

Construction and Validation of a Novel Nomogram for Predicting the Risk of Metastasis in a Luminal B Type Invasive Ductal Carcinoma Population

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Abstract

Background: Postoperative distant metastasis is the main cause of death in breast cancer patients. We aimed to construct a nomogram to predict the risk of metastasis of luminal B type invasive ductal carcinoma.

Methods: We applied the data of 364 luminal B type breast cancer patients between 2008 and 2013. Patients were categorized into modeling group and validation group randomly (1:1). The breast cancer metastasis nomogram was developed from the logistic regression model using clinicopathological variables. The area under the receiver-operating characteristic curve (AUC) was calculated in modeling group and validation group to evaluate the predictive accuracy of the nomogram.

Results: The multivariate logistic regression analysis showed that tumor size, No. of the positive level 1 axillary lymph nodes, human epidermal growth factor receptor 2 (HER2) status and Ki67 index were the independent predictors of the breast cancer metastasis. The AUC values of the modeling group and the validation group were 0.855 and 0.818, respectively. The nomogram had a well-fitted calibration curve. The positive and negative predictive values were 49.3% and 92.7% in the modeling group, and 47.9% and 91.0% in the validation group. Patients who had a score of 60 or more were thought to have a high risk of breast cancer metastasis.

Conclusions: The nomogram has a great predictive accuracy of predicting the risk of breast cancer metastasis. If patients had a score of 60 or more, necessary measures, like more standard treatment meth-

ods and higher treatment adherence of patients, are needed to take to lower the risk of metastasis and improve the prognosis.

Keywords: Nomogram; Luminal B type breast cancer; Breast cancer metastasis; Prognosis prediction

Introduction

Breast cancer is one of the malignant tumors with the highest morbidity, greatly threatening the health of women [1-3]. The Journal of CA has published 250,000 emerging invasive breast cancers and 40,000 deaths owing to breast cancer in American women just in 2017. The risk of breast cancer is 12.4% in a lifetime of American women [4, 5]. Although the development of the molecular subtyping of breast cancer and the improvement of the treatment strategies have ameliorated the prognosis of breast cancer, breast cancer metastasis is still the main cause of the death of breast cancer patients [2, 6-8].

Among the different molecular subtypings, the luminal B type breast cancer has a worse disease-free survival (DFS) and overall survival at 5 or 10 years [9-11]. Luminal B type breast cancer is defined as estrogen receptor (ER) positive, progesterone receptor (PR) negative and the high expression of Ki67 under the condition of human epidermal growth factor receptor 2 (HER2) negative status or ER positive, any status of PR and Ki67 expression under the condition of HER2 positive status [12, 13]. It is the type that most possibly causes the organ-specific metastasis, like bone, brain, lung and other organs [14, 15]. At the 5-year follow-up, the basal-like type has the worst prognosis. But in the case of 10 years, the luminal B type may have a worse survival outcome. In addition, the luminal B type breast cancer represents 30% of all diagnosed breast cancers [16, 17]. Li et al also found a higher proportion of bone metastasis in luminal B breast cancer patients than in non-luminal group breast cancer patients. The risk of breast cancer metastasis in luminal B breast cancer patients is still increased during a 2- to 5-year period and after 5 years, but the risk in non-luminal breast cancer patients is obviously decreased during the same periods [16]. Besides, the chemotherapy and endocrine therapy cannot greatly improve the prognosis of luminal B breast patients at present. Many luminal B

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breast cancer patients are confronted with drug resistance [18, 19]. Therefore, for improving the outcome of luminal B type breast cancer, breast cancer metastasis should be predicted as early as possible.

Currently, the nomograms for predicting breast cancer metastasis are mainly focused on lymph node metastasis [20, 21]. As for the metastasis of other organs or positions, it is often found the moment the metastasis appears after the operation. A few of researches used the clinicopathological characteristics to predict the breast cancer metastasis [22-24]. In this paper, tumor size, No. of positive level 1 axillary lymph nodes (PL-1-ALNs), HER2 status and Ki67 index were used to construct a nomogram to predict the risk of luminal B type breast cancer metastasis.

Clinically, if patients are diagnosed as having a PL-1-ALN, the common surgical procedure includes axillary lymph node dissection (ALND) [25, 26]. Therefore, to control the influence of different operation strategies on the risk of breast cancer metastasis, all the patients included in the study underwent the original tumor's excision and level 1 and level 2 ALND. In other words, all the patients' level 1 axillary lymph nodes included in these two models are positive. By using the nomogram, if certain patient has a high risk of breast cancer metastasis, the therapy strategies can be changed appropriately and reviewed after operation timely. Eventually, the survival time of these patients may be increased and their quality of life may be improved. To our knowledge, this is the first nomogram for predicting the risk of luminal B type breast cancer metastasis.

Materials and Methods

Patients

We collected data of 986 breast cancer patients between 2008 and 2013 at the China Medical University. Among them, 405 patients had luminal B type breast cancer. After excluding the patients who did not meet the following criteria, data of 364 patients with invasive ductal carcinomas of no special type were used to construct the nomogram. The median follow-up period of these 364 patients with luminal B type breast cancer was 56.9 months. Because all of these patients included in the research had luminal B type breast cancer with ER positive status, the ER status did not need to be analyzed.

