Fig. 3. Receiver operating characteristic (ROC) curves for the nomogram in the training cohort and validation cohort. (A–D) (A) shows the ROC curve for the nomogram in the training cohort. Present ROC curves and comparisons of the area under the curve (AUC) between the nomogram and individual independent prognostic factors at 1 year (B), 2 years (C), and 3 years (D) in the training cohort. (E–H) (E) shows the ROC curve for the nomogram in the validation cohort. Corresponding analyses in the validation cohort at 1 year (F), 2 years (G), and 3 years (H).

ing that marital status provides robust psychological and financial support, enhancing survival outcomes in advanced-stage cancer patients [23, 24]. Married individuals benefit from shared emotional burdens, which may contribute to better prognoses [25, 26].

Poor survival outcomes in our cohort were also associated with advanced age, poorer tumor histological differentiation, and larger primary tumor size, consistent with previous studies [27, 28]. Moreover, our study uniquely differentiates between *de novo* and recurrent mBC, as *de novo* BM patients typically exhibit better prognoses compared to those with recurrent BM following primary treatment [29, 30]. This may be due to factors such as solitary metastases at the time of primary diagnosis and the absence of chemotherapy resistance, which enhance therapeutic sensitivity and improve outcomes. All these meant that accurate survival prediction of *de novo* patients made more sense.

BC has long been considered an endocrine-related malignancy, with seminal findings by Beatson [31] showing tumor regression after oophorectomy in advanced BC patients. Additionally, the immunohistochemical expression of HER2 has been established as a critical determinant in therapeutic strategies [32, 33]. Patients with triple-negative BC, which lacks specific therapeutic targets, exhibit the poorest survival outcomes among all BC subtypes [34]. Consistently, our study showed that triple-negative BC had the most significant negative impact on survival in BC patients with BM receiving chemotherapy.

Our findings also highlight the survival benefits of surgery in BC patients with BM undergoing chemotherapy. Surgery may reduce the source of new metastases and reverse tumor-induced immunosuppression, improving outcomes [35, 36]. To the best of our knowledge, this study is the first to focus on survival prediction for BC patients with BM presenting simultaneously with brain, liver, and lung metastases. Patients with BM and additional metastases had significant worse prognoses than those without such metastatic diseases. These observations can be attributed

