Am J Cancer Res 2026;16(5):1761-1775
www.ajcr.us /ISSN:2156-6976/ajcr0171896

Original Article

Survival outcomes in patients with metachronous breast cancer bone metastasis: an 11-year single-institution retrospective study

Lei Wang[1], Mengxiao Wang[1], Weixiang Qi[1,2], Dan Ou[1,2], Lu Cao[1,2], Rong Cai[1,2], Cheng Xu[1,2], Shubei Wang[1,2], Jiayi Chen[1,2], Gang Cai[1,2]

[1]Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China; [2]Shanghai Key Laboratory of Proton-Therapy, Shanghai 201801, China

Received February 4, 2026; Accepted April 24, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: This study aimed to analyze the clinical characteristics of metachronous breast cancer bone metastasis (BCBM) and construct a graded prognostic assessment (GPA) model. A retrospective analysis was conducted on the clinical data of newly diagnosed breast cancer patients with bone metastasis (BM). Data collected included initial involvement of bone substructures and metastatic burden other than BM. Receiver operating characteristic (ROC) curve analysis, calibration curve analysis, and decision curve analysis (DCA) were used to evaluate the efficacy of the Cox regression model, and a GPA model for overall survival (bmOS) after BM was constructed. The DeLong test was used to compare the area under the curve (AUC) of the training and validation sets to validate the model efficacy. A total of 2103 BMs were detected in 308 patients with metachronous BCBM. The most common sites were the thoracic spine (24.8%), lumbar spine (16.7%), ribs (11.9%), and iliac bone (10.2%); 80.1% of the lesions were osteolytic. Independent prognostic risk factors for bmOS included in the GPA model included initial stage, molecular subtype, time to BM (TTBM), BM numbers, and extraosseous visceral metastases (EVM). The model showed no statistically significant difference in AUC between the training and validation sets (DeLong test, $P > 0.05$). Patients were divided into three risk strata based on GPA scores (0-8.5), with significant differences in median survival: 60.3, 40.0, and 32.6 months in the training set ($P < 0.001$), and 64.0, 41.6, and 25.3 months in the validation set ($P < 0.001$). Initial treatment failure was predominantly due to bone progression (39.3%) and visceral progression (28.2%). In conclusion, the prognosis of patients with metachronous BCBM exhibits significant heterogeneity. The GPA model developed in this study can serve as a practical prognostic assessment tool and provide a reference for individualized treatment planning.

Keywords: Breast cancer, bone metastasis, prognostic factors, graded prognostic assessment model

Introduction

Breast cancer (BC) is the most common cancer among women in the United States and the second leading cause of cancer-related death in women [1]. The 5-year survival rate for early-stage BC is approximately 95%; however, once distant metastasis (DM) occurs, the prognosis significantly worsens [2]. Bone metastasis (BM) is the most common site of distant metastasis in BC and also the most common site of first distant recurrence [3]. Breast cancer bone metastasis (BCBM) refers to the spread of cancer cells to the skeletal system via hematogenous or lymphatic routes, causing bone destruction and pain, severely impacting patients' daily activities and mental health [4]. Approximately 30%-50% of patients have bone as their first site of metastasis, and 65%-75% of advanced-stage patients eventually develop BM [5, 6].

In patients with metachronous BCBM, multiple factors influence overall survival (OS) [7, 8]. The optimal treatment plan for BCBM patients should be based on their projected survival [9-12]. The graded prognostic assessment (GPA) scoring model was firstly proposed by Sperduto et al. in a brain metastasis study in 2008 [13]. Subsequently, this model was

https://doi.org/10.62347/QZSE6054

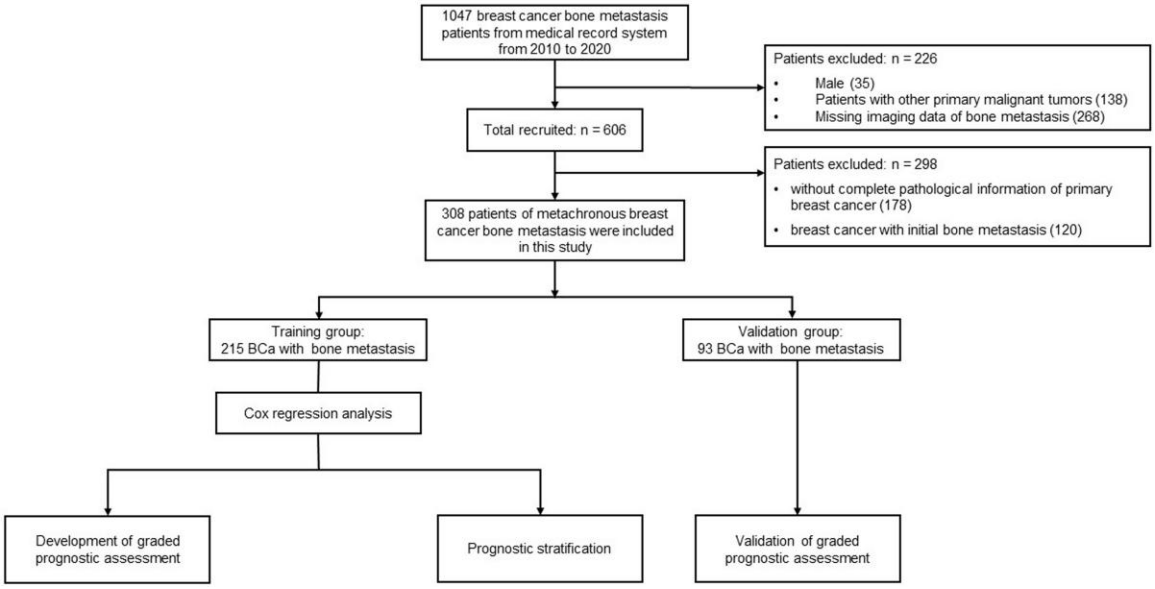

Figure 1. Flow diagram of the study selection process. BC: breast cancer.

adopted and optimized by incorporating disease-specific prognostic factors to improve its prognostic efficacy. Although there is currently no consensus on similar models for bone metastases from solid tumors, several prognostic assessment indicators based on combined analysis of different solid tumors have been established [14-17]. These indicators stratify survival prognosis based on the anatomical location, extent of involvement, patient's overall condition, and extra-bone tumor burden (BTB) of BM. Some indicators can also guide the selection of local treatment regimens.

Metastatic BC exhibits highly heterogeneous prognostic characteristics due to differences in molecular subtypes and corresponding systemic antitumor therapies. Compared to when the aforementioned prognostic indicators were first established, BM patients now have a wider range of local treatment options. Therefore, this study aims to analyze the clinical characteristics of patients with metachronous BCBM and, based on the current level of multidisciplinary comprehensive treatment, construct a GPA model for prognostic evaluation.

Methods and materials

Patients' selection

From January 2010 to December 2020, a retrospective study was conducted at Ruijin Hospital, Shanghai Jiaotong University School of Medicine to include patients newly diagnosed with secondary BM from BC. As shown in **Figure 1**, the inclusion criteria were: (1) histologically confirmed primary BC; (2) confirmed BM by pathological examination or complete imaging data. The exclusion criteria were: (1) male patients; (2) patients with other malignancies that could affect survival; (3) patients with incomplete clinicopathological and follow-up data; and (4) BC patients with BM at initial The metachronous BCBM was defined as BC patients pathologically confirmed with primary invasive BC, and whose BM were confirmed by imaging and/or pathological examination at least 6 months after the initial diagnosis of primary BC. This study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine.