The inclusion criteria were: 1) PL-1-ALN; 2) luminal B type invasive ductal carcinoma; 3) complete immunohistochemistry (IHC) information including ER, PR, HER2, and Ki67; 4) patients combined with local recurrence and distant metastasis. The exclusion criteria were: 1) lacking of data; 2) negative level 1 axillary lymph node; 3) other cancer types except luminal B type invasive ductal cancer; 4) receiving the neoadjuvant chemotherapy. Patients were categorized into modeling group and validation group randomly (1:1). The occurrence of the metastasis was identified by the results of the imaging examinations or the follow-up information that was obtained by telephone or interviewing directly with patients in the outpatient settings. The project was approved by Ethics Committee of China Medical University. The institution review board (IRB) number is 2018PS336K. The study was conducted in compliance with the

ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Treatment

Rational surgical treatment was executed according to the guidelines of China. Operations included the excision of the original tumor and level 1 and level 2 ALND. The level 1 and level 2 lymph nodes' histological status and quality were analyzed. For postoperative drug therapy, all these patients with luminal B type breast cancer have received standard treatment options according to the National Comprehensive Cancer Network guidelines of China, including chemotherapy, endocrine therapy and anti-HER2 therapy for HER2-positive patients.

Data extraction

The following variables were used in this research: age, menopausal status, tumor size, No. of PL-1-ALN, level 2 axillary lymph node status, histological grade, PR status, HER2 status, and Ki67 index.

Pathological evaluation

The guidelines of China were applied to extract the surgical tumors, including the histological grade, PR status, HER2 status and the Ki67 index. ER and PR were graded 0 if there was no expression, 1+ if the expression was 0-10%, 2+ if the expression was 10-50%, and 3+ if the expression was $\geq 50\%$. Grades 2+ and 3+ were considered positive and 1+ or 0 was considered negative [27]. Similar standards were also used for HER2. HER2 positivity was defined as IHC score of 3+ or fluorescence *in situ* hybridization (FISH) 2+ with amplification [28]. The cutoff value of Ki67 expression was 20%. The expression ratio $> 20\%$ was regarded as Ki67 high expression, and the expression ratio $\leq 20\%$ was regarded as Ki67 low expression [29, 30]. The typical pictures are shown in Figure 1.

Statistical analysis

For categorical data, Chi-square test was applied. As for independent samples' between-group comparisons, independent sample *t*-test was used. For construction of the nomogram, univariate logistic regression analysis of the nine factors in the modeling group described above was applied to find factors that were associated with breast cancer metastasis. Variables which were statistically significant after univariate logistic regression were incorporated into multivariate logistic regression. Then independent predictors which were statistically significant in the multivariate logistic regression analysis were obtained using a forward selection procedure. These independent predictors were utilized to construct the nomogram of predicting breast cancer metastasis. Then the receiver-operating characteristic (ROC) curve was obtained and the accuracy of the nomogram was ap-

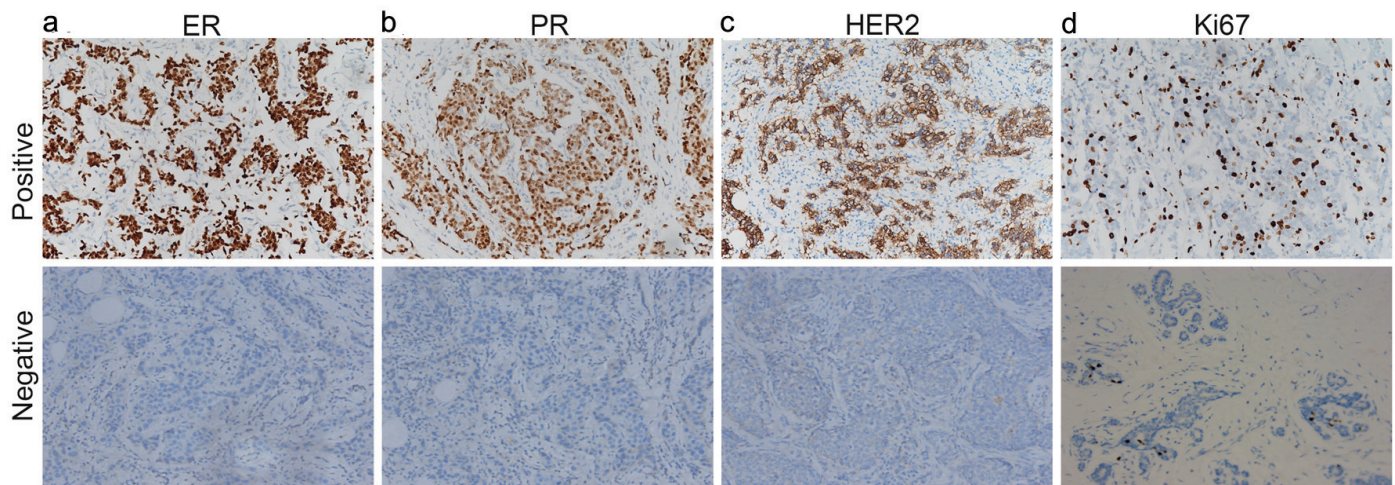


Figure 1. ER (a), PR (b), HER2 (c) and Ki67 (d) were found positive expression and negative expression in breast cancer tissues. ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

praised by area under the ROC curve (AUC). According to the overall rules, a model whose AUC was 0.7 - 0.9 was accepted. The goodness of fit was appraised by Hosmer-Lemeshow test. It showed that the nomogram was well suited if $P > 0.05$. A calibration plot was also drawn to describe the connection between actual probability and predicted probability [31, 32].

For clinical use of the nomogram, the ROC curve was applied to determine the optimal cutoff values calculated by the Youden index (sensitivity + specificity - 1) [33]. And the optimal cutoff value's accuracy was evaluated by the sensitivity, specificity, positive predictive values, negative predictive values, positive likelihood ratios and negative likelihood ratios. For constructing the nomograms which could predict the probability of breast cancer metastasis at specific stage, Cox regression analysis was also used. All the P values were two-sided. $P < 0.05$ was believed statistically significant. Statistical analyses were calculated by SPSS 17.0 and R software (version 3.1.0).

