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Research Paper

Prognostic factors analysis and nomogram construction of breast cancer patients lung metastases and bone metastases☆

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ABSTRACT

Objective: To investigate the clinicopathological factors influencing lung and bone metastasis in breast cancer, and to further construct a nomogram model for predicting the risk of lung and bone metastasis in breast cancer patients at various time points, followed by a prognostic analysis.

Methods: The retrospective analysis included 200 patients with breast cancer, among whom 51 had lung metastases and 57 had bone metastases. The remaining 92 patients without metastases served as the control group. Baseline characteristics were analyzed using the chi-square test; COX univariate and multivariate analyses were applied to explore the influencing factors. A nomogram was constructed to predict the risk of individuals developing lung or bone metastasis at 1, 3, and 5 years. The predictive model was further validated by ROC curves and calibration curves, and decision curves were plotted to assess the clinical application value of the model.

Results: Analysis revealed that age, BMI, tumor size, lymph node status, ER, PR, HER-2, and Ki67 significantly influenced lung metastasis ($P < 0.05$), while age, BMI, tumor size, lymph node status, ER, PR, and Ki67 significantly impacted bone metastasis ($P < 0.05$). The nomogram indicated that HER-2 negativity elevated the risk of breast cancer lung metastases. ROC curves were plotted for 1, 3, and 5 years, with AUC values and 95 % confidence intervals of 0.803 (67.42-93.15), 0.831 (75.93-90.29), and 0.854 (78.43-92.34) in the lung metastasis group, and 0.754 (55.15-95.66), 0.753 (64.91-85.71), and 0.777 (68.64-86.67) in the bone metastasis group, respectively. These results suggest that the model has a superior predictive efficacy and a high degree of predictive reliability. Additionally, the calibration curve demonstrated that the model is well-fitted, and the decision curve indicated that the model possesses clinical utility in practice.

Conclusion: Age, BMI, tumor size, lymph node status, ER, PR, and Ki67 significantly influence lung and bone metastasis in breast cancer. The nomogram developed in this study can evaluate the risk of lung or bone metastasis for individuals at 1, 3, and 5 years, predict prognosis, guide clinical individualized treatment, and bring more benefits, further improving the quality of life for patients. It demonstrates good predictive ability and clinical value.

Key message: The nomogram model constructed in this study can predict prognosis, guide clinical individualized treatment, and bring more benefits, further improving the quality of life for patients. It possesses good predictive ability and holds certain clinical predictive value.

☆ This manuscript is submitted as an original work. It is a retrospective analysis.

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Introduction

Breast cancer is currently the most common female malignant tumor, posing a serious threat to women's lives and health, with its incidence rate ranking first among women worldwide [1–3]. In China, the annual incidence of breast cancer is rising at a rate of 3 % to 4 %, with a 5-year survival rate of 73 %.According to the global cancer data released by the World Health Organization's International Agency for Research on Cancer in 2020, there were 2.26 million new cases of breast cancer and approximately 680,000 deaths [4].The leading cause of death is distant metastasis, and 20-30 % of breast cancer patients develop distant metastases. Bone, lung, and liver are the most common sites of metastasis [5–7].

Bone metastasis is the most common site of metastasis in breast cancer, occurring in approximately 60 % to 75 % of patients with breast cancer metastasis [8].Bone tissue is the initial metastatic site in 26 % to 50 % of patients with metastatic breast cancer. Once a breast cancer patient develops bone metastases, their median survival is only 40 to 65 months, with a 5-year survival rate of just 20 % [9,10].Studies indicate that hormone receptor-positive breast cancer patients are more prone to developing bone metastases, which can result in bone metabolism disorders and thus cause skeletal-related events (SRE), impacting the quality of life for patients and indirectly reducing life expectancy [11,12].The occurrence of SRE can cause symptoms such as bone pain, pathological fractures, and spinal cord compression, all of which can significantly impact the patient's survival. Spinal cord compression, in particular, is a symptom that requires urgent attention [13,14]. Additionally, the central axis bone is the most likely site of metastasis for breast cancer bone metastases [10].

Lung metastases are the second most common site of breast cancer metastases and are associated with a poorer prognosis [15]. Clinical research indicates that 60-70 % of breast cancer patients ultimately succumb to lung metastases [16]. The development of lung metastases in a breast cancer patient markedly reduces their life expectancy. Presently, the median survival time for patients with breast cancer lung metastases is 21 months. Lung function deteriorates in these patients, leading to symptoms such as coughing and breathlessness, which ultimately result in the patient's death [17–19].

Current studies indicate that patients with ER- and PR-positive breast cancer are more prone to developing bone metastases, whereas visceral and brain metastases are more common in those with HER-2-positive and triple-negative breast cancers, potentially linked to tumor aggressiveness [20,21]. The mechanisms behind lung and bone metastasis in breast cancer are intricate, and various molecular subtypes may influence the location of metastasis and its prognosis differently [22]. The incidence of metastasis among different patients and the factors that affect its occurrence remain unclear. For individuals with advanced breast cancer, complete cure is not feasible, but we can extend their survival, alleviate symptoms, and enhance their quality of life through comprehensive treatment. There is an urgent need to investigate as many factors as possible that contribute to metastasis, enabling us to intervene early in the treatment of breast cancer patients and further extend their survival.

Previous studies have indicated [23,24] that clinicopathological factors influencing breast cancer metastasis include tumor size, histological grading, lymphovascular invasion, lymph node status, ER, PR, and HER-2 status. It has also been demonstrated that certain tumors may metastasize to specific organs, a phenomenon referred to as organotropic metastasis [25,26]. A retrospective clinical study [27] revealed that the number of lymph node metastases, endocrine therapy, visceral metastases, the number of initial bone metastatic lesions, and HER-2 expression were independent prognostic factors affecting survival in patients with breast cancer bone metastases. In a study on lung metastases of breast cancer [28], findings indicated that older age, black race, high histological grade, triple-negative subtype, and the number of metastatic sites were independent risk factors, while hormone receptor status was an important prognostic factor.

With the advancement of medical science, not only has the survival rate of breast cancer patients with early and standardized treatment shown continuous improvement [29,30], but the outcomes for those with advanced breast cancer have also improved [31]. The aim of our study was to investigate the prognostic factors for breast cancer patients with lung and bone metastases. Most existing research has concentrated on either bone or lung metastasis of breast cancer separately, with few comparative studies on the timing of metastasis between bone and lung, and even fewer reports on the likelihood of lung and bone metastasis at 1, 3, and 5 years in breast cancer. In this study, we further examined the risk factors for lung and bone metastasis by analyzing clinicopathological features and constructing a nomogram for both. Nomograms are valuable tools for assessing the survival of patients with malignant tumors and offer advantages in predicting the prognosis of such tumors [32–34]. Additionally, the ROC curve and calibration curve were employed to validate the nomogram. This study provides a reference for clinicians to predict lung and bone metastasis in breast cancer patients and offers further assistance for clinical individualized treatment.

Materials and methods

Research objectives

Clinical data

A retrospective analysis was conducted on breast cancer patients treated at Chuxiong Yi Autonomous Prefecture People's Hospital and Yunnan Cancer Hospital from January 2012 to December 2022. A total of 200 patients were enrolled based on the inclusion and exclusion criteria, comprising 51 patients with lung metastasis of breast cancer, 57 patients with bone metastasis, and 92 patients without metastasis in the control group (Fig. 1).