A complete dataset including clinical characteristics, imaging findings at the time of initial BM, and survival data was collected. Clinical factors include the surgical treatment of the primary tumor, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, histological type, T stage, lymph node stage, and visceral metastasis. Tumor staging is determined according to the American Joint Committee on Cancer (AJCC) Staging Manual (8th edition) [18]. BC subtypes were classified based on the expression of ER, PR, HER2, and

Ki67 in the primary tumor: luminal type A, luminal type B (HER2 negative and HER2 positive), HER2 overexpression type (non-luminal), and triple-negative type. ER and PR status are detected by immunohistochemistry (IHC), with a positive criterion of ≥ 10% positive staining cells. HER2 positivity is defined as an IHC expression intensity score of 3+, or a gene amplification ratio > 2.2 detected by fluorescence in situ hybridization (FISH). The Ki67 proliferation index was also detected by IHC.

BM evaluation

Baseline assessment data includes bone imaging, including emission CT, CT, and MRI [17, 18]; positron emission tomography CT data, if available, should also be included. Patients may undergo multiple of these imaging modalities, but at least CT and/or MRI were required. BM sites were categorized into five types: skull; chest (ribs, clavicle, sternum, and scapula); spine (cervical, thoracic, and lumbar vertebrae); pelvis (ilium, ischium, pubis, sacrum, and sacroiliac joint); and extremities (upper and lower extremities) [19].

Biochemical indicator testing

The selection of biochemical biomarkers was based on their clear association with the pathophysiological processes of BC progression and BM: Type I collagen C-terminal β-specific sequence (β-CTX), Type I procollagen N-terminal propeptide (PINP), and osteocalcin (BGP) are core biomarkers reflecting osteoclast/osteogenic activity and bone turnover, and are closely related to the occurrence and development of BCBM; Carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and carbohydrate antigen 15-3 (CA15-3) are classic tumor markers, widely used in the clinical assessment of BC tumor burden and distant metastasis. A 3 mL blood sample was collected from the patient and centrifuged to obtain serum. The levels of CA125 and CEA were detected using enzyme-linked immunosorbent assay (ELISA). The serum CA15-3 level was measured by electrochemiluminescence immunoassay (ECLIA) using a fully automated chemiluminescence analyzer (Roche, Cobas e602 model) with original imported kits. The levels of serum bone metabolism markers, including PINP, β-CTX, and BGP, were detected using the UniCel DxI 800 Access fully automated chemiluminescence immunoassay analyzer.

Follow-up

Patients were followed up through outpatient and/or inpatient visits, combined with telephone follow-up. OS after bone metastasis (bmOS) was defined as the time from diagnosis of BCBM to death or last follow-up. Time to bone metastasis (TTBM) was defined as the time from diagnosis of breast cancer to diagnosis of BM. Progression-free survival (PFS) was defined as the time from the date of diagnosis of BCBM to disease progression or death from any cause. Pattern of failure (POF) was categorized as progression of BM after treatment or progression of visceral metastasis (with or without central nervous system (CNS) metastasis). The last follow-up date was December 31, 2024.

Statistical methods

Statistical analysis was performed using SPSS 26.0 (IBM, USA). Descriptive statistics were used to summarize patient baseline characteristics, BM characteristics, and treatment regimens. Continuous variables were expressed as mean ± standard deviation, and independent samples t-tests were used for comparisons between groups. Categorical variables were expressed as frequency and proportion, and Pearson's chi-square statisticstest or Fisher's exact test was used as appropriate. Survival analysis employed the Kaplan-Meier method and the Log-rank test. Statistically significant parameters from the univariate analysis were incorporated into the multivariate Cox regression model. The variance inflation factor (VIF) was used to assess collinearity among variables in the multivariate Cox regression model; VIF < 2.0 was defined as no significant collinearity. The DeLong test was used to compare the area under the curve (AUC) between the validation and training sets. The power of the Cox regression model was evaluated using receiver operating characteristic (ROC) analysis, calibration curve analysis, and decision curve analysis (DCA). The Hosmer-Lemeshow test combined with 1000 bootstrap resampling was used to plot calibration curves and assess the consistency between predicted and observed survival probabilities. The exact method was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

Table 1. Patients' characteristics at baseline in the training and validation dataset

Characteristic	All patients (N=308)	Training dataset (N=215)	Validation dataset (N=93)	*P* value
Patients (n)	308	215	93	
Tumor Grade (N, %)				0.441
1/2	156 (50.6)	112 (52.1)	44 (47.3)	
3	152 (49.4)	103 (47.9)	49 (52.7)	
Initial stage (N, %)				0.160
I	37 (12.0)	25 (11.6)	12 (12.9)	
II	78 (25.3)	61 (28.5)	17 (18.3)	
III				
IIIA	60 (19.5)	39 (18.1)	21 (22.6)	
IIIB	54 (17.5)	41 (19.1)	13 (14.0)	
IIIC	79 (25.6)	49 (22.8)	30 (32.3)	
HER2 status (N, %)				0.288
Positive	234 (76.0)	167 (77.7)	67 (72.0)	
Negative	74 (24.0)	48 (22.3)	26 (28.0)	
Ki67 value (N, %)				0.827
< 30	142 (46.1)	100 (46.5)	42 (45.2)	
≥ 30	166 (53.9)	115 (53.5)	51 (54.8)	
Molecular subtype (N, %)				0.912
Luminal A	78 (25.3)	54 (25.1)	24 (25.8)	
Luminal B	161 (52.3)	111 (51.6)	50 (53.8)	
HER2 overexpression	25 (8.1)	19 (8.8)	6 (6.5)	
Triple negative	44 (14.3)	31 (14.4)	13 (14.0)	
Age at diagnosis of BM (years) (N, %)				0.964
Median (range)	54 (28, 88)	56 (29, 83)	52 (28, 88)	
TTBM, month				0.231
Median (range)	59 (4, 96)	44 (4, 87)	53 (6, 96)	
KPS at diagnosis of BM (N, %)				0.387
Median (range)	80 (50, 90)	70 (50, 80)	80 (50, 90)	
EVM (N, %)				0.423
0 site	181 (58.8)	128 (59.5)	53 (57.0)	
single site	93 (30.2)	67 (31.2)	26 (28.0)	
more sites	34 (11.0)	20 (9.3)	14 (15.0)	
Number of BM at diagnosis of BM (N, %)				0.264
1-3	154 (50.0)	112 (52.1)	42 (45.2)	
> 3	154 (50.0)	103 (47.9)	51 (54.8)	
SREs at diagnosis of BM (N, %)	111 (36.0)	83 (38.6)	28 (30.1)	0.154
bone pain	104 (33.8)	80 (37.2)	24 (25.8)	0.058
pathological fractures	36 (11.7)	30 (14.0)	6 (6.5)	0.061
spinal cord compression	15 (4.9)	7 (3.3)	8 (8.6)	0.087
surgery for bone complications	14 (4.5)	11 (5.1)	3 (3.2)	0.665
β-CTX (ng/mL)	0.57±0.08	0.58±0.08	0.55±0.10	0.053
PINP (ng/mL)	30.27±1.30	30.22±1.29	30.38±1.34	0.293
BGP (ng/mL)	9.23±1.37	9.16±1.08	9.42±1.89	0.127
CEA (ng/mL)	14.20±3.38	14.22±3.43	14.15±3.27	0.886
CA125 (U/mL)	20.70±2.45	20.62±2.37	20.88±2.65	0.376
CA15-3 (ng/mL)	6.88±1.88	6.95±1.81	6.73±2.01	0.368

KPS: karnofsky performance status; WBI: whole breast radiotherapy; EVM: extraosseous visceral metastases; BM: bone metastasis; TTBM: time from diagnosis of breast cancer to diagnosis of bone metastasis; SREs: skeletal-related events; HER2: human epidermal growth factor receptor 2; β-CTX: Beta-C-terminal telopeptide of type I collagen; PINP: procollagen type I N-terminal propeptide; BGP: Bone Gla Protein; CEA: Carcinoembryonic Antigen; CA125: Cancer Antigen 125; CA15-3: Cancer Antigen 15-3.