Results

Clinicopathological characteristics

The research included 364 breast cancer patients. Their clinicopathological characteristics are shown in Table 1. Because these patients have luminal B type breast cancer, all of their ER status is positive. Therefore, the ER positive status is not shown in Table 1. The breast cancer metastasis rate of both groups is 24.17% (44/182). In these patients with metastasis, the most common organ is bone. However, there is still metastasis of other organs, e.g., lung, liver and so on. The variables in the two groups did not differ significantly ($P > 0.05$). The consequence of univariate logistic regression analysis of the modeling group is depicted in Table 2. After the univariate logistic regression analysis, the tumor size, No. of PL-1-ALN, HER2 status and Ki67 index were then included in the multivariate logistic regression analysis. The results of this analysis

showed that the tumor size, No. of PL-1-ALN, HER2 status and Ki67 index were independently predictors used to construct the nomogram. The results of the multivariate logistic regression analysis are shown in Table 3.

Construction of the breast cancer metastasis nomogram

To evaluate the risk of breast cancer metastasis, based on the results of Table 3, the equation was constructed: $\ln(p/1 - p) = 1.101 \times A + 0.793 \times B + 1.823 \times C + 1.279 \times D - 6.383$. The "p" represents the risk of metastasis [34, 35], "A" represents the No. of PL-1-ALN (1 if 1 or 2 PL-1-ALNs, 2 if 3 or 4 PL-1-ALNs, 3 if ≥ 5 PL-1-ALNs), "B" represents the tumor size, "C" represents HER2 status, and "D" represents Ki67 index. The nomogram is established by the consequences of multivariate logistic regression (Fig. 2).

Validation of the breast cancer metastasis nomogram

The ROC curves of the modeling group (Fig. 3a) and the validation group (Fig. 3b) were utilized to evaluate the accuracy of the nomogram. In the modeling group, the AUC of the ROC curve was 0.855, which represented good accuracy in predicting the risk of breast cancer metastasis. The result of Hosmer-Lemeshow test showed that the nomogram fitted well ($P = 0.147$). Calibration plots graphically (Fig. 3c) indicated that the accuracy of the nomogram is excellent. In the validation group, the AUC of the ROC curve was 0.818, which also represented good accuracy.

Predictive values of the breast cancer metastasis nomogram at the optimal cutoff value

We calculated every score of these 364 patients with breast cancer. After that, according to the Youden index, the optimal

Table 1. Comparison of Clinicopathological Characteristics of Modeling and Validation Groups for the Breast Cancer Metastasis Nomogram

Variables	Modeling group, N (%)	Validation group, N (%)	P-value
No. of patients	182 (100)	182 (100)	
Age (years)			0.286
≤ 45	53 (29.1)	44 (24.2)	
> 45	129 (70.9)	138 (75.8)	
Menopausal status			0.834
Pre-menopausal	89 (48.9)	91 (50.0)	
Post-menopausal	93 (51.1)	91 (50.0)	
Tumor size (cm)			0.568
Median (range)	2.5 (0.8 - 8.0)	2.4 (0.2 - 6.0)	
No. of PL-1-ALN			0.990
1 - 2	123 (67.6)	121 (66.5)	
3 - 4	44 (24.2)	52 (28.6)	
≥ 5	15 (8.2)	9 (4.9)	
L-2-ALNM			0.792
Yes	37 (20.3)	35 (19.2)	
No	145 (79.7)	147 (80.8)	
Histological grade			0.774
I	9 (4.9)	11 (6.1)	
II	155 (85.2)	150 (82.4)	
III	18 (9.9)	21 (11.5)	
PR status			0.086
Positive	159 (87.4)	147 (80.8)	
Negative	23 (12.6)	35 (19.2)	
HER2 status			0.300
Positive	49 (26.9)	58 (31.9)	
Negative	133 (73.1)	124 (68.1)	
Ki67 index			0.276
≤ 20%	71 (39.0)	61 (33.5)	
> 20%	111 (61.0)	121 (66.5)	

PL-1-ALN: positive level 1 axillary lymph node; L-2-ALNM: level 2 axillary lymph node metastasis; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

cutoff value was determined to be 60 in the modeling group and the validation group. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value when used in predicting the breast cancer metastasis were 81.8%, 73.9%, 3.1, 0.25, 50.0% and 92.7% in the modeling group, and 77.3%, 73.2%, 2.9, 0.31, 47.9% and 91.0% in the validation group (Table 4).

Construction and validation of the nomograms which can predict the probability of breast cancer metastasis at specific stage

To further clarify whether these 364 included patients recurred

at an early stage or late stage, we reconstructed nomograms by Cox regression analysis based on these four clinicopathological characteristics and DFS. DFS was defined from the date of the operation to the date of recurrence/metastases. The survival probability in the nomogram represented the probability of recurrence/metastases.

For the early stage, a nomogram was constructed to predict the 1-, 3-, and 5-year metastasis probability of patients with luminal B type breast cancer using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index (Fig. 4a). Calibration curves were created to predict the metastasis probability for the 1-, 3-, and 5-year periods with reasonable accuracy (Fig. 4b). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig.