Criteria for lung and bone metastases from breast cancer

The diagnosis of distant organ metastases from breast cancer is based on diagnostic imaging and/or biopsy pathology histology as the source of the breast cancer. The criteria for diagnosing lung metastasis involve a CT examination suggesting possible lung metastasis and a pathological examination confirming the diagnosis of lung metastasis from breast cancer. Bone metastasis is indicated by an enhanced CT scan showing bone metastasis and a bone scan indicating bone metastasis. These criteria were sourced from the 2019 edition of the Chinese Anti-Cancer Society guidelines.

Inclusion criteria

(1) Female patients with breast cancer confirmed by preoperative biopsy or postoperative pathology.
(2) All patients with lung metastasis were pathologically confirmed as such after lung puncture or partial lobectomy. All patients with bone metastasis were confirmed by enhanced CT and bone scan, showing bone metastasis (The standards are taken from the 2019 edition of the Guidelines of the Chinese Anti-Cancer Association).
(3) The patient had complete general data, imaging, and pathological examination results in our hospital, including height, weight, BMI, pathological report, and breast ultrasound.
(4) There were no patients with other malignant tumors.

Exclusion criteria

(1) The patient has not been confirmed by pathology.
(2) Patients with breast cancer at tumor stage T4.
(3) Patients with incomplete data, including imaging and pathological data.
(4) Male breast cancer patients.
(5) Patients with incomplete treatment and interrupted follow-up.

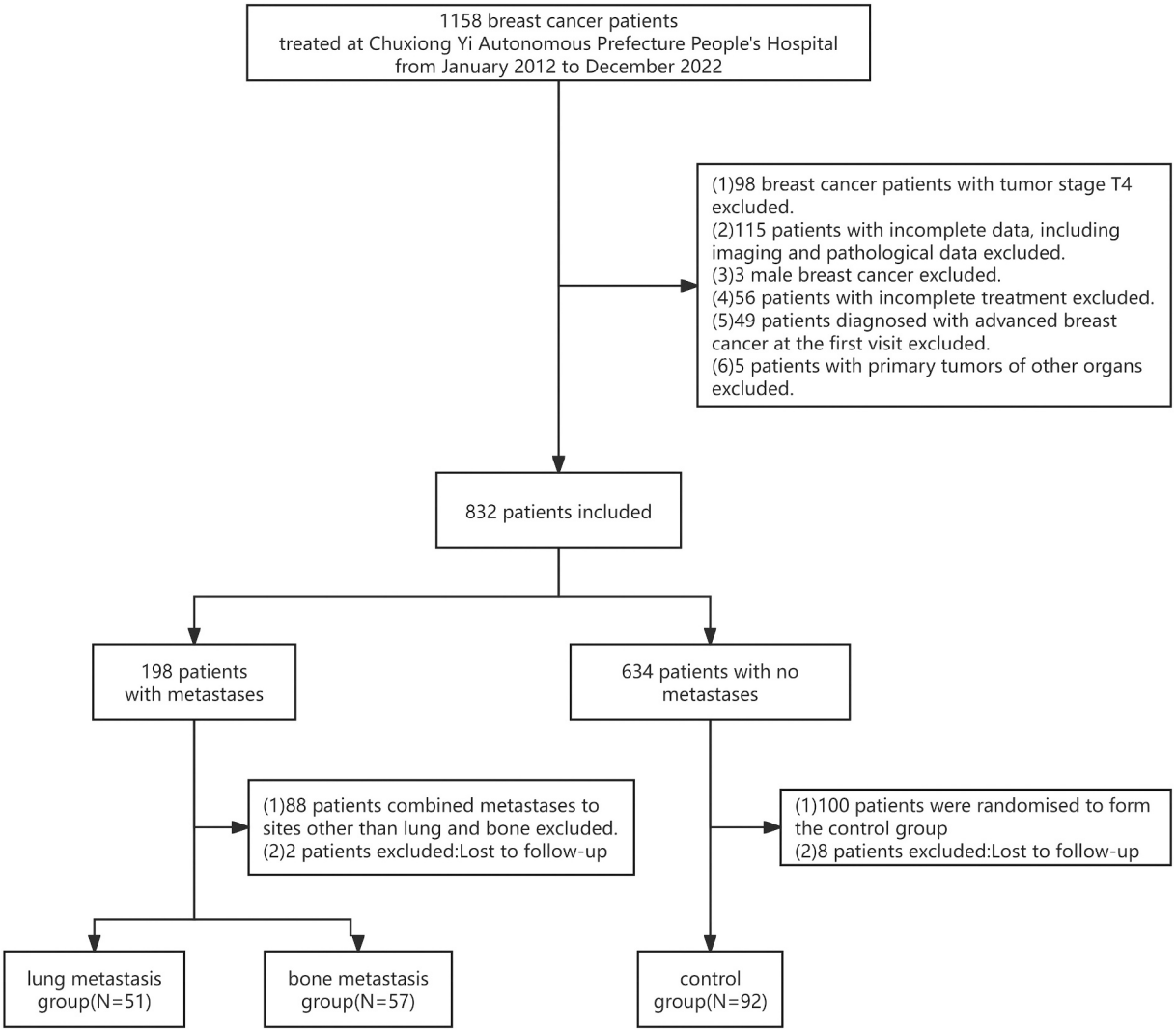

Fig. 1. Flowchart of patient enrollment.

(6) Patients diagnosed with advanced breast cancer at the initial visit, or patients with primary tumors from other organs.
(7) Patients with multi-organ metastases from breast cancer include those in the lung metastasis group, where metastases affect organs other than the lungs, and those in the bone metastasis group, where metastases affect organs other than the bones.

Factors included in the study

The following factors were collected and analyzed: general information (age, height, weight, BMI) and pathological characteristics (T stage, N stage, lymph node metastasis, ER status, PR status, Her-2 status, Ki67 status).

Research method

Follow-up and study endpoint

The enrolled patients had complete treatment and review data at our hospital. The follow-up cut-off time was January 2024. The primary endpoint was the occurrence of lung or bone metastases.

Data collation

The median age, height, and weight were used for analysis; the Body Mass Index (BMI) was categorized using a cutoff of 24, in accordance with international standards. In the pathological data, tumor size was graded as T1, T2, or T3 (patients with tumors classified as T4 were excluded from the study at the time of enrollment). Lymph node status was determined based on postoperative pathological examination and lymph node puncture results, with lymph node metastasis recorded as positive and the absence of cancer metastasis in the lymph nodes recorded as negative. Estrogen Receptor (ER) and Progesterone Receptor (PR) positivity were defined as $\geq$1 % based on immunohistochemical (IHC) results and the criteria set forth by the American Society of Clinical Oncology (ASCO). Human Epidermal Growth Factor Receptor 2 (HER-2) was classified as negative or positive based on IHC results (negative if IHC 1+; for IHC 2+, HER-2 gene amplification was further detected by fluorescence in situ hybridization, with amplification recorded as positive and no amplification recorded as negative; and if IHC 3+, it was recorded as positive). According to the latest treatment guidelines, a cutoff value of 14 % was used for Ki67.