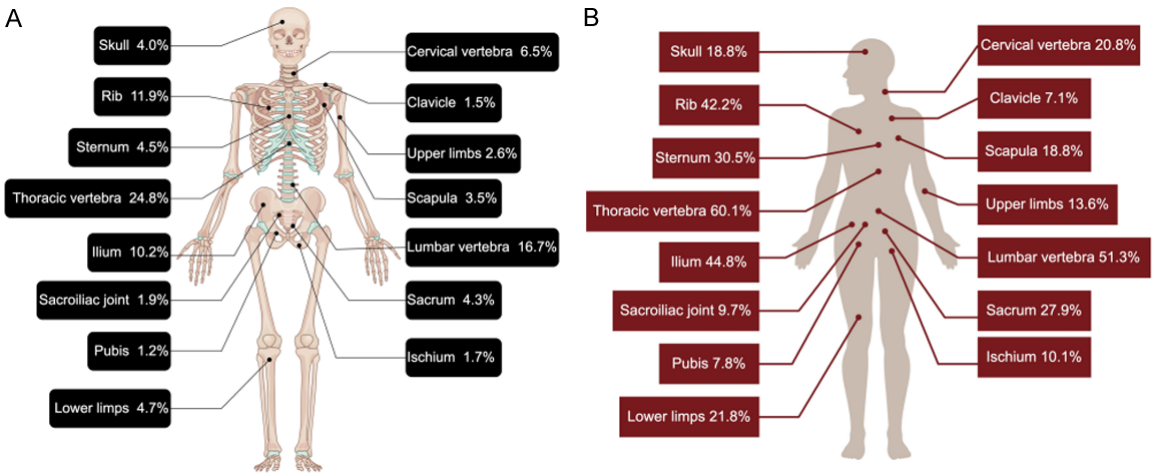

Figure 2. Anatomical distribution of bone metastatic sites at diagnosis of BM in 2103 BM number (A) and 308 female BCBM patients (B). BM: bone metastasis; BCBM: breast cancer bone metastasis.

Construction and validation of GPA model

The entire cohort of 308 patients with metachronous BCBM was divided into a training set and a validation set by simple random sampling using a random number table, with a 7:3 allocation ratio (70% for the training set, 30% for the validation set). The training set (n=215) was used for screening prognostic factors and constructing the GPA model for bmOS, while the validation set (n=93) was used for internal verification of the model's predictive performance. In short, statistically significant variables related to patient survival were selected from the multivariate Cox regression model. The GPA score was the sum of the scores of each risk factor after HR conversion based on the multivariate analysis (conversion rule: integer part was retained; decimal part < 0.5 was counted as 0, > 0.5 was counted as 0.5). For example, HR=0.4 was counted as 0 points, HR=0.6 as 0.5 points; HR=1.4 as 1.0 points, HR=1.6 as 1.5 points; HR=2.4 as 2.0 points, HR=2.6 as 2.5 points, and so on. The total GPA score was the sum of the scores of each independent prognostic factor after the above conversion. The scoring rules of the GPA model were based on the HR from multivariate Cox regression, and this method conformed to the standard graded prognostic assessment criteria, ensuring clinical feasibility and rationality. The GPA model was then validated in the validation set. The cutoff value was determined using X-tile software (version 3.6.1; website: https://medicine.yale.edu/lab/rimm/research/software). After importing the variables into the software, it automatically calculated all possible cutoff values and selected the value with the largest chi-square value and the smallest *P*-value in the Log-rank test for survival stratification. Detailed results of the X-tile analysis are shown in Table S1.

Results

Patient clinicopathologic characteristics

The baseline information of the two cohorts were summarized in **Table 1**. Clinical data of the two groups was comparable (all P > 0.05, **Table 1**).

Anatomical distribution of BM sites

A total of 2103 BM were detected in 308 female BCBM patients. The thoracic spine accounted for 24.8%, the lumbar spine for 16.7%, the ribs for 11.9%, and the iliac bone for 10.2% (**Figure 2A**). Osteolytic lesions were the most common type of BCBM (approximately 80.1%), followed by osteoblastic lesions (7.9%) and mixed lesions (11.9%).

Most patients had metastases in the spine (73.7%), followed by the chest (60.1%) and pelvis (56.5%). Skull and limb metastases were relatively rare. Among chest metastases, rib metastases were the most common (42.2%). The incidence of metastases in the thoracic spine (60.1%) and lumbar spine (51.3%) was higher than that in the cervical spine (20.8%).

Table 2. The univariate and multivariable analyses based on clinicopathological characteristics data for outcomes in the training dataset

Characteristics	Cases (N)	Median bmOS (m)	HR (95% CI) Univariate analysis	*P* value	HR (95% CI) Multivariate analysis	*P* value	VIF
Age at diagnosis BM, years							1.12
< 50	70 (32.6)	48.1	Reference				
≥ 50	145 (67.4)	50	0.894 (0.632-1.265)	0.527			
KPS at diagnosis of BM							1.08
≤ 70	116 (54.0)	48.1	Reference				
> 70	99 (46.0)	47.8	0.911 (0.687-1.206)	0.896			
Stage							1.36
I	25 (11.6)	68.2	Reference				
II	61 (28.5)	55.1	1.414 (0.838-2.387)	0.195	1.306 (0.977-1.980)	0.06	
IIIA	42 (19.5)	52.4	1.676 (0.980-2.865)	0.059	1.772 (1.066-2.946)	0.027	
IIIB	36 (16.7)	50	1.686 (1.031-2.756)	0.037	2.069 (1.187-3.607)	0.01	
IIIC	51 (23.7)	35.6	2.653 (1.825-3.573)	< 0.001	2.862 (1.977-3.837)	< 0.001	
Molecular subtype							1.41
Luminal A	54 (25.1)	56.7	Reference		Reference		
Luminal B	111 (51.6)	54	1.709 (1.278-2.819)	0.005	1.367 (0.937-1.995)	0.061	
HER2 overexpression	19 (8.8)	39.1	2.436 (1.232-3.628)	0.015	1.946 (1.052-3.602)	0.019	
Triple negative	31 (14.4)	30.6	2.792 (1.292-4.681)	0.011	2.488 (1.572-4.034)	< 0.001	
TTBM							1.45
< 60 months	134 (62.3)	41.9	Reference		Reference		
≥ 60 months	81 (37.7)	56.7	0.680 (0.475-0.973)	0.035	0.755 (0.512-0.988)	0.041	
BM numbers							1.43
≤ 3	112 (52.1)	51.2	Reference		Reference		
> 3	103 (47.9)	41	1.369 (1.029-1.891)	0.031	1.536 (1.208-2.215)	0.001	
EVM							1.10
0 site	128 (59.5)	52	Reference		Reference		
single site	67 (31.2)	41.9	1.236 (0.859-1.778)	0.041	1.323 (0.906-1.930)	0.034	
more sites	20 (9.3)	28.7	1.842 (1.197-2.834)	0.005	1.876 (1.168-3.084)	0.003	
SREs at diagnosis of BM							1.06
No	132 (61.4)	51.7	Reference				
Yes	83 (38.6)	41	1.328 (0.939-1.879)	0.109			
β-CTX (ng/mL)	215 (100.0)	0.6	1.887 (0.812-3.628)	0.175			1.27
PINP (ng/mL)	215 (100.0)	30.2	0.992 (0.859-1.145)	0.911			1.21
BGP (ng/mL)	215 (100.0)	9.2	1.102 (0.862-1.188)	0.887			1.15
CEA (ng/mL)	215 (100.0)	14.2	0.977 (0.928-1.029)	0.379			1.52
CA125 (U/mL)	215 (100.0)	20.6	0.940 (0.873-1.012)	0.101			1.13
CA15-3 (ng/mL)	215 (100.0)	6.9	0.996 (0.906-1.096)	0.934			1.11