Table 2. Univariate Logistic Regression Analysis of Different Variables Predicting Breast Cancer Metastasis in the Modeling Group

Variables	Metastasis, N (%)	No metastasis, N (%)	P-value
No. of patients	44 (100)	138 (100)	
Age (years)			0.757
≤ 45	12 (27.3)	41 (29.7)	
> 45	32 (72.7)	97 (70.3)	
Menopausal status			0.118
Pre-menopausal	17 (38.6)	72 (52.2)	
Post-menopausal	27 (61.4)	66 (47.8)	
Tumor size (cm)			< 0.001
Median (range)	3.08 (1.2 - 8.0)	2.28 (0.8 - 5.0)	
No. of PL-1-ALN			< 0.001
1 - 2	19 (43.2)	104 (75.4)	
3 - 4	15 (34.1)	29 (21.0)	
≥ 5	10 (22.7)	5 (3.6)	
L-2-ALNM			0.189
Yes	32 (72.7)	113 (81.9)	
No	12 (27.3)	25 (18.1)	
Histological grade			0.614
I	1 (2.3)	8 (5.8)	
II	38 (86.4)	117 (84.8)	
III	5 (11.3)	13 (9.4)	
PR status			0.453
Positive	37 (84.1)	122 (88.4)	
Negative	7 (15.9)	16 (11.6)	
HER2 status			< 0.001
Positive	26 (59.1)	23 (16.7)	
Negative	18 (40.9)	115 (83.3)	
Ki67 index			< 0.001
≤ 20%	6 (13.6)	65 (47.1)	
> 20%	38 (86.4)	73 (52.9)	

PL-1-ALN: positive level 1 axillary lymph node; L-2-ALNM: level 2 axillary lymph node metastasis; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

Table 3. Results of Multivariate Logistic Regression Testing the Association of Each Variable With the Breast Cancer Metastasis

Variables	Coefficient	SE	Wald value	P-value	OR	95% CI	
						Lower	Upper
No. of PL-1-ALN	1.101	0.338	10.611	0.001	3.006	1.550	5.829
Tumor size	0.793	0.248	10.205	0.001	2.210	1.359	3.595
HER2 status	1.823	0.451	16.347	< 0.001	6.190	2.558	14.978
Ki67 index	1.279	0.534	5.741	0.017	3.594	1.262	10.232
Constant	-6.383	1.065	35.916	< 0.001	0.002		

PL-1-ALN: positive level 1 axillary lymph node; HER2: human epidermal growth factor receptor 2; SE: standard error; OR: odds ratio; CI: confidence interval.

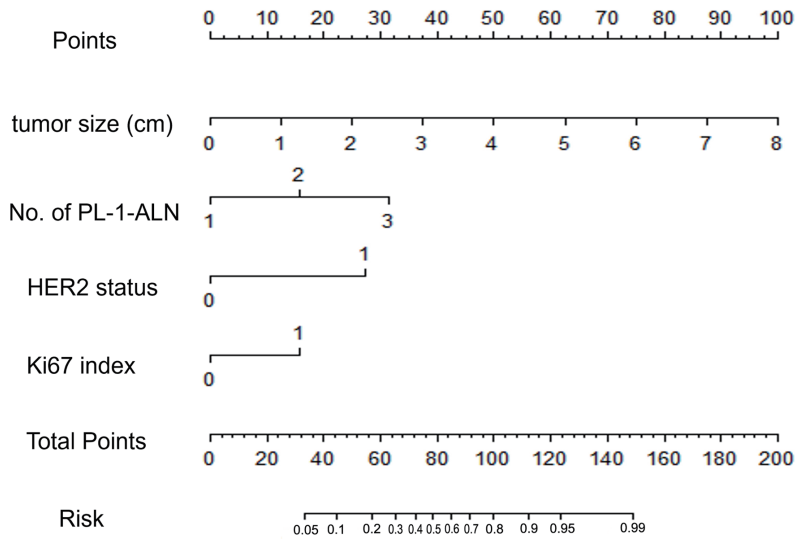


Figure 2. A nomogram for predicting the metastasis of breast cancer in a luminal B type invasive ductal carcinoma population. The nomogram is composed by seven rows. The first one is the point assignment for every variable. For a patient, every variable is assigned a value depending on the variables by painting a vertical line between the exact variable value and points line. As a consequence, the total points can be gained by pulsing all of the points for the four variables. Finally, the predictive probability of the luminal B type breast cancer metastasis can be gained by painting a vertical line between total points and risk (the final row). About the risk, from left to right, it refers to 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, and 0.99.