Statistical method

All data were processed using the SPSS 25.0 statistical software package. Count data were analyzed using variance analysis, with $P<0.05$ considered statistically significant. Clinical and pathological characteristics were included in the COX regression model to analyze the risk factors affecting breast cancer metastasis and prognosis, with $P<0.05$ indicating a statistically significant difference. R software was utilized to construct predictive models by incorporating meaningful

variables from the multifactorial COX analysis into the nomogram model. Column-line plots, ROC curves, and calibration curves were drawn to assess the predictive ability of the nomogram model based on the area under the ROC curves. When the AUC value is closer to 1, it suggests that the model has better predictive ability. An AUC >0.75 indicates that the model has excellent discrimination. Generally, a model is considered acceptable when the AUC value falls between 0.5 and 0.75. For the calibration curve, the relationship between its predicted probability and the actual probability is observed. If the curve closely aligns with the actual probability, it indicates a good fit. Finally, a decision curve was plotted, featuring two reference lines: the None line and the All line. The net return is the vertical coordinate, and the risk threshold is the horizontal coordinate, with the risk threshold ranging from 0 to 1.0. The clinical significance is indicated when the net return is >0.

Results

Clinicopathological features: analysis of patient's general information and clinicopathological data

A total of 200 breast cancer patients were enrolled in this study. The age of the participants ranged from 25 to 81 years old, their height ranged from 148 to 170 cm, and their weight ranged from 42 to 80 kg. The median age was 40 years old, the median height was 157 cm, and the median weight was 55 kg. Other clinical and pathological data, including BMI, tumor size, lymph node status, ER, PR, HER-2, and Ki67, were also collected. Among breast cancer patients with a BMI <24, there were 36 cases of lung metastases, 35 cases of bone metastases, and 66 cases with no metastases. In contrast, patients with a BMI of 24 or greater had 15 cases of lung metastases, 32 cases of bone metastases, and 26 cases with no metastases. Tumor sizes were categorized into T1, T2, and T3 stages. Of those with lung metastases, 6 were in the T1 stage, 34 in the T2 stage, and 11 in the T3 stage. Among patients with bone metastases, 15 were in the T1 stage, 23 in the T2 stage, and 19 in the T3 stage. For patients without metastases, 18 were in the T1 stage, 66 in the T2 stage, and 8 in the T3 stage. In the breast cancer axillary lymph node negative group, there were 14 patients with lung metastasis, 12 with bone metastasis, and 43 without metastasis. In the breast cancer axillary lymph node positive group, there were 37 patients with lung metastasis, 45 with bone metastasis, and 49 without metastasis. According to the statistical analysis of pathological data, among ER-negative breast cancers, there were 19 cases of lung metastasis, 22 cases of bone metastasis, and 31 cases with no metastases. Among ER-positive breast cancers, there were 32 cases of lung metastasis, 35 cases of bone metastasis, and 61 cases with no metastases. For PR-negative breast cancers, there were 18 cases of lung metastasis, 11 cases of bone metastasis, and 33 cases with no metastases. Among PR-positive breast cancers, there were 33 cases of lung metastasis, 46 cases of bone metastasis, and 59 cases with no metastases. In HER-2 negative breast cancer, there were 16 cases of lung metastasis, 33 cases of bone metastasis, and 39 cases with no metastases. In HER-2 positive breast cancer, there were 35 cases of lung metastasis, 34 cases of bone metastasis, and 53 cases with no metastases. Among breast cancers with a Ki67 level <14 %, there were 11 cases of lung metastasis, 19 cases of bone metastasis, and 25 cases with no metastases. For breast cancers with a Ki67 level of 14 % or greater, there were 36 cases of lung metastasis, 32 cases of bone metastasis, and 54 cases with no metastases. The chi-square test results are as follows: age ($\chi^2 = 39.757$, $P < 0.05$), height ($\chi^2 = 5.095$, $P > 0.05$), weight ($\chi^2 = 6.901$, $P < 0.05$), BMI ($\chi^2 = 7.819$, $P < 0.05$), tumor size ($\chi^2 = 20.340$, $P < 0.05$), lymph node status ($\chi^2 = 11.781$, $P < 0.05$), ER ($\chi^2 = 0.414$, $P > 0.05$), PR ($\chi^2 = 5.108$, $P > 0.05$), HER-2 ($\chi^2 = 3.819$, $P > 0.05$), Ki67 ($\chi^2 = 3.624$, $P > 0.05$). The data analysis of the aforementioned clinicopathological characteristics indicates that the differences in height, ER, PR, HER-2, and Ki67 were not statistically significant ($P > 0.05$) for patients with lung metastasis, bone metastasis, and no metastasis. However, age, weight, BMI, tumor size, and lymph node status showed statistically significant differences in patients with breast cancer lung metastasis, bone metastasis, and no metastasis ($P < 0.05$). (Table 1)

Survival prognosis analysis

Univariate and multivariate analysis of breast cancer patients

A univariate COX analysis was conducted for the included variables, and a 95 % confidence interval (CI) was calculated. The results of the univariate COX analysis of lung metastases from breast cancer are presented in Table 2: age (HR = 0.200, 95 % CI = 0.111-0.359, P < 0.05), height (HR = 1.398, 95 % CI = 0.800-2.444, P = 0.240), weight (HR = 1.214, 95 % CI = 0.691-2.136, P = 0.500), BMI (HR = 1.772, 95 % CI = 1.010-3.108, P = 0.046), tumor size (HR = 1.172, 95 % CI = 1.008-1.362, P = 0.039), lymph node status (HR = 2.244, 95 % CI = 1.164-4.324, P = 0.016), ER (HR = 0.393, 95 % CI = 0.206-0.749, P = 0.005), PR (HR = 0.388, 95 % CI = 0.202-0.746, P = 0.005), HER-2 (HR = 0.531, 95 % CI = 0.295-0.956, P = 0.035), and Ki67 (HR = 0.643, 95 % CI = 0.425-0.973, P = 0.037).

Univariate COX analysis of bone metastases from breast cancer showed (Table 3): age (HR = 0.232, 95%CI = 0.132-0.407, P < 0.001), height (HR = 1.136, 95%CI = 0.662-1.950, P = 0.869), weight (HR = 1.295, 95%CI = 0.718-2.500, P = 0.653), BMI (HR = 1.721, 95%CI = 1.007-2.942, P = 0.047), tumor size (HR = 1.521, 95%CI = 1.002-2.310,

Table 1
Clinicopathological features of breast cancer patients with lung metastasis, bone metastasis and no metastasis.

Variable	Lung metastasis (n = 51)	Bone metastasis (n = 57)	No metastasis (n = 92)	χ^2	P
Age (years)					
<40	29	38	17	39.757	<0.05
≥40	22	19	75		
Height (cm)					
<157	23	25	52	5.095	>0.05
≥157	28	32	40		
Weight (kg)					
<55	22	20	52	6.901	<0.05
≥55	29	37	40		
BMI					
<24	36	35	66	7.819	<0.05
≥24	15	32	26		
Tumor size					
T1	6	15	18	20.340	<0.05
T2	34	23	66		
T3	11	19	8		
Lymph node status					
+	37	45	49	11.781	<0.05
–	14	12	43		
ER					
+	32	35	61	0.414	>0.05
–	19	22	31		
PR					
+	33	46	59	5.108	>0.05
–	18	11	33		
HER-2					
+	35	34	53	3.819	>0.05
–	16	33	39		
Ki67 (%)					
<14	11	19	25	3.624	>0.05
≥14	36	32	54		
NA	4	6	13		

ER: estrogen receptor.
PR: progesterone receptor.
HER-2: human epidermal growth factor receptor-2.