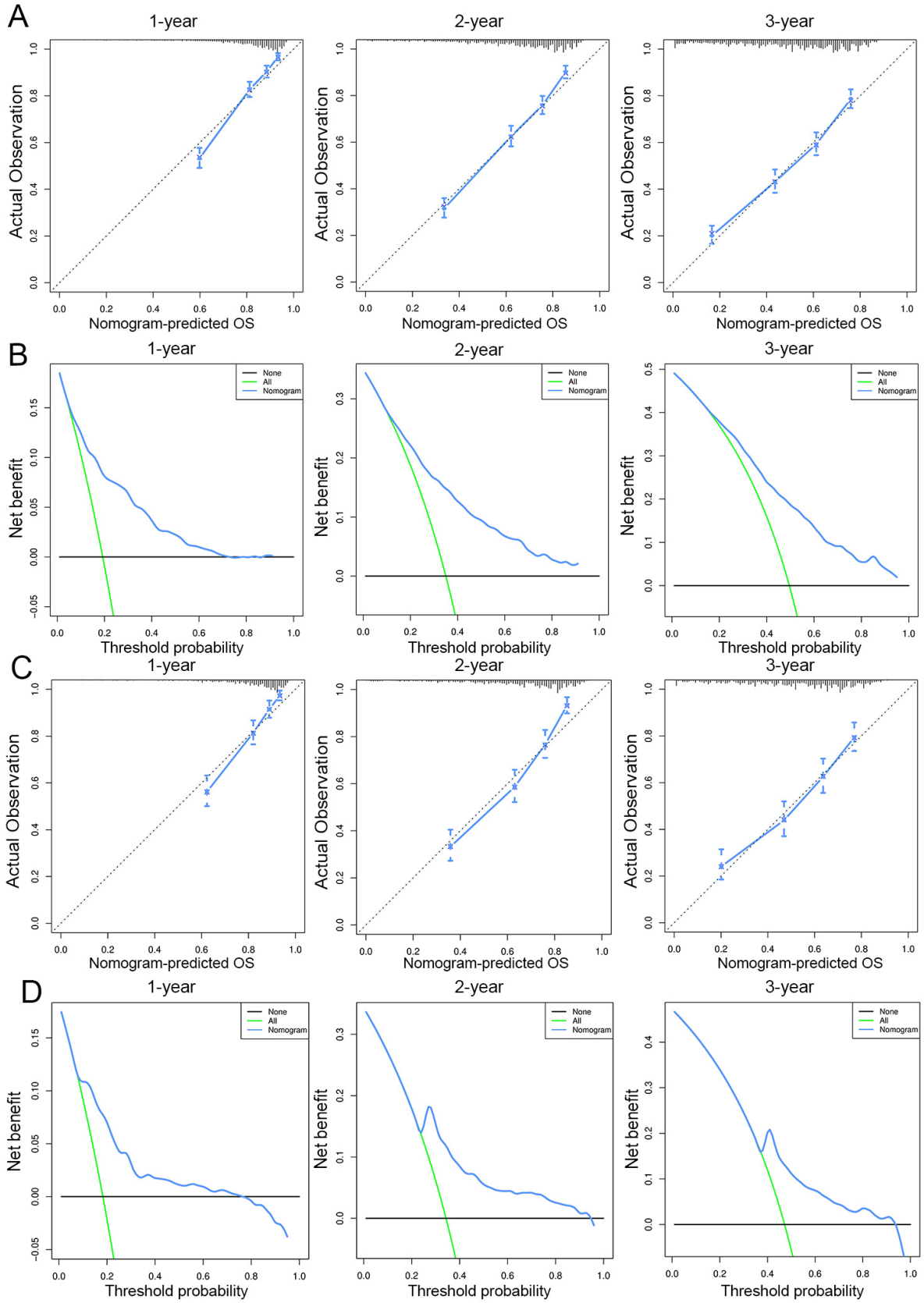

Fig. 4. Calibration curves and decision curve analysis (DCA) of the nomogram. Calibration curves demonstrate the agreement between predicted and observed outcomes in the training cohort (A) and validation cohort (C). DCA evaluates the clinical utility of the nomogram in the training cohort (B) and validation cohort (D).

