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ORIGINAL RESEARCH

A Novel Clinical Prognostic Model for Breast Cancer Patients with Malignant Pleural Effusion: Avoiding Chemotherapy in Low-Risk Groups?

Yichen Wang[1,*], Tao Zhou[2,*], Shanshan Zhao[1,*], Ning Li[3], Siwen Sun[1], Man Li[1]

[1]Department of Oncology, The Second Affiliated Hospital of Dalian Medical University, Dalian, 116023, People's Republic of China; [2]Department of Oncology, The First Affiliated Hospital of Dalian Medical University, Dalian, 116011, People's Republic of China; [3]Department of Foreign Language, Dalian Medical University, Dalian, 116050, People's Republic of China

*These authors contributed equally to this work

Correspondence: Man Li; Siwen Sun, Department of Oncology, The Second Affiliated Hospital of Dalian Medical University, Dalian, 116023, People's Republic of China, Tel +86-17709873580; +86-17709891126, Email man_li@dmu.edu.cn; ssw0728@163.com

Purpose: Malignant pleural effusion (MPE) is a severe complication in patients with advanced cancer that is associated with a poor prognosis. Breast cancer is the second leading cause of MPE after lung cancer. We therefore aim to describe clinical characteristics of the patients with MPE combined with breast cancer and construct a machine learning-based model for predicting the prognosis of such patients.

Methods: This study is a retrospective and observational study. Least absolute shrinkage and selection operator (LASSO) and univariate Cox regression analyses were applied to identify eight key clinical variables, and a nomogram model was established. Model performance was evaluated by receiver operating characteristic (ROC) curve, calibration curve, and decision curve analyses.

Results: 196 patients with both MPE and breast cancer (143 in the training group and 53 in the ex-ternal validation group) were analyzed in this study. The median overall survival in two cohorts was 16.20 months and 11.37 months. Based on the ROC curves for 3-, 6-, and 12-month survival, the areas under the curves were 0.824, 0.824, and 0.818 in the training set and 0.777, 0.790, and 0.715 in the validation set, respectively. In the follow-up analysis, both systemic and intrapleural chemotherapy significantly increased survival in the high-risk group compared to the low-risk group.

Conclusion: Collectively, MPE confers a poor prognosis in breast cancer patients. We have developed a first-ever survival prediction model for breast cancer patients with newly diagnosed MPE and validated the model using an independent cohort.

Keywords: malignant pleural effusion, breast cancer, prognostic model, LASSO, pleural metastases, survival analysis

Introduction

Malignant pleural effusion (MPE), defined as effusion resulting from malignant tumors of the pleura or other metastatic tumors of the pleura, is one of the most serious complications of advanced malignant tumors.[1] With the rising number of oncology patients, the incidence of MPE is gradually increasing.[2] The mechanism for the occurrence and progression of MPE is quite complex, and almost all patients with advanced malignancies are at risk of suffering from MPE, which exhibits rapid progression and is associated with a poor prognosis. Previous research has indicated that patients suffering from MPE have a median survival of only 3–12 months.[3] There is currently no defined treatment protocol for MPE; these patients can only be treated with palliative therapies.[4] Therefore, it is essential to judge the prognosis of patients with MPE to better stratify patients and guide their therapy.

At present, several prognostic scoring models have been developed for patients with MPE, including the LENT score,[5] PROMISE score,[6] and SELECT score.[7] However, no distinction has been made between different tumor types in the above prognostic models. Breast cancer is the second leading cause of MPE after lung cancer.[8,9] MPE occurs a long time after diagnosis in many patients with breast cancer, unlike MPE occurring in patients with other tumors.[10,11]

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In this study, we comprehensively analyzed the clinical and laboratory characteristics of patients at the time of initial diagnosis with MPE. The final aim was to predict the prognosis of these patients. As far as we know, this is the first prognostic model constructed to predict survival probability in breast cancer patients with newly diagnosed MPE.

Materials and Methods

Patient Population

The study population consisted of two datasets: a training set and an external validation set. The training set was selected from the Second Affiliated Hospital of Dalian Medical University. The validation set was selected from the First Affiliated Hospital of Dalian Medical University. Following local guidelines, the study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University. We confirm that all methods were carried out following relevant regulations and that every patient signed an informed consent form. Research conformed to the Declaration of Helsinki.

The inclusion criteria were as follows: (a) females 18 years of age or older; (b) diagnosis of breast cancer verified by biopsy or surgical resection; (c) first occurrence of pleural effusion (PE); and (d) presence of MPE confirmed by cytology. The exclusion criteria were as follows: (a) loss to follow-up immediately after chest drainage; (b) presence of second primary tumors; and (c) absence of a complete medical history.

Data Collection and Variables

We collected data in two stages: a review of medical records and telephone follow-ups. The following clinical data were obtained from the electronic record system: (a) Demographic variables, including age and history of menopause; (b) Information on primary tumor, including history of surgical treatment and radiation, T stage, N stage, M stage, and tumor pathology data (ER, PR, HER-2, ki-67 expression levels); (c) Tumor recurrence information, including date of recurrence, occurrence of visceral metastases, and presence of fluid in pericardial and peritoneal cavities; (d) Laboratory indicators, including the findings of routine blood tests, tumor marker level determination, routine pleural fluid examination, biochemical pleural fluid examination, and cytologic pleural fluid examination; and (e) Other data, including the extent of pleural fluid invasion and the drainage volume of bilateral thoracic ducts. It should be pointed out that all the laboratory indicators collected were measured when the patient was diagnosed with MPE. Overall survival (OS), defined as the time interval between the diagnosis of MPE and the end of follow-up or death, was acquired by telephone communication or follow-up review until August 2022.

Statistical Analysis

We described general demographics and clinical variables. Means and standard deviations were calculated for continuous variables conforming to a normal distribution. The median and 25–75% interquartile range (IQR) were used for continuous variables not conforming to a normal distribution. Categorical variables are expressed as percentages and frequencies. The independent samples *t*-test, nonparametric tests (Mann–Whitney U), and the chi-square test were used to compare the clinical characteristics of the training and validation sets. $P < 0.05$ was considered statistically significant. In addition, missing data were counted in all cases. For categorical variables, missing data were included as a "missing" category. For continuous variables, missing data were imputed using multiple imputation.