Table 2
Univariate and multivariate COX regression analysis of breast cancer patients with lung metastasis.

Variable	Univariate COX regression			Multivariate COX regression		
	HR	95 % CI	P	HR	95 % CI	P
Age	0.200	0.111–0.359	<0.05	0.317	0.171–0.588	<0.05
Height	1.398	0.800–2.444	0.240			
Weight	1.214	0.691–2.136	0.500			
BMI	1.772	1.010–3.108	<0.05	2.145	1.140–4.035	<0.05
Tumor size	1.172	1.008–1.362	<0.05	2.114	1.127–3.964	<0.05
Lymph node status	2.244	1.164–4.324	<0.05	2.241	0.999–5.026	<0.05
ER	0.393	0.206–0.749	<0.05	2.292	1.022–5.140	<0.05
PR	0.388	0.202–0.746	<0.05	0.320	0.159–0.645	<0.05
HER-2	0.531	0.295–0.956	<0.05	0.455	0.229–0.905	<0.05
Ki67	0.643	0.425–0.973	<0.05	0.632	0.412–0.970	<0.05

ER: estrogen receptor.
PR: progesterone receptor.
HER-2: human epidermal growth factor receptor-2.

Table 3
Univariate and multivariate COX regression analysis of breast cancer patients with bone metastasis.

Variable	Univariate COX regression			Multivariate COX regression		
	HR	95 % CI	P	HR	95 % CI	P
Age	0.232	0.132–0.407	<0.05	0.178	0.096–0.332	<0.05
Height	1.136	0.662–1.950	0.869			
Weight	1.295	0.718–2.500	0.653			
BMI	1.721	1.007–2.942	<0.05	1.958	1.019–3.764	<0.05
Tumor size	1.521	1.002–2.310	<0.057	1.954	1.270–3.007	<0.05
Lymph node status	2.363	1.244–4.490	<0.05	2.331	1.175–4.624	<0.05
ER	0.566	0.327–0.981	<0.05	0.349	0.177–0.690	<0.05
PR	1.955	1.006–3.799	<0.05	2.025	0.915–4.482	<0.05
HER-2	1.304	0.742–2.293	0.356			
Ki67	1.691	1.293–2.212	<0.05	1.429	1.019–2.005	<0.05

ER: estrogen receptor.
PR: progesterone receptor.
HER-2: human epidermal growth factor receptor-2.

P = 0.049), lymph node status (HR = 2.363, 95%CI = 1.244-4.490, P < 0.05), ER (HR = 0.566, 95%CI = 0.327-0.981, P = 0.043), PR (HR = 1.955, 95%CI = 1.006-3.799, P = 0.048), HER-2 (HR = 1.304, 95%CI = 0.742-2.293, P = 0.356), and Ki67 (HR = 1.691, 95%CI = 1.293-2.212, P < 0.001).

Indicators that were significant in the univariate analysis were included in the multivariate analysis, and the results are presented in Tables 2 and 3: The differences in height and weight were not statistically significant in patients with breast cancer lung metastases (P > 0.05); however, age, BMI, tumor size, lymph node status, ER, PR, HER-2, and Ki67 were statistically significant in these patients (P < 0.05) (Table 2). The differences in height, weight, and HER-2 were not statistically significant in patients with breast cancer bone metastases (P > 0.05); however, the differences in age, BMI, tumor size, lymph node status, ER, PR, and Ki67 were statistically significant in these patients (P < 0.05) (Table 3).

Survival analysis

The survival analysis of breast cancer patients with lung metastasis, bone metastasis, and without metastasis revealed statistically significant differences in disease-free survival (DFS) among the three groups (P < 0.05) (Fig. 2A). However, the survival analysis of breast cancer patients with lung metastasis compared to those with bone metastasis showed no significant difference in DFS between these two groups (P > 0.05) (Fig. 2B).

Construction and verification of a nomogram for breast cancer patients with lung and bone metastases

Construction of a nomogram for breast cancer patients with lung and bone metastases

Based on COX multifactor analysis, indicators that exhibited statistically significant differences in multivariate analysis were incorporated into the prediction model. For breast cancer lung metastasis, a total of eight factors were included: age, BMI, tumor size, lymph node metastasis, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki67. For breast cancer bone metastasis, seven factors were considered: age, BMI, tumor size, lymph node metastasis, ER, PR, and Ki67. To construct nomograms for predicting the risk factors associated with the clinicopathological characteristics of patients with breast cancer lung and bone metastases, R software (version 4.1.1) was utilized to develop these nomograms for patients with breast cancer lung and bone metastases, respectively. A brief description of the application of nomograms: Nomograms are used to transform complex equations into visual images, making the results of predictive models more readable. By applying nomograms, it is possible to obtain a score corresponding to the status of each predictor, that is, the "Points" scale in the first row. Row 2 starts with the scale of the included independent variables. The Total Points scale sums the scores corresponding to each of the above indicator states into a total score.

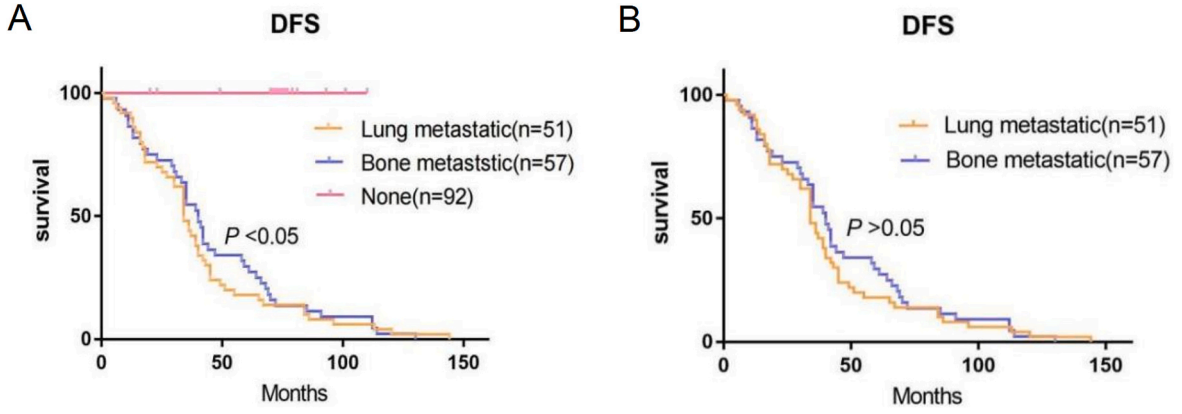

Fig. 2. Survival curves of breast cancer patients with lung metastasis, bone metastasis, and no metastasis.
A. Survival curves of breast cancer patients with lung metastasis, bone metastasis, and the control group without metastasis (P < 0.05).
B. Survival curve of breast cancer patients with lung and bone metastasis (P > 0.05).