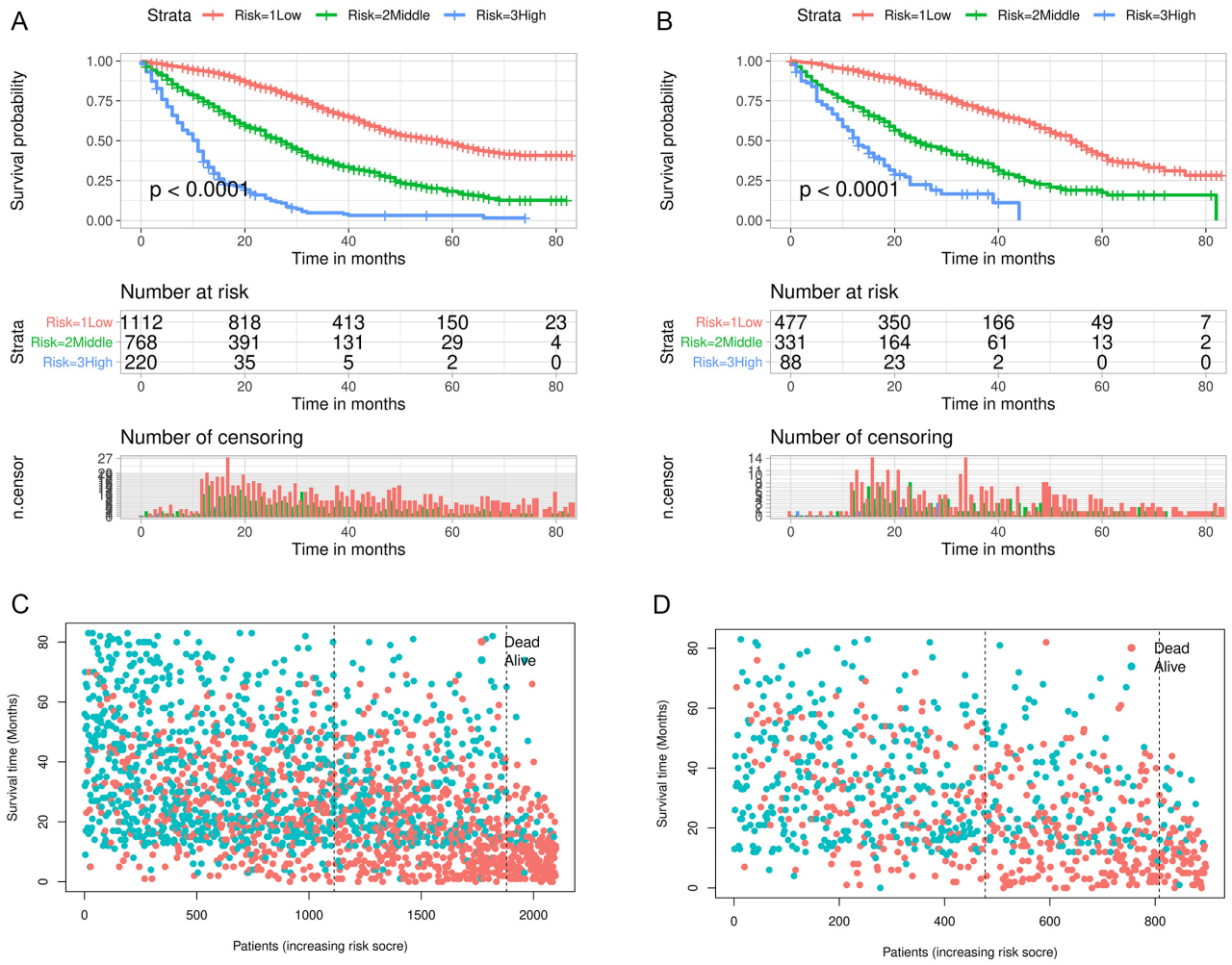

Fig. 5. Kaplan-Meier survival curves and risk analysis. Kaplan-Meier curves show survival probabilities among high-risk, intermediate-risk, and low-risk groups. Patients in the high-risk group demonstrated the poorest prognosis compared to intermediate- and low-risk groups in the training cohort (A,C) and validation cohort (B,D).

to factors such as the blood-brain barrier, which limits the efficacy of therapeutic agents, and hepatic failure caused by liver involvement, further exacerbating disease progression.

Currently, effective survival prognostic tools for BC patients with BM, particularly those undergoing chemotherapy, are lacking. The prognosis for this patient group is generally poor, and treatment decisions often pose significant challenges. By integrating data from the SEER database, we developed a survival prediction model designed to provide an objective and reliable prognostic tool for clinical use. This model facilitates more precise and individualized treatment planning for BC patients with BM, demonstrating superior predictive performance and significant clinical applicability.

The nomogram developed in this study offers a standardized approach to quantifying survival expectations, enabling physicians to make informed, evidence-based decisions. By improving the accuracy of survival predictions, the model minimizes unnecessary interventions and enhances treatment outcomes. In multidisciplinary collaboration, this model assists clinicians in accurately identifying suitable patients and making well-informed treatment decisions. Moreover, it serves to reduce conflicts and alleviate patient anxiety associated with uncertain prognoses. In clinical practice, the confidence of patients in treatment and their involvement in decision-making are significantly influenced by prognostic information. The findings of this study provide patients with a clearer understanding of their survival prospects, fostering greater confidence and encouraging proactive engagement in their treatment plans. Future research should aim to integrate this model into existing clinical decision support systems to enable physicians to assess patient risks more efficiently and optimize treatment plans. Additionally, incorporating individual patient-specific factors, such as socioeconomic status and psychological well-being, could enhance treatment outcomes, improve patient adherence, and elevate quality of life.

This study has several limitations. First, as a retrospective clinical study, the potential for selection bias cannot be entirely ruled out. Second, due to the constraints of the SEER database, we were unable to assess the impact of other treatment approaches, such as targeted therapy and endocrine therapy. Third, while the nomogram provides a valuable reference for clinicians, it does not encompass all factors that could influence the prognosis of BC patients with BM undergoing chemotherapy. Additionally, although machine learning, a pivotal branch of artificial intelligence, is increasingly used in medicine due to its ability to simulate human learning, optimize computational efficiency, and enhance predictive accuracy, we opted for Cox regression analysis to identify prognostic factors and develop the prediction model. While machine learning offers distinct advantages, such as managing complex relationships among variables, its limitations, such as insufficient interpretability and the need for large datasets, make its application challenging in certain contexts. Future studies should address these limitations by incorporating larger sample sizes and exploring more sophisticated machine-learning approaches to improve prediction capabilities. Moreover, complex clinical factors encountered in routine practice should be integrated into treatment planning and prognostic evaluation to better reflect real-world scenarios.