bmOS: overall survival after bone metastasis; HR: Hazard Ratio; CI: Confidence Interval; KPS: karnofsky performance status; WBI: whole breast radiotherapy; EVM: extraosseous visceral metastases; BM: bone metastasis; TTBM: time from diagnosis of breast cancer to diagnosis of bone metastasis; SREs: skeletal-related events; HER2: human epidermal growth factor receptor 2; β-CTX: Beta-C-terminal telopeptide of type I collagen; PINP: procollagen type I N-terminal propeptide; BGP: Bone Gla Protein; CEA: Carcinoembryonic Antigen; CA125: Cancer Antigen 125; CA15-3: Cancer Antigen 15-3; VIF: variance inflation factor.

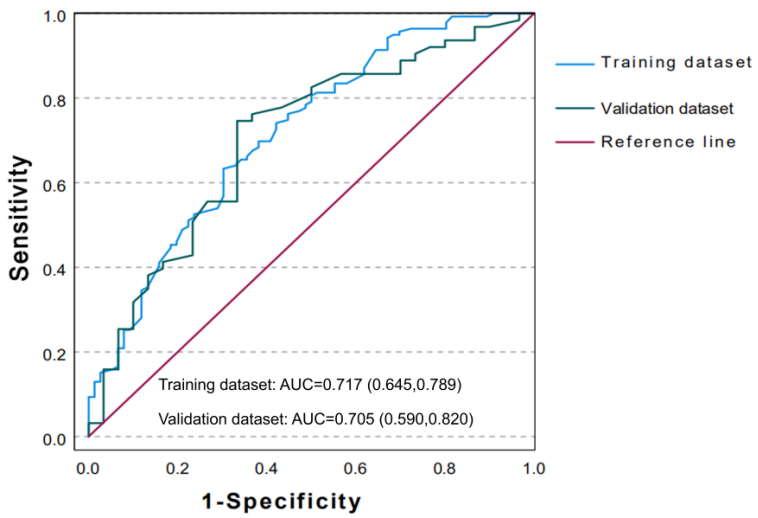

Figure 3. ROC curve for the training and validation datasets. ROC: Receiver Operating Characteristic; AUC: area under the curve.

were 1.946 (1.052-3.602), P= 0.019; and 2.488 (1.572-4.034), P < 0.001, respectively.

The HR, 95% CI and *P*-values for TTBM ≥ 60 months were 0.755 (0.512-0.988), P=0.041.

The HR, 95% CI and *P* value of BM numbers > 3 were 1.536 (1.208-2.215), *P*=0.001. The HR, 95% CI and *P* value of extraosseous-values for single and multiple extra-bone visceral metastases were 1.323 (0.906-1.930), P=0.034; and 1.876 (1.168-3.084), *P*=0.003; respectively.

Pelvic BM were most commonly found in the iliac bone (44.8%) and sacrum (27.9%). Among the bones of the extremities, the incidence of lower extremity bone involvement (21.8%) was higher than that of upper extremity bone (13.6%) (**Figure 2B**).

Survival and prognostic factors in the training dataset

In the training dataset, the median bmOS was 49.5 months (95% CI: 41.0-56.7 months), with 1-year, 3-year, and 5-year survival rates of 95.3%, 65.7%, and 32.2%, respectively. First, all candidate clinicopathological variables (e.g., age, initial stage, molecular subtype, TTBM, BM numbers) were included as independent variables with bmOS as the dependent variable in a univariate Cox regression analysis. Independent variables with P < 0.1 in the univariate analysis were included in the multivariate analysis. The results showed that initial stage, molecular subtype, TTBM, BM numbers and extraosseous and visceral metastases were all independent prognostic factors for bmOS (all *P* < 0.05).

The HR, 95% CI and *P*-values for initial stage IIIA, IIIB, and IIIC were 1.772 (1.066-2.946), P=0.027; 2.069 (1.187-3.607), P=0.01; and 2.862 (1.977-3.837), P < 0.001, respectively.

The HR, 95% CI and *P* value of HER2 overexpression subtype and triple-negative subtype

Detailed univariate and multivariate analyses of bmOS are shown in **Table 2**. Subsequently, models were constructed using the aforementioned five predictors of bmOS on both the training dataset (AUC=0.717, 95% CI=0.645-0.789) and the validation dataset (AUC=0.705, 95% CI=0.590-0.820), and the DeLong test was performed on the AUCs of the two sets (**Figure 3**; **Table 3**). The results indicated that the AUC of the five-indicator joint model had no statistically significant difference between the training and validation datasets (P > 0.05), indicating that the model has good predictive performance. The calibration curve demonstrated good model fit (**Figure 4A**, **4B**). DCA showed that the model achieved a positive net benefit when the threshold probability was between 5% and 20% (**Figure 4C**, **4D**).

Development and validation of graded prognostic assessment

Based on five significant influencing factors identified through multivariate analysis and their corresponding HRs (**Table 2**), a GPA model was constructed using the training cohort. GPA scores were assigned based on the risk level of each parameter, including stage, molecular subtypes, TTBM, extraosseous and visceral metastases, and BM number (**Table 4**). That is, the total GPA Score = Stage Score + Molecular Subtype Score + TTBM Score + BM number Score + Extraosseous Visceral Metastasis Score.