The predicted probability of the patient's breast cancer developing lung metastasis or bone metastasis at 1, 3, and 5 years is then derived from the total score projected to the last three rows, respectively. With these nomograms, we can easily obtain the probability of each breast cancer patient developing metastasis at the corresponding site at 1, 3, and 5 years at the initial diagnosis. For breast cancer lung metastases (Fig. 3A), a score of 0 was assigned when age was ≥40 years, and 99 when age was <40 years; a score of 0 was given for BMI <24 and 34 for BMI ≥24; a score of 0 was assigned when the tumor size stage was T2, 9 for T1, and 97 for T3; axillary lymph nodes were scored 0 for negative and 42 for positive; ER-negative was assigned 87 points and positive 0 points; PR-negative was assigned 0 points and positive 15 points; HER-2-negative was assigned 98 points and positive 0 points; 59 points were given when Ki67 < 14 % and 89 points when Ki67 ≥ 14 %. For breast cancer bone metastases (Fig. 3B), a score of 0 was assigned when age was ≥40 years, and 99 when age was <40 years; a score of 0 was given for BMI <24 and 47 for BMI ≥24; a score of 0 was assigned when the tumor size stage was T2, 29 for T1, and 74 for T3; axillary lymph nodes were scored 0 for negative and 28 for positive; 67 points were given for ER-negative and 0 points for positive; 0 points were assigned for PR-negative and 72 points for positive; 25 points were given when Ki67 < 14 % and 55 points when Ki67 ≥ 14 %. A comparison of the nomograms indicates that ER-negative and PR-positive increase the risk of breast cancer lung and bone metastases. The nomograms offer a comprehensive assessment

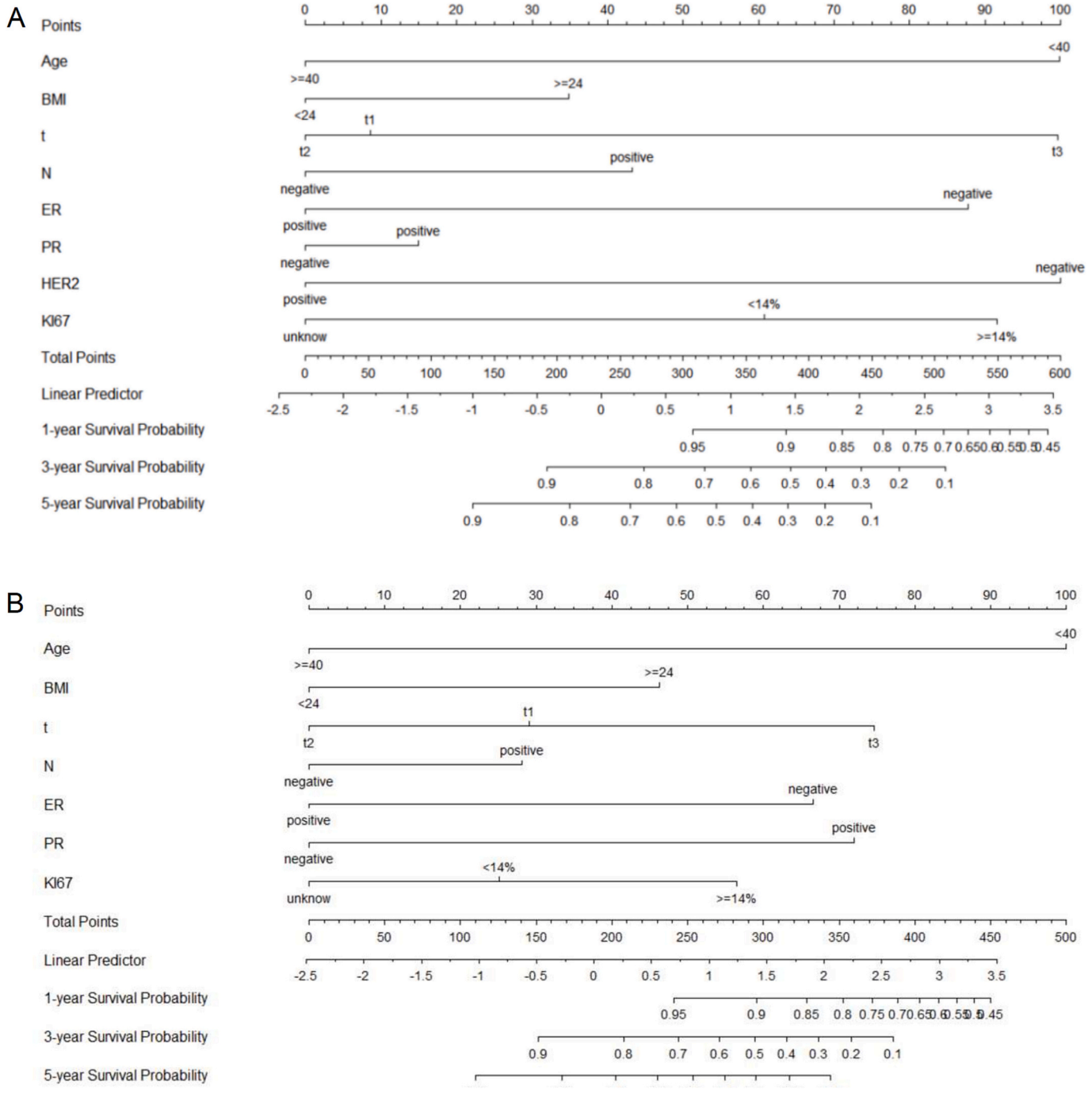

Fig. 3. Nomogram of breast cancer with lung and bone metastasis.
A. Construction of the nomogram for patients with lung metastasis from breast cancer.
B. Construction of the nomogram for patients with bone metastasis from breast cancer.

of the risk and probability of lung and bone metastases at 1, 3, and 5 years for individuals with breast cancer (Fig. 3).

ROC curves

The reliability of the prediction model is assessed by its differentiation and calibration. Consequently, we utilized the R software to plot and analyze the 1-year, 3-year, and 5-year working curves (ROC curves) for the nomograms of lung and bone metastases from breast cancer, respectively, and to derive their AUC values. The findings indicated that the ROC curves and their AUC values, along with 95 % confidence intervals for the 1, 3, and 5-year ROC curves of the nomogram for breast cancer lung metastases, were 0.803 (67.42-93.15), 0.831 (75.93-90.29), and 0.854 (78.43-92.34), respectively (Fig. 4A). For the nomogram of breast cancer bone metastases, the ROC curves with their AUC values and 95 % confidence intervals were 0.754 (55.15-95.66), 0.753 (64.91-85.71), and 0.777 (68.64-86.67) for the 1, 3, and 5-year ROC curves, respectively (Fig. 4B). Based on the ROC curve and 95 % confidence interval, it is evident that the AUC for 1 year, 3 years, and 5 years is >0.75 for both breast cancer lung and bone metastases, signifying that the prediction model exhibits high sensitivity and specificity with excellent discriminative ability, and its predictions are accurate and reliable with superior predictive performance.