The R language was used to construct and validate the model. On univariate analysis, we identified potential clinical risk factors associated with MPE. The statistically significant features (*P values<0.1) were included in the least absolute shrinkage and selection operator (LASSO) regression analysis. As a modified form of least squares regression, LASSO regression constructs a penalty function to compress the coefficients of the variables. The L1 penalty reduces some coefficients to zero, leading to inherent variable selection and, ultimately, arriving at the most parsimonious models. Based on variables screened out by the above method, we constructed a nomogram to predict the 3-, 6- and 12-month survival of each MPE patient. To measure the performance of the models, we performed external and internal model validation. Internal validation was performed using the bootstrap method with 1000 resamples. For external validation testing, we used an independent cohort. The discrimination ability of the model was assessed with the receiver operating

characteristic (ROC) curve. The calibration of the nomogram was assessed using a calibration curve, and whether the model improved the predicted net outcome was evaluated using decision curve analysis DCA.

For user convenience, we created an online predictive calculator using Shiny in the R language as an open-source tool. As a result of the risk score, patients were grouped into either the high- or low-risk group. The cutoff value was established by the X-tile program, and we analyzed the differences in survival between the low- and high-risk groups using Kaplan–Meier (KM) curves and the Log rank test.

Results

Patient Characteristics

Between December 2012 and April 2022, 196 eligible patients were included after the inclusion and exclusion criteria were applied, with 143 patients in the training set and 53 patients in the validation set. The flowchart is shown in Figure 1. Before thoracentesis, all patients had a wide range of MPE-related symptoms, including chest tightness, cough, and shortness of breath. The median follow-up period was 32.6 months and 56.3 months in the training and validation groups, respectively. The median OS in the training cohort was 16.20 months (95% CI: 12.27–20.14), and 90 (62.94%) patients were known to have died. In the validation cohort, the median OS was 11.37 months (95% CI: 6.73–16.01), and 42 (79.25%) patients were known to have died. As shown in Table 1, the two cohorts exhibited consistent demographic distributions except for a marginal difference in the site of pleural fluid accumulation.

Predictive Factors

Initially, in the missing value analysis, 9 laboratory indicators with missing values were multiply imputed using the multiple imputation method. The percentage of missing values varied between 7.9% and 12.6%. As a second step, we conducted univariate Cox proportional regression analysis to identify the risk factors for survival among the training set.

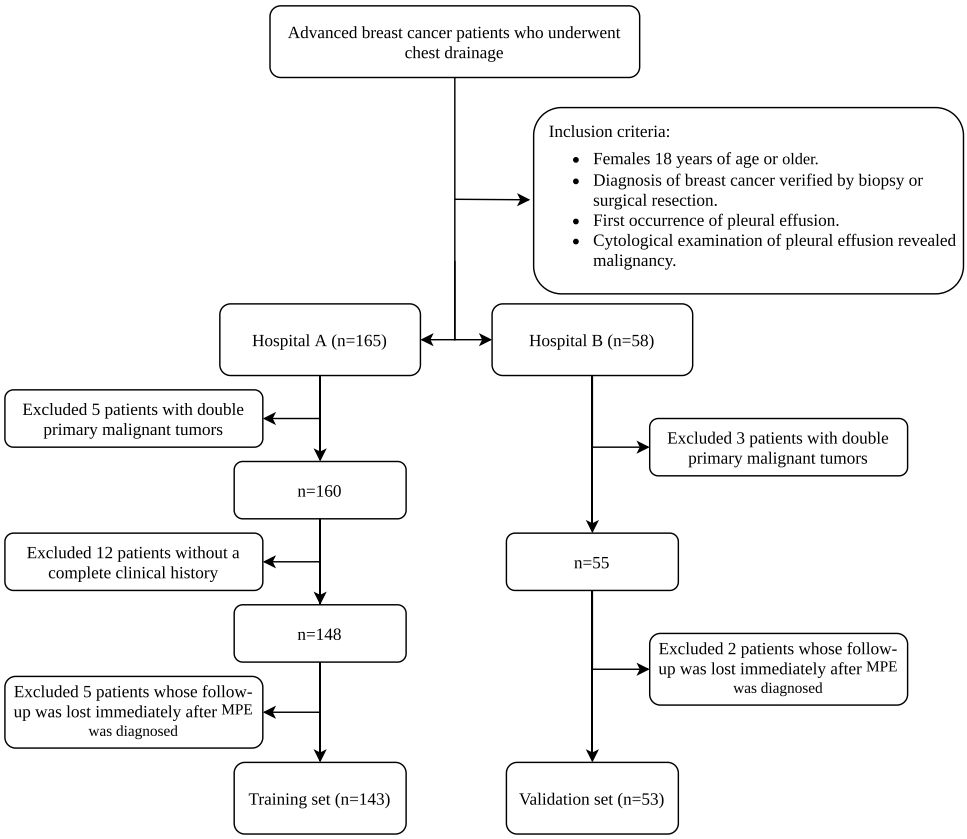

Figure 1 Flow diagram of enrolled patients in the training and validation cohorts.