Table 3. The AUC values and DeLong test for each predictor

	Feature	AUC	Z	P
Training dataset	Stage	0.524	-	-
	Molecular subtype	0.584	-	-
	TTBM	0.415	-	-
	BM numbers	0.562	-	-
	EVM	0.545	-	-
	Combined all	0.717	-	-
	Stage-Molecular subtype	-	-1.019	0.308
	Stage-TTBM	-	1.913	0.056
	Stage-EVM	-	-0.665	0.506
	Stage-BM numbers	-	-0.371	0.710
	Molecular subtype-TTBM	-	2.934	0.003
	Molecular subtype-EVM	-	0.444	0.657
	Molecular subtype-BM numbers	-	0.701	0.483
	TTBM-EVM	-	-3.200	0.001
	TTBM-BM numbers	-	-2.681	0.007
	EVM-BM numbers	-	0.344	0.731
Validation dataset	Stage	0.520	-	-
	Molecular subtype	0.567	-	-
	TTBM	0.423	-	-
	BM numbers	0.578	-	-
	EVM	0.560	-	-
	Combined all	0.705	-	-
	Stage-Molecular subtype	-	-0.555	0.579
	Stage-TTBM	-	1.192	0.233
	Stage-EVM	-	-0.697	0.486
	Stage-BM numbers	-	-0.452	0.651
	Molecular subtype-TTBM	-	1.562	0.118
	Molecular subtype-EVM	-	-0.136	0.892
	Molecular subtype-BM numbers	-	0.083	0.934
	TTBM-EVM	-	-1.986	0.047
	TTBM-BM numbers	-	-1.828	0.067
	EVM-BM numbers	-	0.215	0.830
All	Combined all in training dataset	0.717	-	-
	Combined all in validation dataset	0.705	-	-
	Combined all in training dataset-Combined all in validation dataset	-	0.172	0.864

BM: bone metastasis; TTBM: time from diagnosis of breast cancer to diagnosis of bone metastasis; AUC: area under the curve; EVM: extraosseous visceral metastases.

According to the cutoff values determined by X-tile software, patients in the training dataset were divided into three groups according to their total GPA score: low-risk group (LRG, 0-3.5 points, 84 cases, 39.1%), middle-risk group (MRG, 4.0-5.5 points, 93 cases, 43.3%), and high-risk group (HRG, 6.0-8.5 points, 38 cases, 17.7%). In the training dataset, the median bmOS of the training set was 60.3 months (95% CI: 55.8-77.7), 40.0 months (95% CI: 37.2-57.4), and 32.6 months (95% CI: 26.9-47.9), respectively, for patients in the low-risk, middle-risk, and high-risk groups ($P < 0.001$, **Table 4**; **Figure 5A**).

In the validation dataset, the median bmOS was 48.7 months (95% CI: 30.5-60.0 months) and the 1-year, 3-year, and 5-year survival

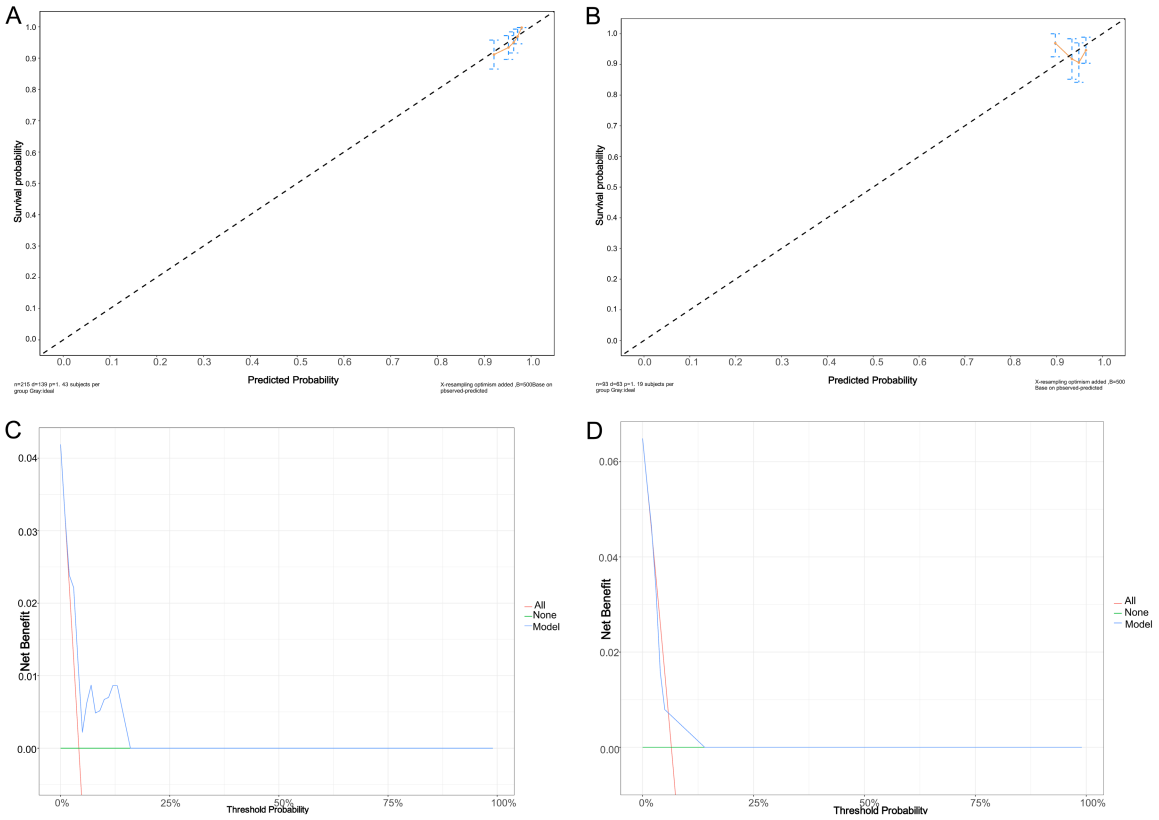

Figure 4. Analysis of the model's predictive performance. A. Calibration curve for the training dataset. B. Calibration curve for the validation dataset. The x-axis represents the model-predicted probability, and the y-axis represents the actual observed frequency. The dashed diagonal line indicates perfect prediction (ideal calibration). The solid line represents the performance of the nomogram. The closer the solid line is to the dashed line, the better the calibration. C. DCA for the training dataset. D. DCA for the validation dataset. The y-axis measures the net benefit, calculated by summing the benefits (true positives) and subtracting the harms (false positives) weighted by the threshold probability (x-axis). The horizontal green line at y=0 represents the strategy of "Treat None". The red sloping line represents the strategy of "Treat All". The blue line represents the net benefit of using the current model to guide intervention decisions. DCA: Decision Curve Analysis.

rates were 93.5%, 55.2%, and 35.1%, respectively. After stratification based on the GPA scores, the median bmOS for the low-risk, middle-risk, and high-risk groups within the validation set were 64.0 months (95% CI: 58.7-79.2), 41.6 months (95% CI: 30.0-55.6) and 25.3 months (95% CI: 20.1-34.6), respectively ($P < 0.001$, **Table 5** and **Figure 5B**).

POF following treatment

Throughout the study cohort, 39.3% of patients experienced bone lesion progression during follow-up, and 28.2% experienced visceral lesion progression (**Table 6**). The risk of both bone and visceral lesion progression increased from the LRG to the MRG and HRG, with visceral metastases being more pronounced in the MRG and HRG. The median PFS for the three groups of patients was 30.0 months (95% CI: 29.0-35.0), 23.0 months (95% CI: 22.0-23.5) and 16.6 months (95% CI: 14.0-20.5) in the 3 risk groups, respectively ($P < 0.001$, **Figure 6**).