Calibration curves

The calibration curves for lung metastasis (Fig. 5A, C, E) and bone metastasis (Fig. 5B, D, F) of breast cancer at 1, 3, and 5 years are plotted, respectively. It is evident that both models exhibit a superior fit and strong similarity, thereby demonstrating that the nomogram possesses a high degree of accuracy in predicting lung and bone metastases of breast cancer, and holds significant reference value.

Decision curves

Previously, we demonstrated that the nomogram models for breast cancer bone metastasis and lung metastasis exhibit high sensitivity and specificity, with both models showing a good fit and similarity. However, no model can be constructed with 100 % accuracy. If used to guide clinical decisions, false-positive and false-negative patients are inevitable. The predictive model will only have practical clinical value if the benefits to true-positive and true-negative patients outweigh the harm to false-positive and false-negative patients. To further explore how the constructed predictive model can benefit clinical decision-making, we plotted the Decision Curve Analysis (DCA) for lung metastasis (Fig. 6A) and bone metastasis (Fig. 6B) in breast cancer patients, which can better assess the clinical utility of the model. Plotting a decision curve with the net clinical benefit as the vertical axis and the risk threshold as the horizontal axis, the curve features two reference lines. One is the None line, representing the clinical benefit of assuming all patients are free of metastases, meaning no intervention is applied to any patient. Consequently, there are no true positives or false positives, resulting in a net benefit of zero. The other reference line is the All line, which assumes the clinical benefit of intervention occurs in all patients. This line has a negative slope, and its intersection with the None line corresponds to the transfer rate calculated from the dataset. When the risk threshold is below the transfer rate, the net benefit of the All line is higher than that of the None line. Conversely, when the threshold exceeds the transfer rate, the net benefit of the All line becomes negative and lower than that of the None line. These two lines represent two extreme scenarios (refer to Fig. 6A and B). Decision curves 365, 1095, and 1825 illustrate the net benefit of the 1-year, 3-year, and 5-year probabilities of lung or bone metastasis risk, estimated using the established prediction model of the nomogram, within a risk threshold ranging from 0 to 1.0. The curve is clinically meaningful when the net benefit is >0. For breast cancer lung metastases, the 1-year decision curve falls partly above and partly below the two extreme models, indicating that the clinical value of the model should be carefully considered. However, most decision curves for breast cancer lung metastases at 3 and 5 years and for breast cancer bone metastases at 1, 3, and 5 years lie above the two extreme models, suggesting that the model has good clinical applicability.

Discussions

Breast cancer has become the most prevalent female malignant tumor worldwide. According to the global cancer statistics released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) in 2020, there were 2.26 million new cases of breast cancer, making it the most diagnosed type of cancer. Approximately 680,000 deaths occurred, ranking it as the fifth leading cause of cancer-related deaths globally. Its incidence and mortality rates have surpassed those of the former top cancer, lung cancer [4]. Due to the subtle nature of its early symptoms, many women miss the optimal window for early detection and treatment. The recurrence and metastasis of breast cancer are closely linked to prognosis. Studies indicate [35,36] that in about 90 % of patients with advanced breast cancer, the direct cause of death is due to distant metastases, a situation that is

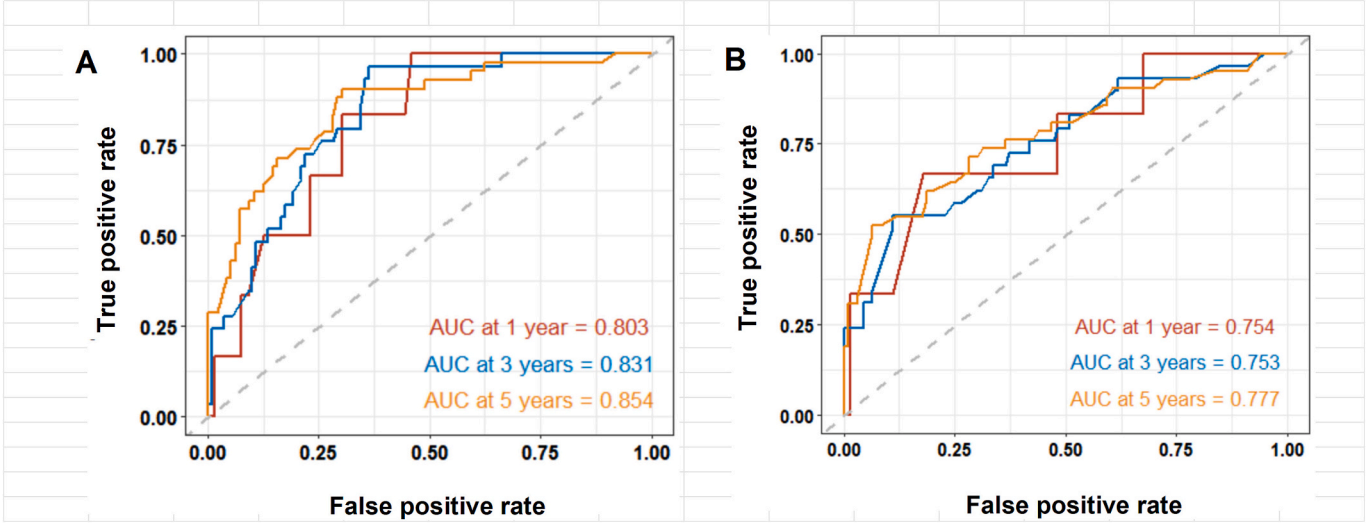

Fig. 4. ROC curves at 1, 3, and 5 years.
A. ROC curves for lung metastasis of breast cancer at 1, 3, and 5 years.
B. ROC curves for bone metastasis of breast cancer at 1, 3, and 5 years.