Table 1 Patient Characteristics in the Training and Validation Cohorts

Patient Characteristics	Training Set (N=143)	External Validation Set (N=53)	*P* value
Age (years, Median ±IQR)	59.23 (49.67–63.93)	58.97 (53.03–68.00)	0.998
DFS (years, Median ±IQR)	34.50 (12.90–76.13)	33.53 (5.41–96.38)	0.915
Time from cancer diagnosis to MPE diagnosis (years, Median ±IQR)	48.27 (26.60–107.40)	59.40 (23.35–118.9)	0.888
AJCC-8 Stage			0.055
I stage	18 (12.59)	5 (9.43)	
II stage	58 (40.56)	13 (24.53)	
III stage	48 (33.57)	29 (54.72)	
IV stage	19 (13.29)	6 (11.32)	
ER/PR status			0.868
Positive	109 (76.22)	41 (77.36)	
Negative	34 (23.78)	12 (22.64)	
HER-2 status			0.220
Positive	29 (20.27)	8 (15.10)	
Negative	101 (70.63)	36 (67.92)	
Missing	13 (9.10)	9 (16.98)	
Surgical procedure			0.414
Modified/standard radical mastectomy	107 (74.82)	44 (83.02)	
Breast conserving surgery	16 (11.19)	3 (5.66)	
No surgery	20 (13.99)	6 (11.32)	
Chest radiotherapy			0.905
Yes	58 (40.56)	21 (39.62)	
No	85 (59.44)	32 (60.38)	
First appearance of distant metastasis			0.430
Yes	48 (33.57)	21 (39.62)	
No	95 (66.43)	32 (60.38)	
Menopausal status			0.943
Postmenopausal	122 (85.31)	45 (84.91)	
Menopausal	21 (14.69)	8 (15.10)	
Visceral metastatic			0.765
Yes	95 (66.43)	34 (64.15)	
No	48 (33.57)	19 (35.85)	

(*Continued*)

Table 1 (Continued).

Patient Characteristics	Training Set (N=143)	External Validation Set (N=53)	*P* value
Site of pleural effusions			0.050
Ipsilateral	71 (49.65)	18 (33.96)	
Contralateral/Bilateral	72 (50.35)	35 (66.04)	
Peritoneal effusion			0.362
Yes	14 (9.79)	3 (5.66)	
No	129 (90.21)	50 (94.34)	
Pericardial effusion			0.294
Yes	25 (17.48)	6 (11.32)	
No	118 (82.52)	47 (88.68)	

Abbreviations: SD, standard deviation; IQR, interquartile range; AJCC-8, the eighth edition of the American Joint Committee on Cancer; DFS, disease-free survival; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

OS, hazard ratio (HR), and *P* values were also tabulated (Table 2). The mean age of these patients was 57 years. A total of 109 (76.2%) of the 143 patients had luminal breast cancer. MPE was diagnosed as the first recurrence in 48 patients (33.57%).

Table 2 Results of Univariate Cox Regression Analyses

Patient Characteristics	No. of Patients (%)	OS (Months) Median 95% CI	HR (95% CI)	*P* value
Clinical Parameters				
Age (years, Median ±IQR)	59.23 (49.67–63.93)		1.007 (0.988–1.027)	0.459
DFS (years, Median ±IQR)	34.50 (12.90–76.13)		0.996 (0.992–1.000)	0.047*
Time from cancer diagnosis to MPE diagnosis (years, Median ±IQR)	48.27 (26.60–107.40)		0.999 (0.996–1.002)	0.459
AJCC-8 Stage				0.878
I stage	18 (12.59)	18.07 (0.00–36.89)	Reference	
II stage	58 (40.56)	16.20 (11.93–20.48)	1.105 (0.577–2.115)	
III stage	48 (33.57)	20.67 (3.33–38.01)	1.008 (0.510–1.994)	
IV stage	19 (13.29)	9.97 (5.19–14.75)	1.315 (0.589–2.935)	
ER/PR status				0.010*
Positive	109 (76.22)	16.87 (13.54–20.20)	Reference	
Negative	34 (23.78)	7.70 (6.40–9.00)	1.848 (1.160–2.943)	
HER-2 status				0.747
Positive	29 (20.27)	17.60 (9.93–25.27)	Reference	
Negative	101 (70.63)	13.63 (7.71–19.56)	1.106 (0.667–1.834)	
Missing	13 (9.10)	16.63 (5.85–27.41)	0.834 (0.352–1.975)	

(*Continued*)

Table 2 (Continued).

Patient Characteristics	No. of Patients (%)	OS (Months) Median 95% CI	HR (95% CI)	*P* value
Surgical procedure				0.081*
Modified/standard radical mastectomy	107 (74.82)	16.63 (12.76–20.50)	Reference	
Breast conserving surgery	16 (11.19)	5.83 (1.27–10.39)	2.018 (1.084–3.757)	
No surgery	20 (13.99)	11.17 (5.32–17.02)	0.987 (0.507–1.924)	
Chest radiotherapy				0.212
Yes	58 (40.56)	16.200 (6.60–25.80)	Reference	
No	85 (59.44)	14.20 (10.37–18.03)	0.767 (0.505–1.164)	
First appearance of distant metastasis				0.003*
Yes	48 (33.57)	32.33 (17.24–47.42)	Reference	
No	95 (66.43)	10.10 (5.52–14.68)	2.023 (1.278–3.203)	
Menopausal status				0.371
Postmenopausal	122 (85.31)	16.20 (12.16–20.24)	Reference	
Premenopausal	21 (14.69)	10.43 (0.00–30.43)	0.756 (0.411–1.394)	
Visceral metastatic				0.129
Yes	95 (66.43)	11.17 (5.30–17.04)	Reference	
No	48 (33.57)	16.77 (12.27–21.27)	0.723 (0.476–1.099)	
Site of pleural effusions				0.308
Ipsilateral	71 (49.65)	16.63 (12.84–20.42)	Reference	
Contralateral/Bilateral	72 (50.35)	10.43 (4.27–16.59)	1.241 (0.820–1.877)	
Peritoneal effusion				0.008*
Yes	14 (9.79)	4.57 (3.564–5.576)	Reference	
No	129 (90.21)	16.63 (13.39–19.87)	0.406 (0.208–0.792)	
Pericardial effusion				0.282
Yes	25 (17.48)	11.17 (5.72–16.62)	Reference	
No	118 (82.52)	16.33 (13.04–19.62)	0.757 (0.456–1.257)	
Hematological parameters				
Hb (g/L, Median ±IQR)	121 (107–135)		0.991 (0.981–1.000)	0.056*
D-dimer (ug/mL, Median ±IQR)	1.2 (0.8–2.0)		1.032 (0.920–1.158)	0.591
WBC, ×109/L, (Median ±IQR)	6.3 (4.7–7.8)		1.027 (0.983–1.074)	0.229
NLR (Median ±IQR)	3.55 (2.48–5.55)		1.096 (1.040–1.154)	<0.001*
CEA (ng/mL, Median ±IQR)	5.7 (1.6–31.5)		1.002 (1.001–1.003)	0.005*
CA15-3 (U/mL, Median ±IQR)	71.7 (19.4–71.7)		1.000 (1.000–1.001)	0.089*

(*Continued*)

Table 2 (Continued).