Discussion

In the current study, we established a GPA model to predict the prognosis and estimate the survival of metachronous BCBM patients. Metastatic breast cancer represents a population with high heterogeneity. Understanding the clinical characteristics of metachronous BCBM and establishing a practical prognostic model will help to tailor individualized treatment [20]. The results of this study show that initial stage, molecular subtype, TTBM, BM

Table 4. The score of significant survival factors in training dataset of Graded Prognostic Assessment

Factors	Score
Initial Stage	
I	0
II	1.0
IIIA	1.5
IIIB	2
IIIC	2.5
Molecular sub-type	
Luminal A	0
Luminal B	1.0
HER2 overexpression	1.5
Triple negative	2.0
TTBM	
≥ 60 months	0
< 60 months	1.0
BM numbers	
≤ 3	0
> 3	1.5
EVM	
0 site	0
single site	1.0
more sites	1.5

BM: bone metastasis; TTBM: time from diagnosis of breast cancer to diagnosis of bone metastasis; HER2: human epidermal growth factor receptor 2; EVM: extraosseous visceral metastases.

numbers and EVM were independent prognostic factors for survival in patients with BCBM.

Patients with advanced BC (stage III-IV) have higher tumor burden and wider lymph node metastasis than those with early BC (stage I-II), resulting in higher mortality [21]. Accumulation of lactic acid and enhanced glycolysis promote the metastasis and immune escape of triple-negative breast cancer (TNBC), which may explain the poor prognosis of this subtype [22]. HER2 overexpression drives aggressive tumor behavior primarily through the constitutive activation of downstream PI3K/AKT and MAPK signaling pathways, which promote uncontrolled proliferation and inhibit apoptosis [23].

In patients with long TTBM (≥ 60 months in our study), tumor cells remain in a dormant state after entering the bone microenvironment, which is related to the regulation of dormant signals such as transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMPs) [6]. A longer TTBM was associated with significantly better survival.

Patients with a large number of BM have significantly increased BTB, and the “vicious cycle” between tumor cells and the bone microenvironment is more intense. Parathyroid hormone-related protein (PTHrP) secreted by tumor cells promotes osteoclast activation, and growth factors released by bone resorption (e.g., insulin-like growth factor [IGF], osteocalcin) further accelerate tumor proliferation, forming a positive feedback loop [3]. Our results showed that patients had a significantly worse prognosis when the BM number exceeded three.

The presence of EVM (especially multiple organ metastases) suggests that tumor cells have broken through the limitations of bone tissue and possess stronger systemic dissemination ability. The underlying mechanism is related to an increased proportion of cancer stem cells (CSCs) and enhanced immune escape ability [6]. In our study, not only the presence but also the number of extraosseous visceral metastatic sites significantly impacted prognosis ($P < 0.05$).

From the radiological data of our study, BCBM were predominantly osteolytic, and metastases were more frequent in the vertebra followed by the chest, which is consistent with the literature [24]. The distribution of BM was more frequent in the thoracic and lumbar vertebrae, ribs, and ilium, and relatively infrequent in the upper limbs and skull. Currently, BM are believed to be hematogenous; however, sternal metastasis in BC remains relatively uncommon, especially when presenting as a solitary lesion [25]. Regardless of whether classified by the number of metastatic sites or by the number of BCBM patients, the majority of bone lesions are situated in the lower body, including the lower vertebrae and lower extremities, which are more subject to skeletal-related events (SREs) [26]. With the advancement of targeted therapy and immunotherapy, cancer patient survival has significantly prolonged; consequently, 30%-70% of all malignant tumors involve the skeleton, leading to a markedly increased incidence of SREs [27]. Bone-modifying agents, including bisphosphonates, constitute the cornerstone of therapy for the prevention and treatment of SREs [28].

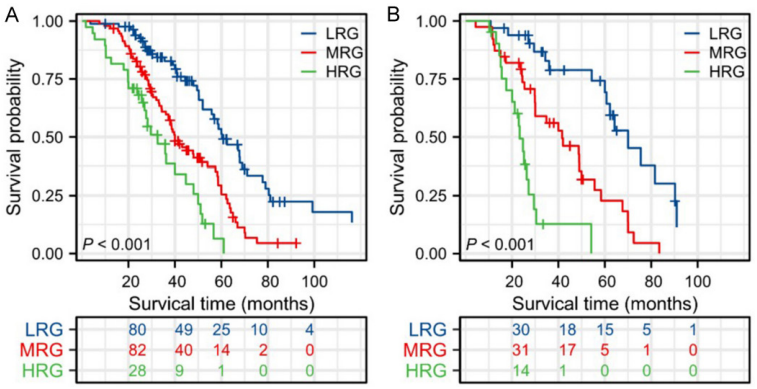

Figure 5. Survival curves of the different groups in the training dataset (A) and validation dataset (B). LRG: low-risk group; MRG: middle-risk group; HRG: high-risk group.

Previous studies have shown that the BM incidence as a first event varies among different molecular subtypes [29]. Hormone receptor (HR)-positive status (HR+/HER2- and HR+/HER2+) was significantly associated with initial BM, and HR expression was positive in most patients with initial BM. Our results confirm that luminal types have a higher incidence compared with HER2-overexpressing and TNBC subtypes. In the SEER database, HR+/HER2+ BCBM patients had the best prognosis and TNBC patients the worst; in the Fudan University Shanghai Cancer Center (FUSCC) database, HR+/HER2- BCBM patients had the best prognosis and TNBC the worst [30]. Our results are closer to the FUSCC data, and the difference may be due to the long time period covered by the SEER database, which lacked anti-HER2 treatment. However, these studies either provided only qualitative descriptions or did not integrate subtype into a practical scoring tool.

The GPA model incorporates the five parameters described above and can provide a practical prediction of OS in female patients with metachronous BCBM. The GPA model was generated from the training set and proved to have similar predictive power in the validation set. The model also predicts the POF following initial treatment.

Based on the substantial differences in OS among the 3 risk groups, the GPA model provides a practical "prognostic stratification - treatment strategy" matching pathway for clinical practice:

Low-risk patients (GPA 0.0-3.5): With an estimated 5-year OS, aggressive local treatment (SBRT or minimally invasive surgery) combined with subtype-specific systemic therapy (endocrine therapy for luminal, anti-HER2 therapy for HER2-positive, chemotherapy + immunotherapy for TNBC) is recommended to control BM and prevent SREs. Long-term treatment-related toxicity needs to be carefully addressed given their prolonged survival.

Medium-risk patients (GPA 4.0-5.5): Combined local therapy (palliative radiotherapy for symptomatic lesions) and intensified systemic therapy (combination targeted therapy/chemotherapy) with regular monitoring for visceral metastasis is recommended.

High-risk patients (GPA 6.0-8.5): With an estimated OS above 2 years, palliative care (bone-modifying agents, short-course radiotherapy) should be prioritized to relieve pain and improve quality of life, with systemic therapy individualized based on performance status.

This stratified strategy addresses the limitations of traditional "one-size-fits-all" treatment.

The innovation of this study is the identification of five independent prognostic factors based on multivariate Cox regression and the development of a quantitative scoring system ranging from 0 to 8.5 points according to the HR of each factor. Patients were divided into low-, middle-, and high-risk groups, achieving accurate prognostic stratification. The scoring rules are simple and convenient for rapid clinical application. The model's performance was verified using ROC curves, calibration curves, and DCA. The GPA model provides transparency, repeatability, and bedside stratification, which is far more clinically feasible than recently proposed machine learning or multi-omics models [31].

Several limitations should be acknowledged. First, this was a single-center retrospective study, which inevitably introduced selection

Table 5. The score and survival of different groups in training dataset and validation dataset

Subgroup	Score	Training dataset			Validation dataset		
		Cases (N)	Median bmOS (m)	*P* value	Cases (N)	Median bmOS (m)	*P* value
LRG	0.0-3.5	84	60.3	< 0.001	33	64.0	< 0.001
MRG	4.0-5.5	93	40.0		39	41.6	
HRG	6.0-8.5	38	32.6		21	25.3	

bmOS: overall survival after bone metastasis; LRG: low-risk group; MRG: middle-risk group; HRG: high-risk group.