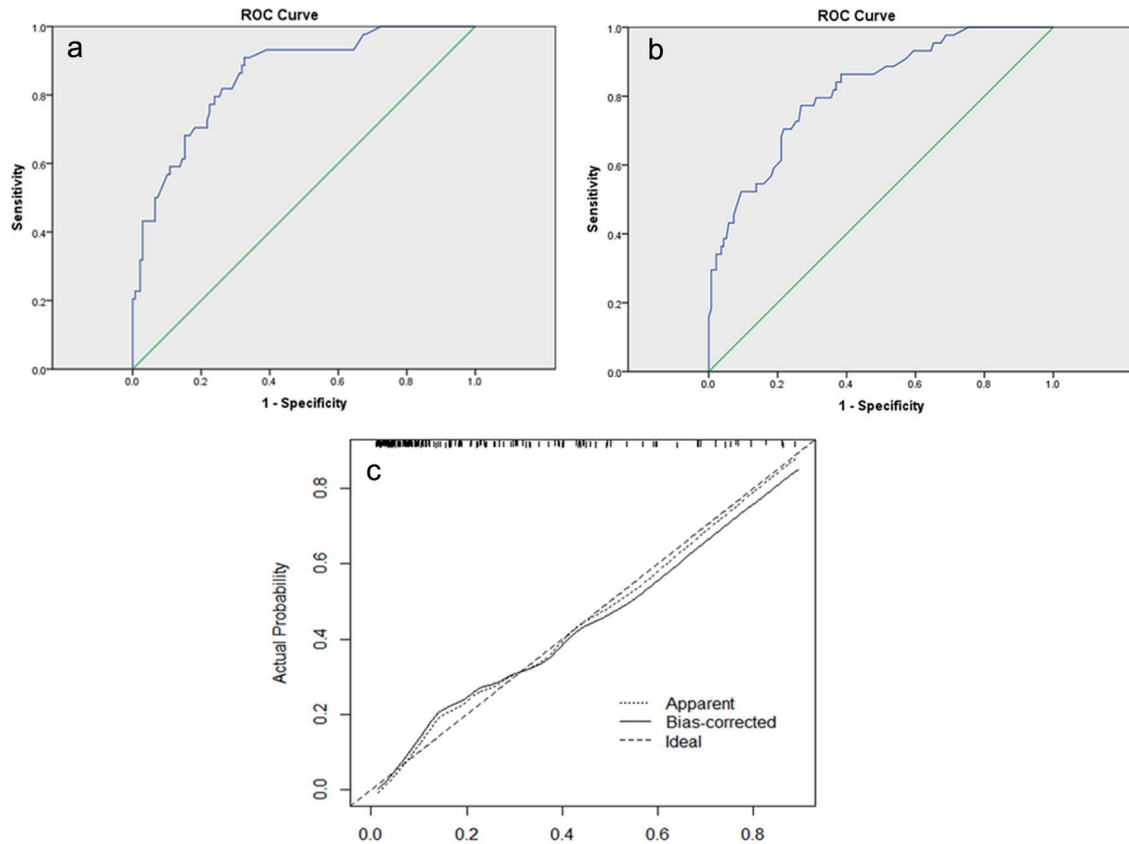


Figure 3. (a) The ROC curve of the modeling group. The AUC is 0.855 (95% CI: 0.793 - 0.917). (b) The ROC curve of the validation group. The AUC is 0.818 (95% CI: 0.747 - 0.888). (c) Calibration plot of the nomogram for predicting the probability of breast cancer metastasis. ROC: receiver-operating characteristic; AUC: area under the ROC curve; CI: confidence interval.

Table 4. Predictive Values of the Breast Cancer Metastasis Nomogram at the Optimal Cutoff Value in the Modeling Group and the Validation Group

Variable	Modeling group	Validation group
Area under ROC curve	0.855	0.818
Cutoff score	60	60
Sensitivity (%)	81.8	77.3
Specificity (%)	73.9	73.2
Positive predictive value (%)	49.3	47.9
Negative predictive value (%)	92.7	91.0
Positive likelihood ratio	3.1	2.9
Negative likelihood ratio	0.25	0.31

ROC: receiver-operating characteristic.

4c). The ROC curves are significantly above the diagonal dashed lines, with AUC values above 0.7. The above results showed that this nomogram had significant high diagnosis ability for the early metastasis probability of patients with luminal B type breast cancer.

cer. For the late stage, a nomogram was constructed to predict the 6- and 7-year metastasis probability of patients with luminal B type breast cancer using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index (Fig. 4d). Calibration curves were created to predict the metastasis probability for the 6- and 7-year periods with reasonable accuracy (Fig. 4e). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig. 4f). The ROC curves are significantly above the diagonal dashed lines, with AUC values even above 0.8. The above results showed that this nomogram had significant high diagnosis ability for the late metastasis probability of patients with luminal B type breast cancer.

For patients with luminal B type breast cancer, hormonal environments are different depending on the menopausal status [36]. Therefore, we have separated the pre-menopausal patients (180/364) and post-menopausal patients (184/364) in these 364 cases. Among different subgroups based on menopausal status, we constructed nomograms which could predict the probability of breast cancer metastasis at specific stage.

For the pre-menopausal patients, a nomogram was constructed to predict the 1-, 3-, and 5-year metastasis probability of patients using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index for the early stage (Fig. 5a). Calibration curves