Patient Characteristics	No. of Patients (%)	OS (Months) Median 95% CI	HR (95% CI)	*P* value
Pleural Fluid Parameters				
Pleural fluid appearance				0.661
Yellow	109 (76.22)	10.43 (1.88–18.98)	Reference	
Red	34 (23.78)	16.23 (12.95–19.51)	1.111 (0.695–1.775)	
PE lymphocytes, %, (Median ±IQR)	81 (62–90)		0.986 (0.977–0.994)	<0.001*
PE glucose (mmol/L, Median ±IQR)	6.7 (5.7–8.1)		1.131 (1.044–1.225)	0.003*
PE protein (g/L, Median ±IQR)	43.7 (36.7–47.3)		0.953 (0.926–0.981)	0.001*
PE LDH (U/L, Median ±IQR)	253.9 (171.8–472.1)		1.000 (0.999–1.000)	0.530
PE ADA (U/L, Median ±IQR)	11.3 (6.9–16.5)		0.997 (0.968–1.027)	0.854
Drainage volume (L, Median ±IQR)	1.6 (1.2–2.3)		1.141 (0.995–1.308)	0.058*

Note: *P<0.1.

Abbreviations: CI, confidence internal; SD, standard deviation; AJCC-8, the eighth edition of the American Joint Committee on Cancer; Hb, hemoglobin; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; CEA, carcinoembryonic antigen; CA15-3, cancer antigen 15–3; PE, pleural effusion; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

LASSO Analyses

Thirteen indicators with a P value <0.1 in the univariate analyses were further analyzed by LASSO analyses. Figure 2A shows a regression coefficient plot for the model. Each curve represents one prognostic factor. At each of the different inputs, the factors with nonzero coefficients and the corresponding nonzero coefficients constitute a LASSO risk model. The LASSO feature selection process is shown in Figure 2B. We chose 10-fold cross-validation to further determine the optimal model. When λ=0.1213, the model showed the lowest cross-validation error. The final Cox regression model included 8 variables. A high PE glucose level, low PE protein level, low percentage of PE lymphocytes, and

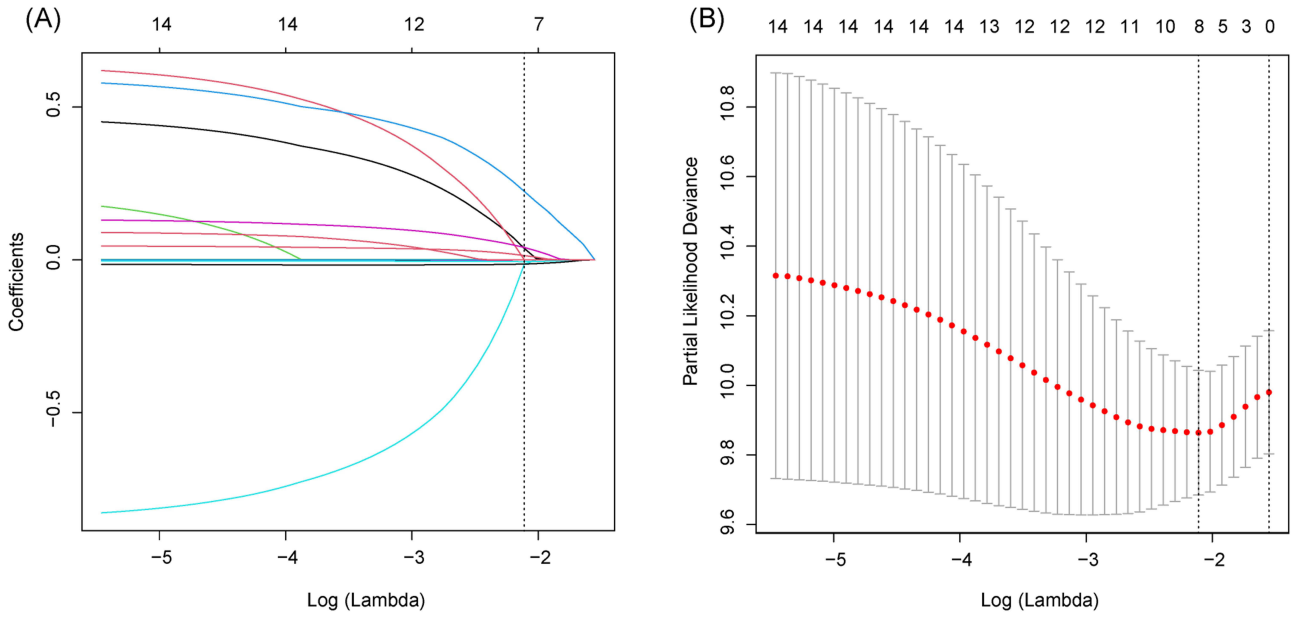

Figure 2 LASSO feature selection process.

Notes: (**A**) Profiles of LASSO coefficients for clinical variables and laboratory indicators. (**B**) A tenfold cross-validation approach was used to select the tuning parameter (lambda) in the LASSO regressions.

the presence of ascites were considered to be risk factors for breast cancer patients with MPE. A high neutrophil-to-lymphocyte ratio (NLR), long disease-free survival (DFS), hormone receptor positivity, and the first appearance of distinct metastasis were considered protective factors.

Constructing and Verifying the Nomogram

The nomogram model was created to predict the 3-, 6- and 12-month OS probability of each patient (Figure 3). PE glucose was the largest prognosis-influencing factor, followed by DFS and NLR. By adding the points attributable to each risk factor, an overall risk score was calculated for each patient. Clinicians can use the score to conveniently predict individualized survival. In addition, to facilitate the calculation of the survival of MPE patients, we constructed a web calculator (https://mpenomogram.shinyapps.io/MPE_Nomogram/).