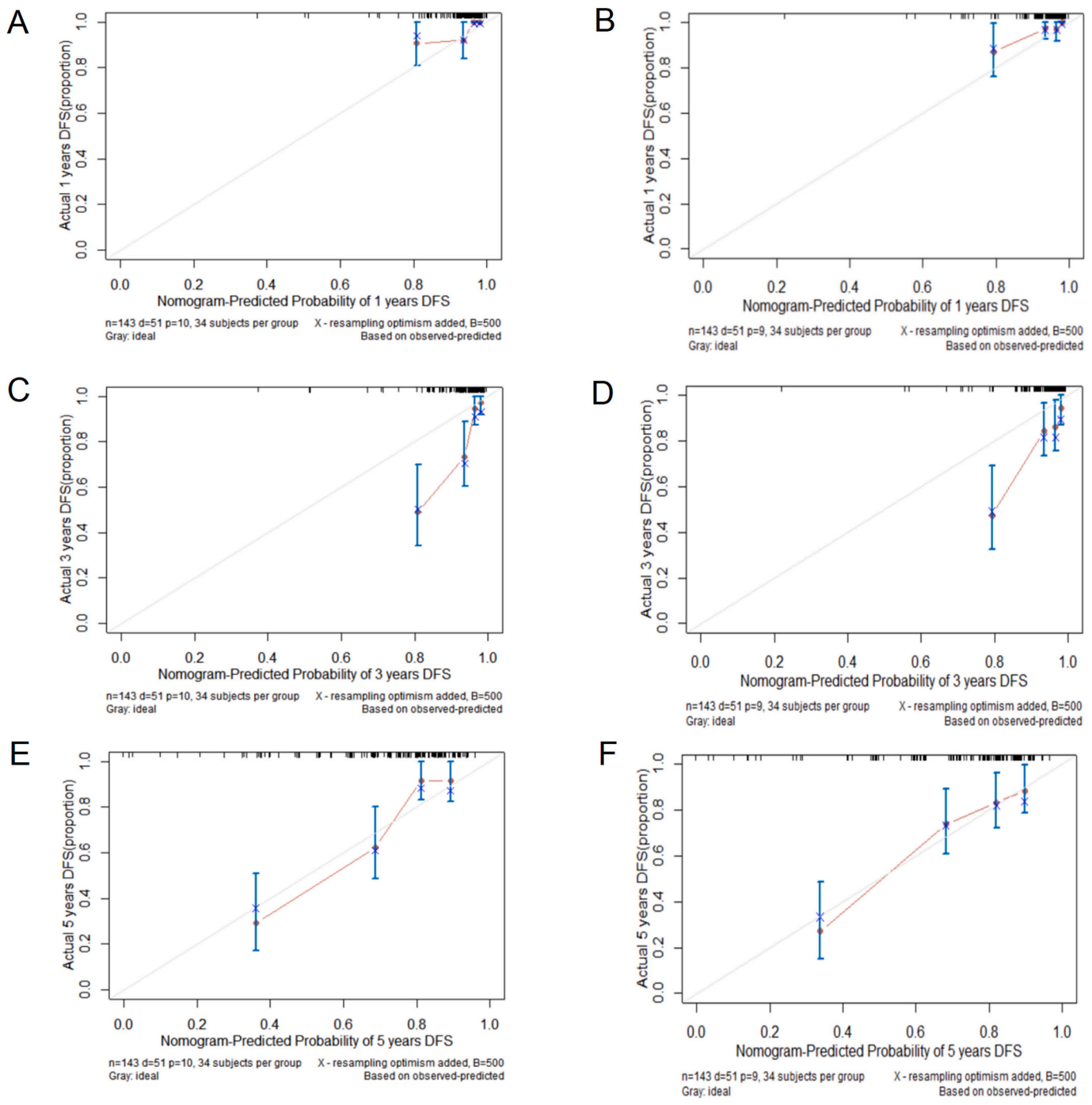

Fig. 5. Calibration curve for the breast cancer lung and bone metastasis nomogram.
A. Calibration curve for the breast cancer lung metastasis nomogram at 1 year.
B. Calibration curve for the breast cancer bone metastasis nomogram at 1 year.
C. Calibration curve for the breast cancer lung metastasis nomogram at 3 years.
D. Calibration curve for the breast cancer bone metastasis nomogram at 3 years.
E. Calibration curve for the breast cancer lung metastasis nomogram at 5 years.
F. Calibration curve for the breast cancer bone metastasis nomogram at 5 years.

closely associated with the site of metastasis. Consequently, for breast cancer patients, alongside standardized treatment, close monitoring is essential to achieve the goals of prevention, early detection, and control of disease progression. To investigate the factors influencing lung and bone metastases in breast cancer and the timing of their onset, this study analyzed the clinicopathological data of this patient group and developed a nomogram prediction model.

Studies have shown [37] the median survival time of patients with visceral metastases from breast cancer is significantly shorter than that of patients with non-visceral metastases, and visceral metastases are an independent influence on prognosis. Among all distant metastases, patients with bone metastases have the best prognosis [38], while lung metastasis is one of the common metastatic sites following bone metastasis in breast cancer. Breast cancer bone metastases can lead to

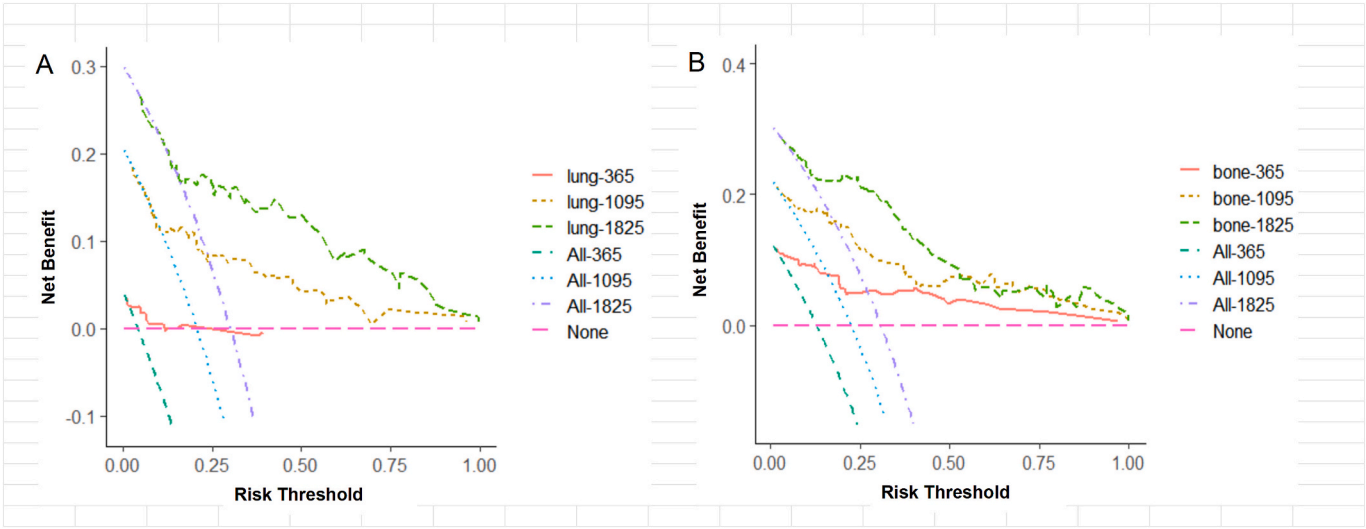

Fig. 6. Decision curve.
A. Decision curve for breast cancer lung metastases.
B. Decision curve for breast cancer bone metastases.

pain, pathological fractures, hypercalcaemia, impairment of neurological function, and other complications. Tumor cells entering the bone tissue interact with the bone microenvironment, creating a vicious cycle that greatly reduces the survival rate of breast cancer patients [9,39]. For breast cancer lung metastasis, despite significant progress in current treatment techniques, the prognosis remains poor due to the difficulty in showing clinical symptoms before lung cells are completely replaced by tumor cells [40,41].

In a study based on the SEER database [42] , older age, black race, higher tumor histological grade, triple-negative subtype, and number of metastatic sites were identified as independent risk factors for breast cancer lung metastasis. Age, body weight, BMI, tumor size, and lymph node status exhibited significant differences in lung and bone metastasis of breast cancer ($P < 0.05$). Another study [43,44] concluded that estrogen receptor (ER), progesterone receptor (PR), tumor T-stage, and N-stage were also risk factors for bone metastasis in breast cancer patients, and the difference was statistically significant. For small tumors at an early stage, histological grading can be a good predictor of tumor behavior [45]. Similar findings were obtained in our study, and the aforementioned studies provide strong evidence for our findings. However, since this study primarily used the time of patients' metastasis as its endpoint, it may yield certain discrepancies. On the other hand, the study focused on the Chinese population, specifically in the southwestern region of China, which is a more geographically limited area and could introduce specific regional differences. In contrast, the aforementioned study was based on the SEER database, which compiles tumor incidence and survival data from 18 tumor registries representing 30 % of the U.S. population [46–48]. Therefore, differences in ethnicity, geography, treatment approaches, and study methodologies could all influence the outcomes.