Table 6. POF following treatment for metachronous breast cancer bone metastasis

POF	All	LRG	MRG	HRG	*P* value
Patients (n)	308	117	132	59	
Bone failure	121 (39.3)	22 (18.8)	47 (35.6)	52 (88.1)	< 0.001
SREs					
radiation to bone	72 (23.4)	13 (11.1)	25 (18.9)	34 (57.6)	< 0.001
pathological fractures	16 (5.2)	3 (2.6)	6 (4.5)	7 (11.9)	0.029
spinal cord compression	21 (6.8)	4 (3.4)	7 (5.3)	10 (16.9)	0.002
surgery for bone complications	29 (9.4)	6 (5.1)	10 (7.6)	13 (22.0)	< 0.001
Visceral failure	87 (28.2)	3 (2.6)	37 (28.0)	47 (79.7)	< 0.001
CNS	19 (6.2)	1 (0.9)	6 (4.5)	12 (20.4)	< 0.001
Non-CNS	68 (22.0)	2 (1.7)	31 (23.5)	35 (59.3)	< 0.001

POF: pattern of failure; LRG: low-risk group; MRG: middle-risk group; HRG: high-risk group; SREs: skeletal-related events; CNS: central nervous system.

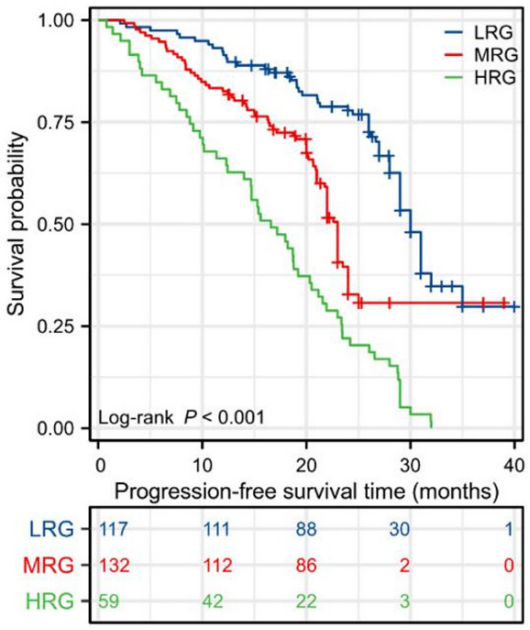

Figure 6. PFS curves of the different groups in the entire cohort. PFS: progression-free survival; LRG: low-risk group; MRG: middle-risk group; HRG: high-risk group.

bias. Only patients with complete medical records and effective follow-up were enrolled; those lost to follow-up, with poor compliance, or with incomplete data were excluded, which may reduce the representativeness of the study population. Second, heterogeneous post-metastasis treatment and inconsistent outpatient surveillance may have introduced follow-up bias, affecting the accuracy of survival and failure data. Third, the GPA model lacks external validation and has not been compared with existing classical BM prognostic models; therefore, a standardized evaluation system that can be widely promoted has not yet been established. Fourth, most existing BM prognostic scoring systems are based on patients with solid tumor BM, including indicators such as systemic status and spinal stability, but do not consider disease-specific factors such as BC molecular subtypes and TTBM, resulting in insufficient prognostic prediction accuracy for BCBM patients. Fifth, most studies did not distinguish between “newly diagnosed BM” and “metachronous BM” in BC. The tumor burden, treatment timing, and performance status of these two types of patients differ significantly, which may have led to bias in the screening of prognostic factors. Future multicenter, large-sample external validation studies should be

conducted to verify the generalizability of the model.

Conclusion

The prognosis of patients with metachronous BCBM as the first metastatic site is significantly influenced by initial stage, molecular subtype, TTBM, BM numbers and EVM. A GPA model was developed in this study to predict survival, which can provide a reference for clinical treatment decisions. No statistically significant difference in AUC was observed between the training dataset and the validation dataset. External validation of the model is necessary.

Acknowledgements

This work was supported by Shanghai Science and Technology Innovation Action Plan (grant number 23Y41900100), the National Key Research and Development Program of China (grant number 2022YFC2404602), National Key R&D Program of China (grant number 2023ZD0502206), Shanghai Hospital Development Center Foundation (grant number SHDC12023108), Scientific and Technological Innovation Action Plan of Shanghai Science and Technology Committee (grant number 22Y31900103), Clinical Research of Shanghai Municipal Health Commission (grant number 20224Y0025), Clinical Research Special Project of Shanghai Municipal Health Commission Health Industry (grant number 202340226), Shanghai Science and Technology Innovation Action Plan Medical Innovation Research Project (grant number 23Y11904700). Beijing Science and Technology Innovation Medical Development Foundation (grant number KC2021-JX-0170-9), National Natural Science Foundation of China (grant number 82373514, 82373202).

Disclosure of conflict of interest

None.

Address correspondence to: Jiayi Chen and Gang Cai, Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, No. 197 Ruijin 2nd Road, Shanghai 200025, China. Tel: +86-021-64370045-602400; E-mail: chenjiayi0188@aliyun.com (JYC); E-mail: caigangcg1@163.com (GC)

References

[1] Upadhyay R and Bazan JG. Advances in radiotherapy for breast cancer. Surg Oncol Clin N Am 2023; 32: 515-536.

[2] Zhang C, Qi L, Cai J, Wu H, Xu Y, Lin Y, Li Z, Chekhonin VP, Peltzer K, Cao M, Yin Z, Wang X and Ma W. Clinicomics-guided distant metastasis prediction in breast cancer via artificial intelligence. BMC Cancer 2023; 23: 239.

[3] Shao H and Varamini P. Breast cancer bone metastasis: a narrative review of emerging targeted drug delivery systems. Cells 2022; 11: 388.

[4] Wang X, Zhang T, Zheng B, Lu Y, Liang Y, Xu G, Zhao L, Tao Y, Song Q, You H, Hu H, Li X, Sun K, Li T, Zhang Z, Wang J, Lan X, Pan D, Fu YX, Yue B and Zheng H. Lymphotoxin-β promotes breast cancer bone metastasis colonization and osteolytic outgrowth. Nat Cell Biol 2024; 26: 1597-1612.

[5] de Maar JS, Luyendijk M, Suelmann BBM, van der Kruijssen DEW, Elias SG, Siesling S and van der Wall E. Comparison between de novo and metachronous metastatic breast cancer: the presence of a primary tumour is not the only difference-a Dutch population-based study from 2008 to 2018. Breast Cancer Res Treat 2023; 198: 253-264.

[6] Nolan E, Kang Y and Malanchi I. Mechanisms of organ-specific metastasis of breast cancer. Cold Spring Harb Perspect Med 2023; 13: a041326.

[7] Feng M, Kang Y, Li S, Yang D, Ren S, Tang S, Mo D and Lei H. Prognostic factors analysis and nomogram construction of breast cancer patients lung metastases and bone metastases. Surg Open Sci 2025; 26: 28-38.