The ROC curves of the training and validation sets are shown in Figure 4. The areas under the curves (AUCs) were 0.824, 0.824, and 0.818 in the training set and 0.777, 0.790, and 0.715 in the validation set, respectively. The C-index based on the training set was 0.741 (0.714–0.768), and the C-index based on the validation set was 0.702 (0.657–0.745). As indicated by the calibration curve, the prediction of the nomogram was generalized to the actual observations with a high degree of agreement in the training group and validation group (Figure 5). In the DCAs of the modeling and external validation groups, the prediction model provided greater net benefits than providing treatment to all patients or not providing treatment at all (Figure 6). Collectively, these data suggest that our model exhibits better prognostic performance than existing approaches.

Patients in the training set were subdivided into high-risk (score > 163.4) and low-risk groups (score<163.4) based on the optimal cutoff value of the risk score obtained from X-tile software. There were 107 patients in the low-risk group and 36 patients in the high-risk group, with a median OS of 19.97 (10.80–29.14) months and 4.40 (2.32–6.48) months, respectively (Log rank test, $P < 0.0001$; Figure 7A). Meanwhile, the cutoff value was also applied to the validation set (Log rank test, $P = 0.0212$; Figure 7B).

Subgroup Analyses

We analyzed the effect of administering chemotherapy on the survival of breast cancer patients with MPE in the training set. After the diagnosis of MPE, 82 (57.3%) patients received systemic chemotherapy, and 108 (75.5%) patients received

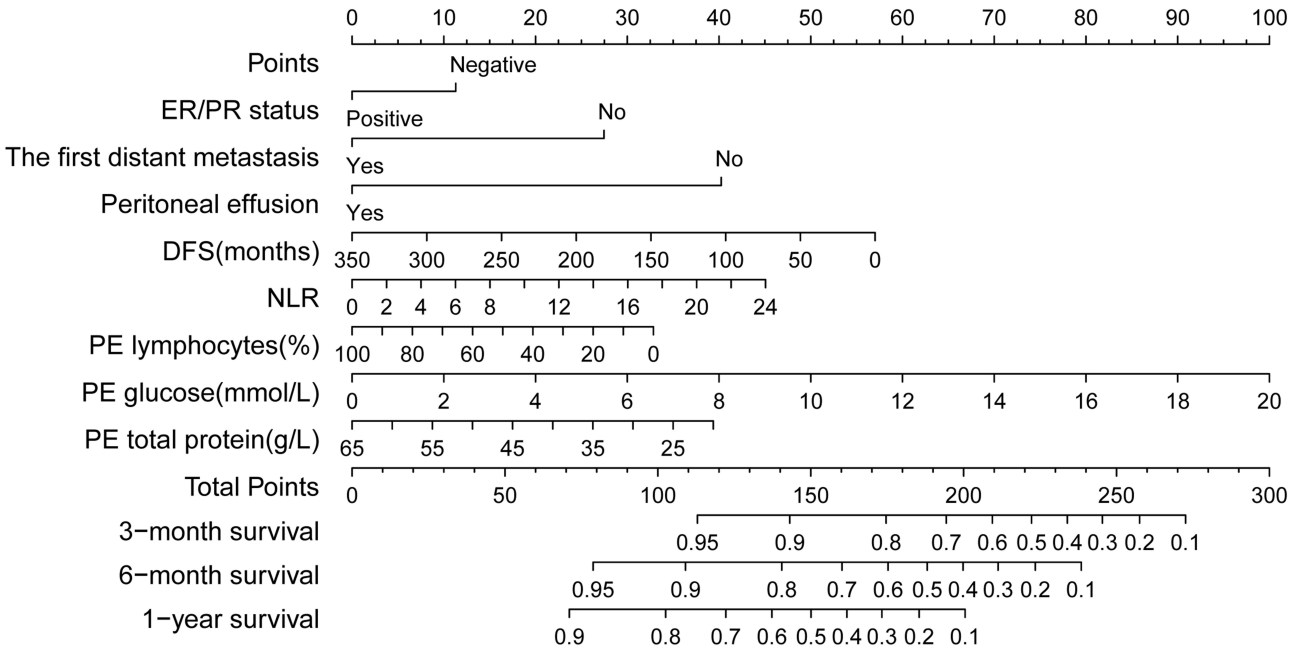

Figure 3 Nomogram for predicting 3-, 6-, and 12-month OS in breast cancer patients with MPE.

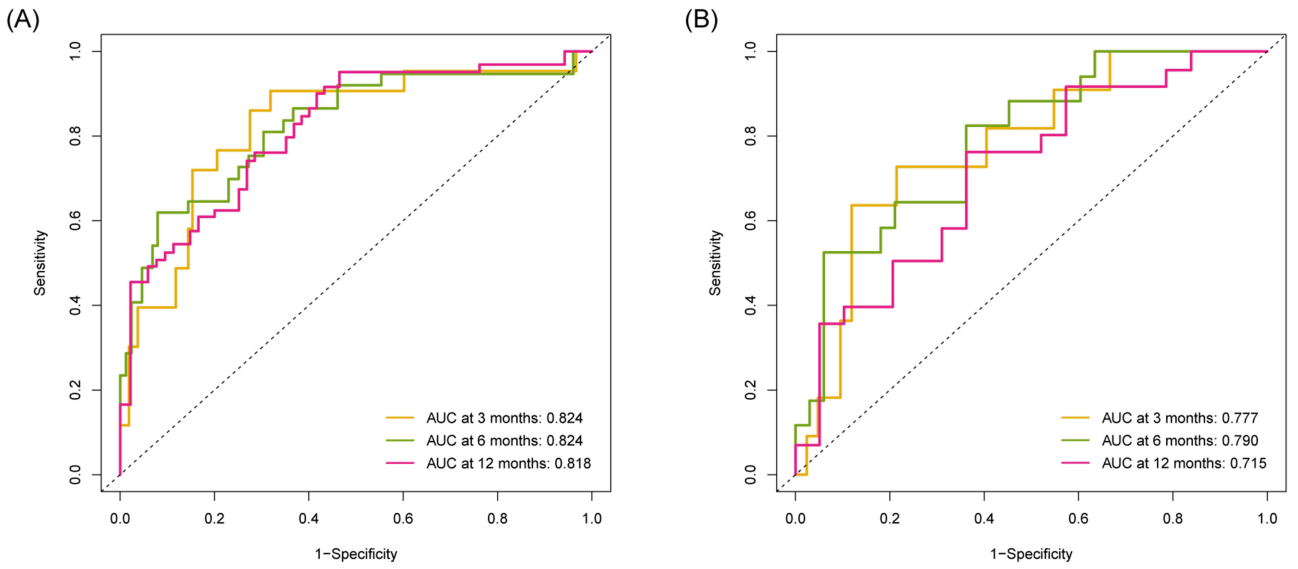

Figure 4 Performance of the proposed nomogram model.
Notes: ROC curves of the model for predicting 3-, 6-, and 12-month OS in the training (**A**) and validation cohorts (**B**), with AUCs of the model at each time point of interest.