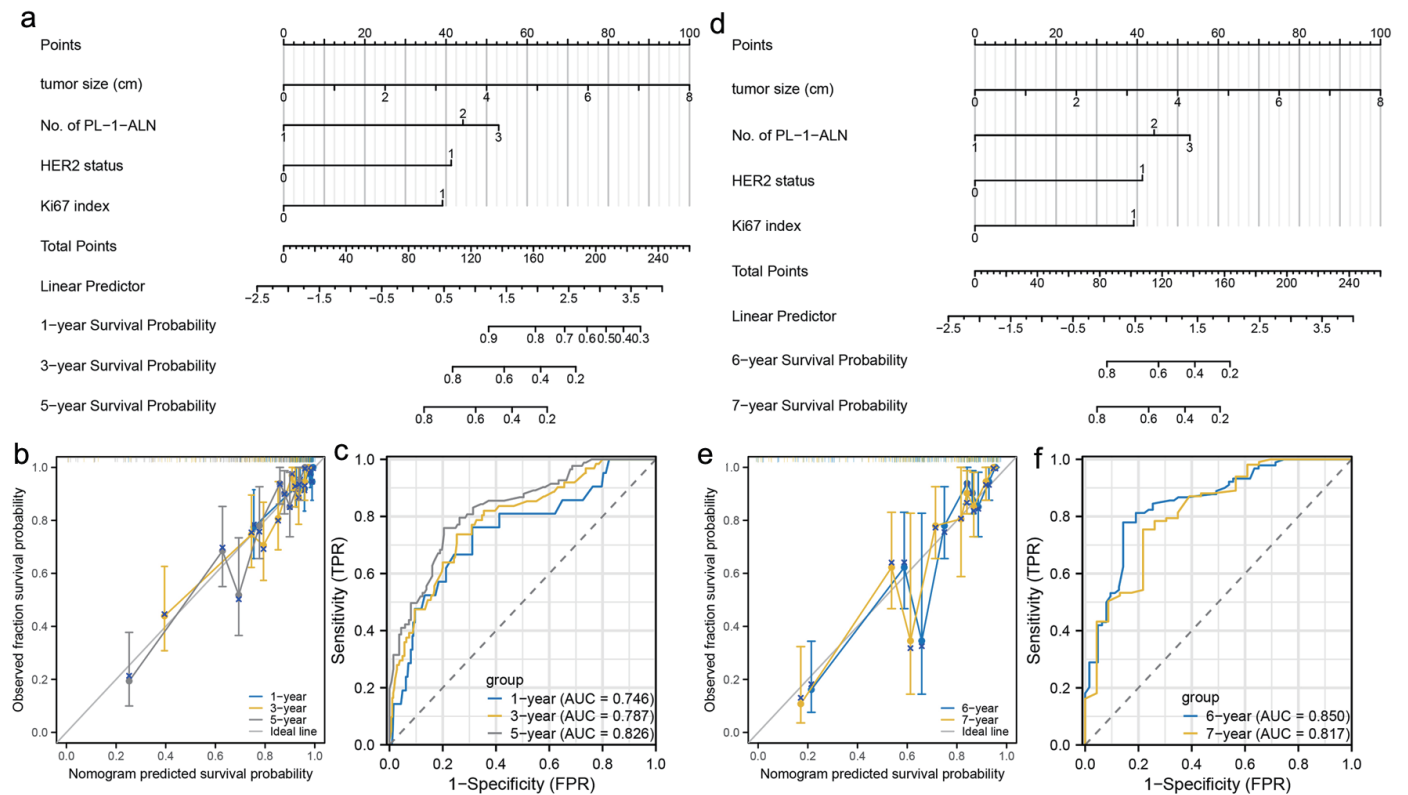


Figure 4. Construction and validation of nomograms which can predict the probability of breast cancer metastasis at specific stage. (a) Prognostic nomogram for the 1-, 3-, and 5-year metastasis probability of patients with luminal B type breast cancer. (b) Calibration curves of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of patients with luminal B type breast cancer. (c) ROC curves and AUC values of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of patients with luminal B type breast cancer. (d) Prognostic nomogram for the 6- and 7-year metastasis probability of patients with luminal B type breast cancer. (e) Calibration curves of the nomogram for predicting 6- and 7-year metastasis probability of patients with luminal B type breast cancer. (f) ROC curves and AUC values of the nomogram for predicting 6- and 7-year metastasis probability of patients with luminal B type breast cancer. ROC: receiver-operating characteristic; AUC: area under the ROC curve.

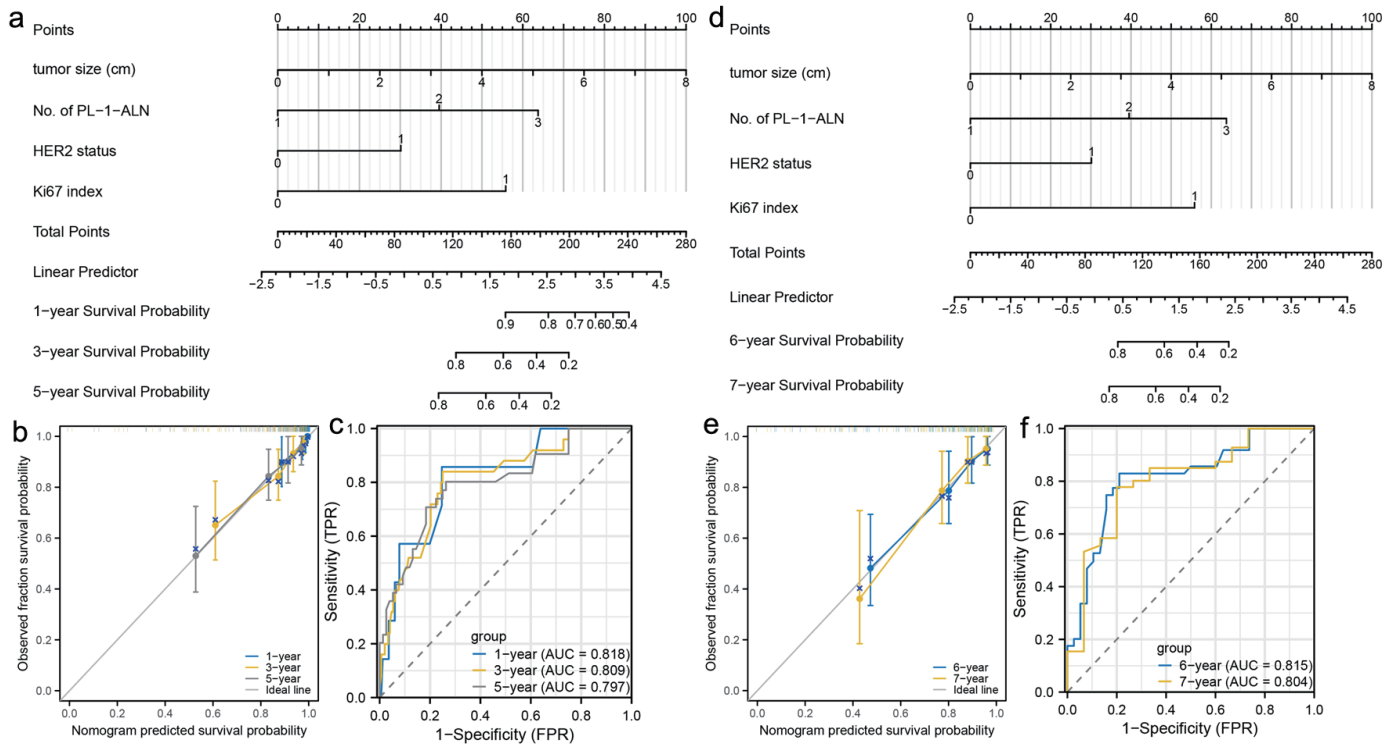


Figure 5. Construction and validation of nomograms which can predict the probability of breast cancer metastasis in pre-menopausal patients. (a) Prognostic nomogram for the 1-, 3-, and 5-year metastasis probability of pre-menopausal patients. (b) Calibration curves of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of pre-menopausal patients. (c) ROC curves and AUC values of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of pre-menopausal patients. (d) Prognostic nomogram for the 6- and 7-year metastasis probability of pre-menopausal patients. (e) Calibration curves of the nomogram for predicting 6- and 7-year metastasis probability of pre-menopausal patients. (f) ROC curves and AUC values of the nomogram for predicting 6- and 7-year metastasis probability of pre-menopausal patients. ROC: receiver-operating characteristic; AUC: area under the ROC curve.