[8] Koyama Y, Horimoto Y, Yamada A, Narui K, Yamamoto S, Kaise H, Yamada K and Ishikawa T. Organ-specific clinicopathological features that are associated with post-relapse survival of metastatic breast cancer in Japanese women: a multicenter cohort study. World J Oncol 2025; 17: 52-62.

[9] Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J and Cardoso F. Breast cancer. Nat Rev Dis Primers 2019; 5: 66.

[10] Zulauf N, Brüggmann D, Groneberg D and Oremek GM. Expressiveness of bone markers in breast cancer with bone metastases. Oncology 2019; 97: 236-244.

[11] Parkes A, Clifton K, Al-Awadhi A, Oke O, Warneke CL, Litton JK and Hortobagyi GN. Characterization of bone only metastasis patients with respect to tumor subtypes. NPJ Breast Cancer 2018; 4: 2.

[12] Pelizzari G, Basile D, Zago S, Lisanti C, Bartoletti M, Bortot L, Vitale MG, Fanotto V, Barban S, Cinausero M, Bonotto M, Gerratana L, Mansutti M, Curcio F, Fasola G, Minisini AM and Puglisi F. Lactate dehydrogenase (LDH) response to First-Line treatment predicts survival in metastatic breast cancer: first clues for a cost-effective and dynamic biomarker. Cancers (Basel) 2019; 11: 1243.

[13] Sperduto PW, Berkey B, Gaspar LE, Mehta M and Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008; 70: 510-514.

[14] Katagiri H, Okada R, Takagi T, Takahashi M, Murata H, Harada H, Nishimura T, Asakura H and Ogawa H. New prognostic factors and scoring system for patients with skeletal metastasis. Cancer Med 2014; 3: 1359-1367.

[15] Tokuhashi Y, Matsuzaki H, Oda H, Oshima M and Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. Spine (Phila Pa 1976) 2005; 30: 2186-2191.

[16] Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H and Akamaru T. Surgical strategy for spinal metastases. Spine (Phila Pa 1976) 2001; 26: 298-306.

[17] Choi D, Pavlou M, Omar R, Arts M, Balabaud L, Buchowski JM, Bunger C, Chung CK, Coppes MH, Depreitere B, Fehlings MG, Kawahara N, Lee CS, Leung Y, Martin-Benlloch JA, Massicotte EM, Mazel C, Meyer B, Oner FC, Peul W, Quraishi N, Tokuhashi Y, Tomita K, Ulbricht C, Verlaan JJ, Wang M and Crockard HA. A novel risk calculator to predict outcome after surgery for symptomatic spinal metastases; use of a large prospective patient database to personalise surgical management. Eur J Cancer 2019; 107: 28-36.

[18] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR and Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017; 67: 93-99.

[19] Yu Y, Ren W, Mao L, Ouyang W, Hu Q, Yao Q, Tan Y, He Z, Ban X, Hu H, Lin R, Wang Z, Chen Y, Wu Z, Chen K, Ouyang J, Li T, Zhang Z, Liu G, Chen X, Li Z, Duan X, Wang J and Yao H. MRI-based multimodal AI model enables prediction of recurrence risk and adjuvant therapy in breast cancer. Pharmacol Res 2025; 216: 107765.

[20] Zhong X, Lin Y, Zhang W and Bi Q. Predicting diagnosis and survival of bone metastasis in breast cancer using machine learning. Sci Rep 2023; 13: 18301.

[21] Bekele K, Nugusu F, Beressa G, Hollis T, Ferreres A, Duguma D, Guta B, Gutnik L, Lemesse B and Gezahegn H. Proportion of early-stage breast cancer at diagnosis in Ethiopia: a systematic review and meta-analysis. BMC Cancer 2024; 24: 1017.

[22] Huang L, Chen X, Yan M, Xiang Z and Wu J. Lactate and lactylation in breast cancer: current understanding and therapeutic opportunities. Cancer Biol Med 2025; 22: 789-805.

[23] Swain SM, Shastry M and Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nat Rev Drug Discov 2023; 22: 101-126.

[24] Öner İ, Anık H, Kurt İnci B, Kubilay Tolunay P, Ateş Ö, Yalçıntaş Arslan Ü and Karaçin C. A comparison of the efficacy and safety of denosumab and zoledronic acid in patients with bone metastatic breast cancer receiving CDK4/6 inhibitor therapy. Medicina (Kaunas) 2025; 61: 360.

[25] Carsote M, Terzea D, Vasilescu F, Cucu AP, Ciuche A and Nistor C. Sternum metastases: from case-identifying strategy to multidisciplinary management. Diagnostics (Basel) 2023; 13: 2698.

[26] Choi S, Friedrichs J, Song YH, Werner C, Estroff LA and Fischbach C. Intrafibrillar, bone-mimetic collagen mineralization regulates breast cancer cell adhesion and migration. Biomaterials 2019; 198: 95-106.

[27] Harada H, Shikama N, Notsu A, Shirato H, Yamada K, Uezono H, Koide Y, Kubota H, Yamazaki T, Ito K, Heianna J, Okada Y, Tonari A, Katoh N, Wada H, Ejima Y, Yoshida K, Kosugi T, Takahashi S, Komiyama T, Uchida N, Miwa M, Watanabe M, Nagakura H, Ikeda H, Saito T, Asakawa I, Takahashi T and Shigematsu N. Multi-institutional prospective observational study of radiotherapy for metastatic bone tumor. J Radiat Res 2024; 65: 701-711.

[28] van Broekhoven DL, Dootjes LW, van der Veldt A, Zillikens C and van Oldenrijk J. Effect of bisphosphonates on skeletal related events in long bone metastases of renal cell carcinoma: a systematic review. Clin Genitourin Cancer 2023; 21: e190-e197.

[29] Xiong Z, Deng G, Huang X, Li X, Xie X, Wang J, Shuang Z and Wang X. Bone metastasis pattern in initial metastatic breast cancer: a population-based study. Cancer Manag Res 2018; 10: 287-295.

[30] Adrada BE, Moseley TW, Kapoor MM, Scoggins ME, Patel MM, Perez F, Nia ES, Khazai L, Arribas E, Rauch GM and Guirguis MS. Triple-negative breast cancer: histopathologic features,

genomics, and treatment. Radiographics 2023; 43: e230034.
[31] Fontana A, Barbano R, Pasculli B, Mazza T, Palumbo O, Binda E, Trivieri N, Mencarelli G, Laurenzana I, Lamorte D, De Luca L, Caivano A, Biagini T, Rendina M, Lo Mele A, Prencipe G, Bravaccini S, Murgo R, Ciuffreda L, Morritti M, Valori VM, Di Lisa FS, Vici P, Castelvetere M, Carella M, Graziano P, Maiello E, Copetti M, Esteller M and Parrella P. Development of a microRNA-based prognostic model for accurate prediction of distant metastasis in breast cancer patients. Breast Cancer Res 2025; 27: 170.

Table S1. The specific results of X-tile analysis

Analysis Index	TTBM Cutoff Value Analysis	GPA Score Stratification Analysis (Training Cohort)	GPA Score Stratification Verification (Validation Cohort)
Analysis Cohort (n)	308	215	93
Optimal Cutoff Value(s)	60 months	3.5 points, 5.5 points	3.5 points, 5.5 points
Log-rank χ^2	4.482	36.892 (overall)	29.764 (overall)
Log-rank *P* Value	0.035	< 0.001	< 0.001
Prognostic Misclassification Rate	12.70%	8.90%	9.60%
Survival Separation Degree	High	Very high	Very high