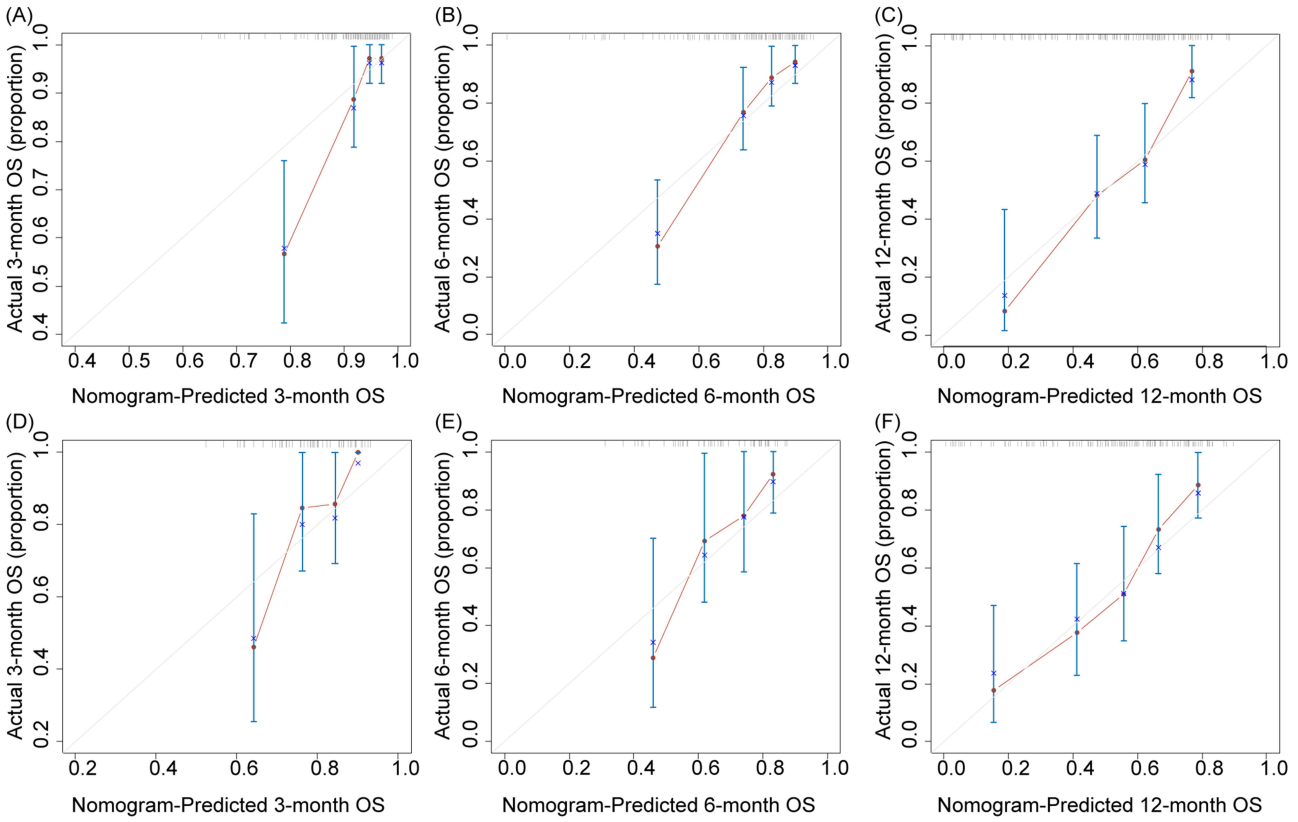

Figure 5 The calibration curves comparing predicted and actual survival proportions at 3, 6 and 12 months in the training (**A**–**C**) and validation cohorts (**D**–**F**).
Notes: In this plot, each point represents a group of patients. The y-axis shows the actual survival ratio, and the x-axis shows the predicted probability of survival. Survival probability distributions are plotted at the top. Error bars represent the 95% CI.

intrapleural chemotherapy. In the high-risk subgroup, patients who received systemic chemotherapy had notably longer OS than those who did not receive it (log-rank P =0.0085; Figure 8A). In contrast, systemic chemotherapy did not improve the OS of patients in the low-risk group (log-rank P =0.1346; Figure 8B). Concerning local intrapleural