were created to predict the metastasis probability for the 1-, 3-, and 5-year periods with reasonable accuracy (Fig. 5b). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig. 5c). The ROC curves are significantly above the diagonal dashed lines, with AUC values above 0.7. The above results showed that this nomogram had significant high diagnosis ability for the early metastasis probability of patients. For the late stage, a nomogram was constructed to predict the 6- and 7-year metastasis probability of patients using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index (Fig. 5d). Calibration curves were created to predict the metastasis probability for the 6- and 7-year periods with reasonable accuracy (Fig. 5e). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig. 5f). The ROC curves are significantly above the diagonal dashed lines, with AUC values even above 0.8. The above results showed that this nomogram had significant high diagnosis ability for the late metastasis probability of patients.

For the post-menopausal patients, a nomogram was constructed to predict the 1-, 3-, and 5-year metastasis probability of patients using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index for the early stage (Fig. 6a). Calibration curves were created to predict the metastasis probability for the 1-, 3-, and

5-year periods with reasonable accuracy (Fig. 6b). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig. 6c). The ROC curves are significantly above the diagonal dashed lines, with AUC values above 0.7. The above results showed that this nomogram had significant high diagnosis ability for the early metastasis probability of patients. For the late stage, a nomogram was constructed to predict the 6- and 7-year metastasis probability of patients using tumor size, No. of PL-1-ALN, HER2 status and Ki67 index (Fig. 6d). Calibration curves were created to predict the metastasis probability for the 6- and 7-year periods with reasonable accuracy (Fig. 6e). The predictions made by the nomogram were close to the actual outcomes. Subsequently, the ROC curves and AUC values were calculated (Fig. 6f). The ROC curves are significantly above the diagonal dashed lines, with AUC values even above 0.8. The above results showed that this nomogram had significant high diagnosis ability for the late metastasis probability of patients.

Discussion

Breast cancer is a kind of heterogeneous diseases. Different molecular classification of breast cancer has different biologi-