Conclusions

We constructed a predictive nomogram to predict 1-, 2-, and 3-year OS for BC patients with BM undergoing chemotherapy. Additionally, we analyzed the survival benefits associated with various treatment strategies in different risk groups. This study represents a significant advancement in the pursuit of personalized medicine, offering a valuable reference to guide treatment planning and optimize therapeutic strategies.

Abbreviations

BC, breast cancer; BM, bone metastasis; SEER, Surveillance, Epidemiology and End Results; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, human epidermal growth factor receptor-2; BCS, breast-conserving surgery; OS, overall survival.

Availability of Data and Materials

The datasets generated and analyzed during the current study are available in the SEER database (https://seer.cancer.gov/).

Author Contributions

XF, PFC and JHW contributed to the study design. WZ and KSX conducted the literature search and also contributed to the study design. XF, PFC and ZQY acquired the data and performed data analysis. XF wrote the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Maintained by the National Cancer Institute, the SEER program is the largest publicly available cancer dataset worldwide. Ethical review and informed consent were exempted as the data did not include personally identifiable information.

Acknowledgment

We are thankful for the contribution of the SEER database and the 18 registries supplying cancer research information, and thank all colleagues involved in the study for their contributions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: a Cancer Journal for Clinicians. 2020; 70: 7–30.

[2] Miller JW, Smith JL, Ryerson AB, Tucker TC, Allemani C. Disparities in breast cancer survival in the United States (2001-2009): Findings from the CONCORD-2 study. Cancer. 2017; 123 Suppl 24: 5100–5118.

[3] Unger-Saldaña K. Challenges to the early diagnosis and treatment of breast cancer in developing countries. World Journal of Clinical Oncology. 2014; 5: 465–477.

[4] Valachis A, Carlqvist P, Ma Y, Szilcz M, Freilich J, Vertuani S, *et al*. Overall survival of patients with metastatic breast cancer in Sweden: a nationwide study. British Journal of Cancer. 2022; 127: 720–725.

[5] Gilbert A, Williams C, Azuero A, Burkard ME, Kenzik K, Garrett-Mayer E, *et al*. Utilizing Data Visualization to Identify Survival and Treatment Differences Between Women With De Novo and Recurrent Metastatic Breast Cancer. Clinical Breast Cancer. 2021; 21: 292–301.

[6] Svensson E, Christiansen CF, Ulrichsen SP, Rørth MR, Sørensen HT. Survival after bone metastasis by primary cancer type: a Danish population-based cohort study. BMJ Open. 2017; 7: e016022.

[7] Body JJ, Quinn G, Talbot S, Booth E, Demonty G, Taylor A, *et al*. Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone