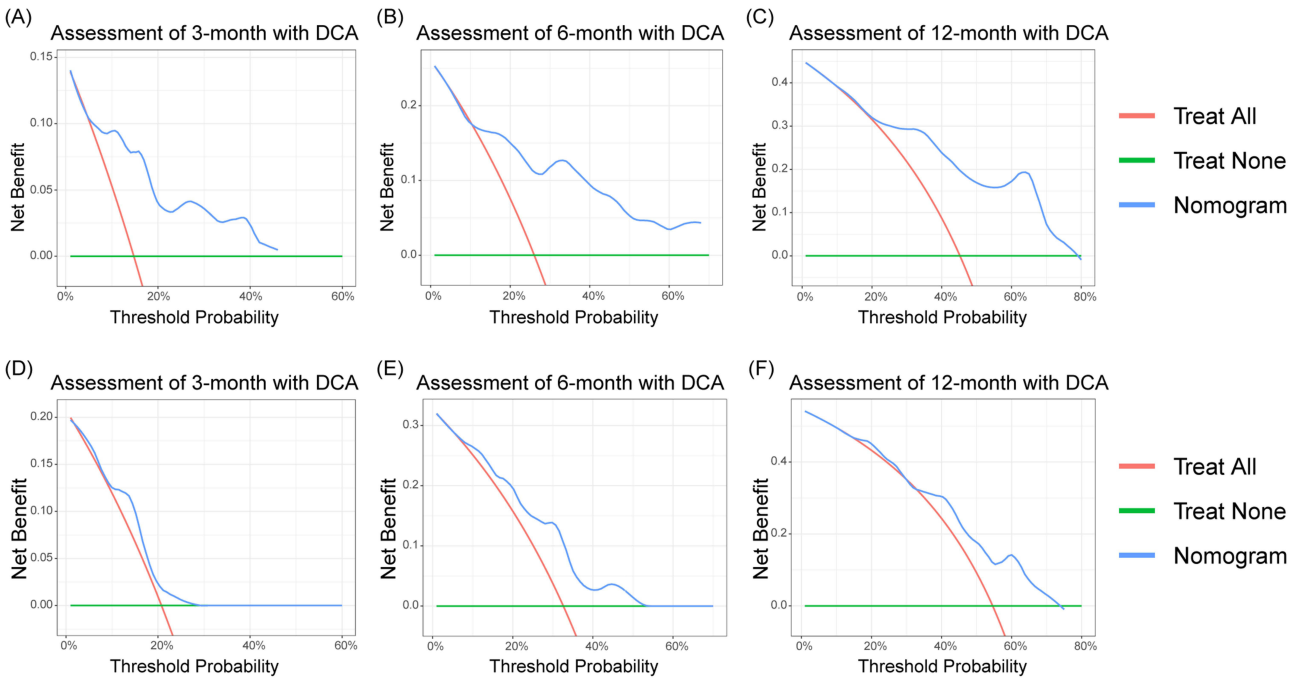

Figure 6 DCA curves of the OS prognostic model in the training (**A**–**C**) and validation cohorts (**D**–**F**).
Notes: The x-axis represents threshold probabilities, and the y-axis represents the net benefit.

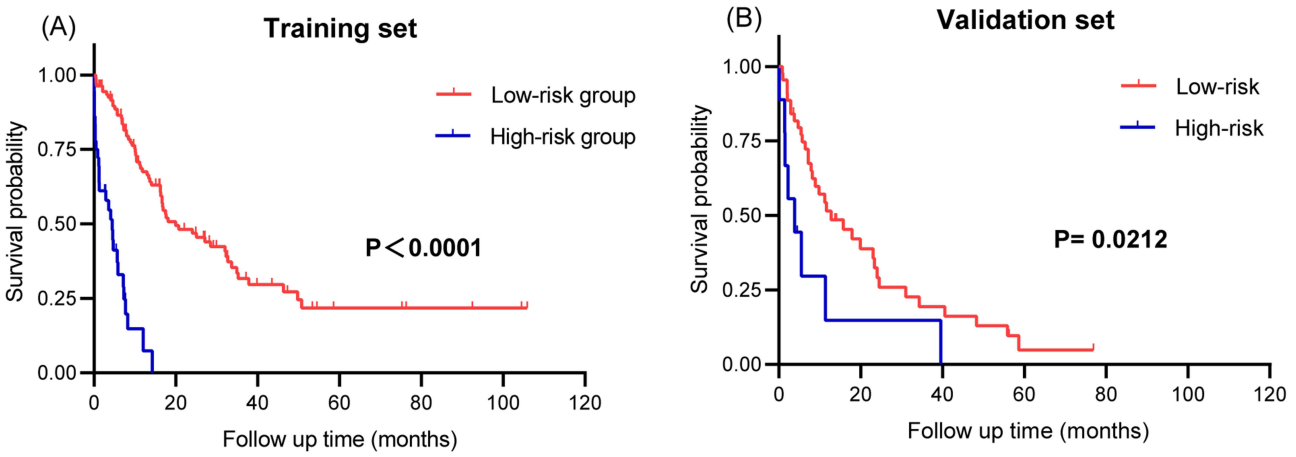

Figure 7 Kaplan–Meier survival analysis of OS according to the risk score in the training and validation cohorts.
Notes: (**A**) Training cohort, *P* <0.0001. (**B**) Validation cohort, *P* =0.0212.

chemotherapy, a greater benefit was found in patients receiving it than in those not receiving it in the high-risk group (log-rank *P* <0.0001; Figure 8C); however, this difference was not observed in the low-risk group (log-rank *P* =0.3322; Figure 8D).

Discussion

The incidence of MPE is high in patients with breast cancer, with approximately 7–11% of patients suffering from MPE during their disease course.[12] The mechanisms for the development and progression of MPE are highly complex and may be related to a range of factors, including impaired lymphatic drainage and pleural invasion.[13] Previous studies have illustrated that the humoral and mechanical milieus of the body are substantially altered after the development of MPE. Patients with MPE often report symptoms of cough, chest tightness, and breathlessness if their presentation is