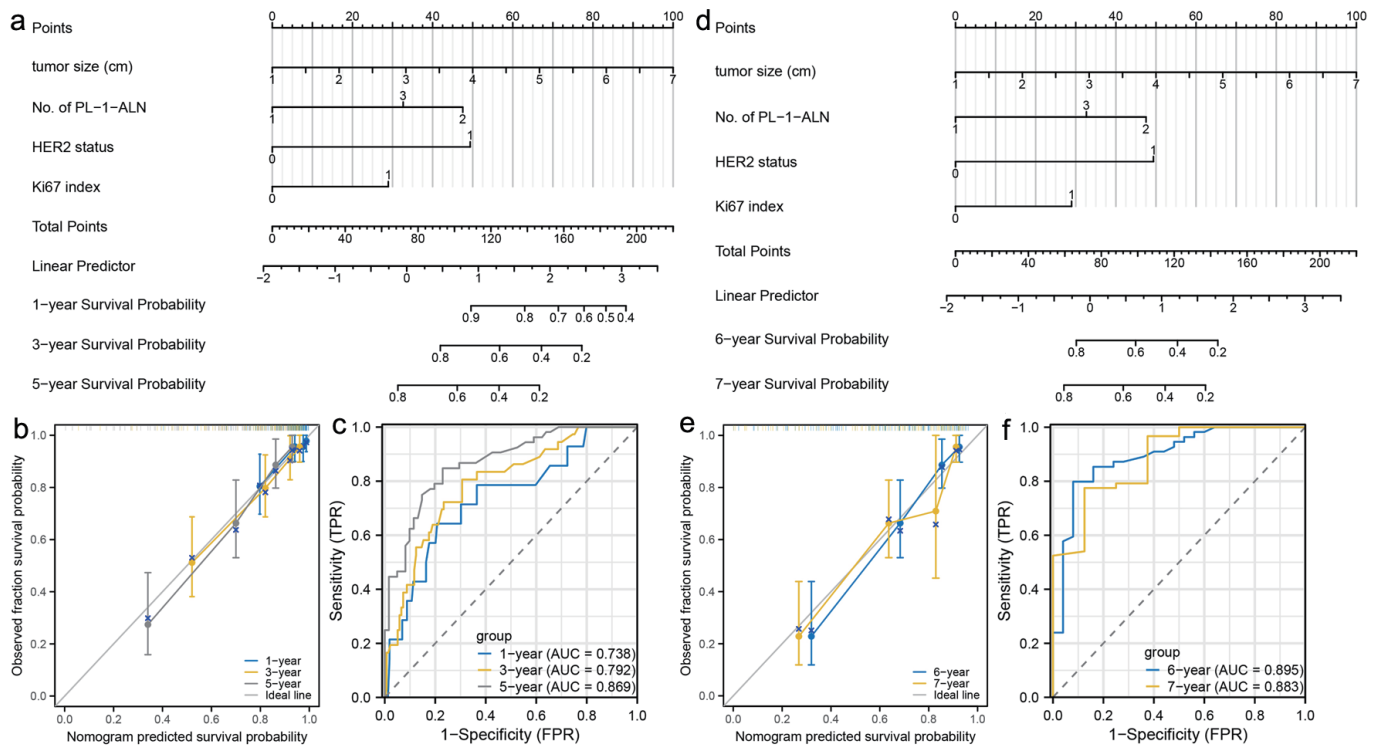


Figure 6. Construction and validation of nomograms which can predict the probability of breast cancer metastasis in post-menopausal patients. (a) Prognostic nomogram for the 1-, 3-, and 5-year metastasis probability of post-menopausal patients. (b) Calibration curves of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of post-menopausal patients. (c) ROC curves and AUC values of the nomogram for predicting 1-, 3-, and 5-year metastasis probability of post-menopausal patients. (d) Prognostic nomogram for the 6- and 7-year metastasis probability of post-menopausal patients. (e) Calibration curves of the nomogram for predicting 6- and 7-year metastasis probability of post-menopausal patients. (f) ROC curves and AUC values of the nomogram for predicting 6- and 7-year metastasis probability of post-menopausal patients. ROC: receiver-operating characteristic; AUC: area under the ROC curve.

cal behavior and prognosis [37]. Although the treatment of breast cancer has made great progress, there still is 20-30% metastasis developed in breast cancer patients [38, 39]. Luminal B type breast cancer particularly with HER2 positive was obviously connected with poor DFS and disease-specific survival regardless of the treatment strategy [11, 40]. Tumor size, lymph node status, histological stage, PR status, HER2 status and others are all predictors of breast cancer metastasis [41-44]. But there are a few models that can predict the exact risk of breast cancer metastasis using these clinicopathological characteristics before we found the metastasis after the surgery.

Jin et al have made a nomogram for predicting the risks of distant failures in patients with invasive breast cancer [21]. In the nomogram, they found age, molecular subtypes, T stage and N stage were predictors of distant failure. But they did not make full use of all the clinicopathological characteristics and further validate the accuracy of the nomogram like using the ROC curve or setting a validation group. Besides this model, we did not find any other nomograms predicting the metastasis.

In our nomogram, we found four independent predictors to predict the metastasis of luminal B type invasive ductal carcinoma. It is the first model to use the clinicopathological variables to predict the risk of breast cancer metastasis. With the larger tumor size, greater No. of PL-1-ALN, positive HER2

status and the higher Ki67 index, patients are more likely to develop breast cancer metastasis. The AUC of the ROC curve is 0.855 in the modeling group and 0.818 in the validation group. Generally, the AUC of the ROC curve is accepted between 0.7 and 0.9. And the four predictors are easily available before and after the surgery. The consequence of the research showed that our nomogram was useful and reliable in a Chinese breast cancer population. Indeed, there are still some researches constructing nomograms to predict the survival percent of breast cancer patients in 1, 3, 5 or 10 years after the operation [45-47]. However, the main goal of our study was only to predict the risk of breast cancer metastasis occurring after surgery. The key point is not when it will occur. And this is the main difference between our study and others.

For the clinical significance of the nomogram, according to the Youden index, sensitivity, specificity, positive predictive value and negative predictive value, 60 was determined as the cutoff value. The breast cancer patients with the score of 60 or more are thought to have a high risk of metastasis. In the nomogram, score of 60 corresponds to that the risk of distant metastasis is 25% which is almost the normal metastasis risk reported by most studies [38, 48, 49]. Based on these clinicopathological variables, the nomogram can be a useful tool to predict the probability of metastasis in these luminal B type

breast cancer patients; if the score is over 60, the doctor needs to tell the patient to reduce the interval between periodic reviews and prolong the time of endocrine therapy appropriately.

The reduction of the risk of breast cancer metastasis may have a great improvement in survival outcomes of breast cancer patients [50-52]. If we can get the probability of breast cancer metastasis before it occurs and take some measures to deal with it, the patients may have a better survival outcome and a high quality of life. This nomogram provides a new way for predicting the probability of breast cancer metastasis and the accuracy of predicting the metastasis would be increased by using this nomogram.

The nomogram also has some limitations. First, our nomogram was constructed by a retrospective, single-institution research. The nomogram needs to be further validated in other centers. Second, only these patients with invasive ductal carcinoma were included in the research. It reduced the scope of the nomogram's application. Prospective research with larger samples is needed to further validate the nomogram. Third, although the nomogram has a great predictive accuracy, with a cutoff score of 60, the false-negative rate and false-positive rate are 18.2% and 26.8% in the modeling group and 22.7% and 26.8% in the validation group for predicting the risk of breast cancer metastasis. Therefore, it also needs a prospective study with larger samples to improve the predictive value of the nomogram. Finally, there must be other factors including the specific treatment options which can also affect the survival outcomes of patients with breast cancer. This point is also an important limitation of our study. Therefore, in the future, we will focus on the impact of different treatment options on the survival outcomes of patients with same molecular subtype and screen other important factors to construct a more comprehensive nomogram.

In short, in this study, we constructed a nomogram which had a great predictive accuracy of predicting the risk of luminal B type breast cancer patients' metastasis. If the patient had a score of 60 or more, necessary measures, like more standard treatment methods and higher treatment adherence of patients, are needed to take to lower the risk of breast cancer metastasis and improve the prognosis.

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Conflict of Interest

The authors declare that they do not have any competing interests.

Informed Consent

Not applicable.

Author Contributions

Xu Dong Zhu and Jie Lin designed this research. Xu Dong Zhu, Jia Hui Yu, Fu Lu Ai, Yue Wang, Wu Lv, Gui Lin Yu, and Xian Kui Cao analyzed the data and constructed this nomogram. Xu Dong Zhu and Jie Lin wrote this paper. All authors have read and approved this final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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