metastases. Critical Reviews in Oncology/hematology. 2017; 115: 67–80.
[8] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2006; 12: 6243s–6249s.
[9] Lopez-Tarruella S, Escudero MJ, Pollan M, Martín M, Jara C, Bermejo B, *et al*. Survival impact of primary tumor resection in de novo metastatic breast cancer patients (GEICAM/El Alamo Registry). Scientific Reports. 2019; 9: 20081.
[10] Orlandi A, D'Archi S, Garufi G, Franco A, Carnassale B, Palazzo A, *et al*. Impact on survival of primary tumor resection in patients with metastatic breast cancer: preliminary results of a retrospective analysis. Minerva Surgery. 2021; 76: 506–511.
[11] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, *et al*. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2020; 31: 1623–1649.
[12] Deluche E, Antoine A, Bachelot T, Lardy-Cleaud A, Dieras V, Brain E, *et al*. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. European Journal of Cancer (Oxford, England: 1990). 2020; 129: 60–70.
[13] Liu J, Su M, Hong S, Gao H, Zheng X, Wang S. Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study. Oncotarget. 2017; 8: 49861–49868.
[14] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database (1975-2021), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2024, based on the November 2023 submission.
[15] James JJ, Evans AJ, Pinder SE, Gutteridge E, Cheung KL, Chan S, *et al*. Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features. British Journal of Cancer. 2003; 89: 660–665.
[16] Li Q, Yan H, Zhao P, Yang Y, Cao B. Efficacy and Safety of Bevacizumab Combined with Chemotherapy for Managing Metastatic Breast Cancer: A Meta-Analysis of Randomized Controlled Trials. Scientific Reports. 2015; 5: 15746.
[17] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2004; 10: 7252–7259.
[18] Vickers AJ, Holland F. Decision curve analysis to evaluate the clinical benefit of prediction models. The Spine Journal: Official Journal of the North American Spine Society. 2021; 21: 1643–1648.
[19] Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Seminars in Cancer Biology. 2020; 60: 14–27.
[20] Jiang Z, Li J, Chen S, Guo Q, Jing Z, Huang B, *et al*. Zoledronate and SPIO dual-targeting nanoparticles loaded with ICG for photothermal therapy of breast cancer tibial metastasis. Scientific Reports. 2020; 10: 13675.
[21] Tripathy D, Brufsky A, Cobleigh M, Jahanzeb M, Kaufman PA, Mason G, *et al*. De Novo Versus Recurrent HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from the SystHERs Registry. The Oncologist. 2020; 25: e214–e222.
[22] Xiong Z, Deng G, Huang X, Li X, Xie X, Wang J, *et al*. Score for the Survival Probability in Metastasis Breast Cancer: A Nomogram-Based Risk Assessment Model. Cancer Research and Treatment. 2018; 50: 1260–1269.
[23] Nelson RA, Bostanci Z, Jones V, Mortimer J, Polverini A, Taylor L, *et al*. Insurance Status Predicts Survival in Women with Breast Cancer: Results of Breast and Cervical Cancer Treatment Program in California. Annals of Surgical Oncology. 2020; 27: 2177–2187.
[24] Franzoi MA, Schwartsmann G, de Azevedo SJ, Geib G, Zaffaroni F, Liedke PER. Differences in Breast Cancer Stage at Diagnosis by Ethnicity, Insurance Status, and Family Income in Young Women in the USA. Journal of Racial and Ethnic Health Disparities. 2019; 6: 909–916.
[25] Li Y, Zhu MX, Qi SH. Marital status and survival in patients with renal cell carcinoma. Medicine. 2018; 97: e0385.
[26] Zhu S, Lei C. Association between marital status and all-cause mortality of patients with metastatic breast cancer: a population-based study. Scientific Reports. 2023; 13: 9067.
[27] Mahmood H, Faheem M, Mahmood S, Sadiq M, Irfan J. Impact of age, tumor size, lymph node metastasis, stage, receptor status and menopausal status on overall survival of breast cancer patients in Pakistan. Asian Pacific Journal of Cancer Prevention: APJCP. 2015; 16: 1019–1024.
[28] Han Y, Wang J, Sun Y, Yu P, Yuan P, Ma F, *et al*. Prognostic Model and Nomogram for Estimating Survival of Small Breast Cancer: A SEER-based Analysis. Clinical Breast Cancer. 2021; 21: e497–e505.
[29] Lao C, Kuper-Hommel M, Elwood M, Campbell I, Edwards M, Lawrenson R. Characteristics and survival of de novo and recurrent metastatic breast cancer in New Zealand. Breast Cancer (Tokyo, Japan). 2021; 28: 387–397.
[30] Lord SJ, Bahlmann K, O'Connell DL, Kiely BE, Daniels B, Pearson SA, *et al*. *De novo* and recurrent metastatic breast cancer - A systematic review of population-level changes in survival since 1995. EClinicalMedicine. 2022; 44: 101282.
[31] Beatson GT. On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases. Transactions. Medico-Chirurgical Society of Edinburgh. 1896; 15: 153–

179.
[32] Tapia M, Hernando C, Martínez MT, Burgués O, Tebar-Sánchez C, Lameirinhas A, *et al*. Clinical Impact of New Treatment Strategies for HER2-Positive Metastatic Breast Cancer Patients with Resistance to Classical Anti-HER Therapies. Cancers. 2023; 15: 4522.
[33] Oh DY, Bang YJ. HER2-targeted therapies - a role beyond breast cancer. Nature Reviews. Clinical Oncology. 2020; 17: 33–48.
[34] Denkert C, Liedtke C, Tutt A, von Minckwitz G. Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. Lancet (London, England). 2017; 389: 2430–2442.
[35] Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Research. 2004; 64: 2205–2211.
[36] Soran A, Dogan L, Isik A, Ozbas S, Trabulus DC, Demirci U, *et al*. The Effect of Primary Surgery in Patients with De Novo Stage IV Breast Cancer with Bone Metastasis Only (Protocol BOMET MF 14-01): A Multi-Center, Prospective Registry Study. Annals of Surgical Oncology. 2021; 28: 5048–5057.