A clinical study on bone metastases in breast cancer [49] screened variables using the COX proportional hazards model and revealed that ER and PR status, as well as histological grading, were risk factors for bone metastases in patients with breast cancer. Ozlem Yavas [50] et al. conducted a retrospective study involving 248 patients with breast cancer bone metastases. The study revealed that the size of the primary tumor, lymph node metastasis, estrogen receptor (ER) status, progesterone receptor (PR) status, the presence of vascular cancer embolism, visceral metastasis, and disease-free survival time were significantly correlated with the prognosis of patients with breast cancer bone metastases. Additionally, some studies [51] have suggested that hormone receptor positivity may increase the likelihood of bone metastases. Another study on breast cancer lung metastases [52] revealed that age, number of lung metastases, tumor size, and lymph node metastasis had a statistically significant impact on the prognosis of patients with lung metastases ($P<0.05$). In our study, the differences in age, BMI, tumor size stage, lymph node status, ER, PR, and Ki67 were statistically significant in patients with breast cancer bone metastases ($P < 0.05$); and age, BMI, tumor size stage, lymph node status, ER, PR, HER-2, and Ki67 were statistically significant in patients with breast cancer lung metastases ($P < 0.05$). Our study reached similar conclusions to those of the aforementioned studies. Previous studies [53] have shown that HER-2-positive patients are more likely to develop lung metastases, and a similar pattern was found in our study, which provides strong evidence for our findings.

Several previous studies have utilized nomograms to construct prediction models for breast cancer metastasis, encompassing research on bone metastasis [43,54,55] and lung metastasis [19,28,56] based on the SEER database. Furthermore, Delpech et al. [57] established a relatively prominent MDACC model related to bone metastasis of breast cancer in 2015. Our study also utilized a nomogram to construct its predictive model for the occurrence of lung or bone metastasis in breast cancer patients. It was found that being ER-negative and PR-positive increased the risk of lung and bone metastasis in these patients, aligning with the aforementioned study. Additionally, the nomogram offers an individualized and comprehensive assessment of breast cancer patients, predicting their likelihood of developing lung or bone metastases at 1, 3, and 5 years. This provides reliable evidence for assessing the risk of metastasis in breast cancer patients. At present, the TNM staging system for breast cancer is predominantly used to evaluate patient prognosis, based on three key factors: tumor size and extent of invasion, regional lymph node metastasis, and distant metastasis [58]. Despite the widespread adoption of the TNM staging criteria, there remain several issues and limitations in their prognostic evaluation. The most significant of these is that they overlook the tumor as a multifactorial outcome, making it challenging to comprehensively assess metastatic risk and prognosis through a single factor. Consequently, nomogram models pertinent to breast cancer prognosis are now widely constructed, proving increasingly advantageous in clinical decision-making [59].

The nomogram is a visual predictive tool based on statistical regression models that measures the influence of various factors on the probability of an event occurring [60]. It serves as a method for calculating the probability of a clinical event using complex formulas and is increasingly utilized across various fields [61]. Currently, clinicians are

increasingly using column charts as a common tool for risk prediction and prognostic assessment. By incorporating the different influencing factors into the mapping, we obtain a more intuitive and precise tool to assess the patient's prognosis and provide a more individualized reference for the patient's treatment. This serves as an important guide for clinical work and decision-making. Nomograms are now widely used in the assessment and prediction of survival in cancer patients [34]. Currently, there are numerous survival prediction models for breast cancer with lung and bone metastases, but relatively few models predict the timing of lung and bone metastasis. Therefore, we highlighted the construction of such a model in our study. We also utilized the ROC curve and calibration curve to test the model's predictive performance. The results indicate that the area under the ROC curve is >0.75, suggesting high sensitivity and accuracy. Furthermore, the calibration curve of the model demonstrates a high degree of agreement between predicted values and actual observed values, indicating a good fit. This further proves that our nomogram has a strong predictive effect.

The mechanisms behind the distant metastasis of breast cancer are diverse and complex, with multiple factors collectively determining and promoting its occurrence and progression. Some metastatic lesions severely impact the survival and quality of life of patients. To enhance the survival quality of those with advanced breast cancer, early detection and personalized treatment are essential. With ongoing changes and advancements in the treatment paradigm for breast cancer, an increasing number of patients have significantly extended their survival and enhanced their quality of life through standardized management and treatment. Consequently, people's desires for a better life and the need for a high quality of life have become more prominent, leading to the growing importance of individualized assessment and treatment. Thus, our study examines the factors influencing breast cancer metastasis to the lungs and bones, with a particular focus on clinicopathological factors that affect the progression of metastasis. The aim is to offer early intervention and treatment strategies to prevent metastasis in patients with breast cancer. Concurrently, the study has developed a predictive model to evaluate the risk of metastasis and forecast the prognosis for individual patients. This model is intended to guide the customization of clinical treatments, thereby providing greater benefits to patients and further enhancing their quality of life.

The study was a retrospective one with a relatively small sample size. Additionally, it primarily focused on the breast cancer population in Southwest China, which differs in height and weight from the northern region, thus inherently carrying certain geographical limitations. At the same time, patients have varying economic and educational backgrounds, which may lead to differences in treatment choices despite standardized treatment protocols. These differences could be a factor in the progression of the disease. Previous treatments may play a significant role in the development of metastases in breast cancer, but this study did not include a comparative analysis of such treatments. All these factors could have introduced some bias into the results. Moreover, the study only conducted internal validation without external validation, which also presents certain limitations. The sample size is crucial in medical research, as it directly affects the reliability, generalizability, and ethical rationality of the study's results. A larger sample size increases statistical power, reducing the rate of false negatives and potentially decreasing random errors, thereby making the results more reliable and supportive of subgroup analyses. This leads to more detailed conclusions and enhances the practicality of the research findings. However, scientific research must balance sample size with costs, ethics, and other factors to ensure the scientific integrity of the study. In summary, the results obtained in this study require validation through further expansion of the sample size and the incorporation of additional clinicopathological factors for the construction of predictive models to better predict prognosis and guide clinical practice.

Patient consent for publication

Not applicable.

CRediT authorship contribution statement

Mengya Feng: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Yihua Kang:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Data curation. **Sijia Li:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Dechun Yang:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Shengnan Ren:** Visualization, Validation, Supervision, Software, Data curation. **Shicong Tang:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Dan Mo:** Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Hai Lei:** Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The author is responsible for all aspects of the work to ensure that issues related to the accuracy and completeness of any part of the work are properly investigated and resolved. Subjects have given their written informed consent and that the study protocol was approved by the institute's committee on human research. Study approval statement: This study complies with the Declaration of Helsinki (revised in 2013) and was approved by the ethics committee. Written informed consent was obtained from participants to participate in the study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Data availability

The data generated in the present study may be requested from the corresponding author.

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