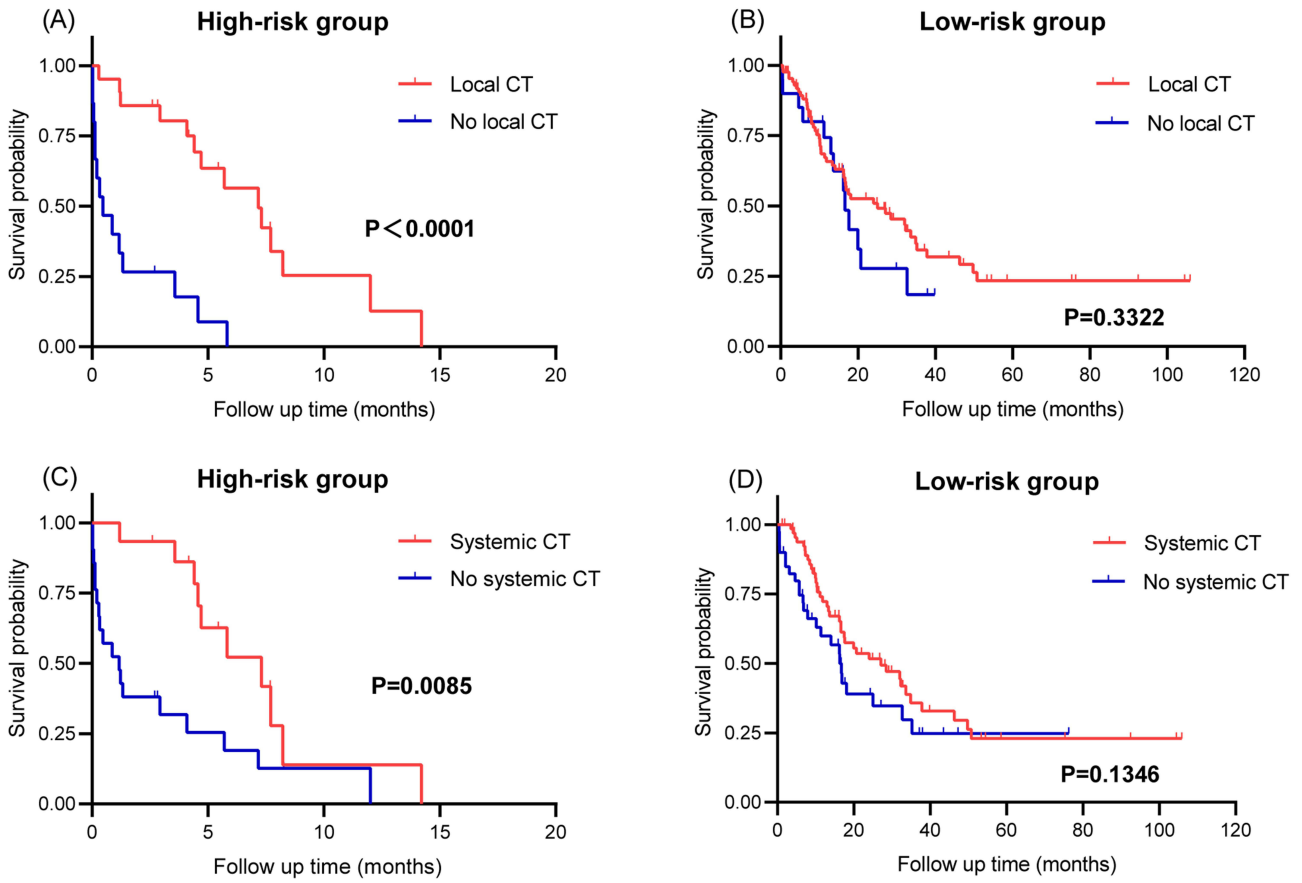

Figure 8 (**A** and **B**) Kaplan–Meier survival curves for patients in the training set stratified by whether they received local intrapleural chemotherapy in the high-risk group (*P* <0.0001) and low-risk group (*P* =0.3322). (**C** and **D**) Kaplan–Meier survival curves for patients in the validation set stratified by whether they received systemic chemotherapy in the high-risk group (*P* =0.0085) and low-risk group (*P* =0.1346).

Notes: Systemic CT, received systemic chemotherapy; No systemic CT, did not receive systemic chemotherapy; Local CT, received local chemotherapy; No local CT, did not receive local chemotherapy.

compounded by dysfunction of the heart, lungs, and other organs, which can easily result in a poor prognosis. Currently, guideline recommendations on therapy after the diagnosis of MPE are not uniform and focus mainly on the relief of symptoms.[3,14–16] A possible reason is that such patients have highly variable outcomes, which prevents physicians from reaching a more accurate assessment of the prognosis.[17,18] Several prognostic models aiming to predict the OS of pancancer patients with MPE have emerged thus far. However, the numbers of breast cancer patients included in the analyses were relatively small.[5–7] Since then, several models focusing on lung cancer and mesothelioma have been developed.[19,20] With breast cancer as the second leading cause of MPE, it is essential to construct a model for prognostication in a cohort of breast cancer patients. Based on the clinical characteristics and laboratory indicators determined via the first thoracentesis, we constructed a nomogram to predict the survival probability of individual breast cancer patients with MPE for the first time. The modeling data sources are derived from real-world healthcare data, and a wide range of variables can be collected.

Our results reconfirmed that MPE confers a poor prognosis in breast cancer patients, with substantial heterogeneity. The model was built using univariate Cox regression and LASSO regression analyses. The latter is considered to be able to screen multiple variables in cases of relatively small sample sizes and has been widely used in the construction of prognostic models.[21,22] In our final nomogram, eight prognostic variables were retained. Several of these have previously been shown to be significantly relevant to the survival of cancer patients, including the EP/PR status, NLR, and DFS.[23–25] Whether the levels of biochemical indicators in the PE can serve as a predictor in MPE prognosis has been controversial and the cutoff values of these markers have varied widely among studies.[26–29] In the present study, laboratory indicators

were included as continuous variables in the analyses, which increased the statistical power. As shown in the mentioned nomogram, glucose in PE contributed the most to the predictive capability of the model, with patients with higher PE glucose levels showing longer survival. However, previous in vitro experiments have shown that a high-glucose environment can promote tumor growth, and in contrast with our findings, a study of MPE in lung cancer reported that lower PE glucose levels (60 mg/dL) predicted shorter survival.[30] The results are still inconclusive. Notably, the presence of ascites and non-first recurrence acted as risk factors in our model. Few studies concerning these two factors have been performed, and it is not clear if this result is specific to MPE in breast cancer. Otherwise, the LENT score, based on the LDH level in pleural fluid, is considered to be associated with the outcome.[5] However, this association was not confirmed by the results of our study and deserves further investigation.

Breast cancer represents a heterogeneous group of tumors that were originally classified into distinct molecular subtypes by their clinicopathological features. It has previously been shown that there are important differences in the metastatic behavior of breast cancer subtypes. However, there are similar odds of metastasis to the pleural and peritoneal regions.[31] In our study, patients with luminal-type tumors had a median survival of 16.87 months, which was significantly better than the median survival observed in patients with nonluminal subtype tumors (7.7 months). In addition, the receptor status included in the study was determined based on the pathological report at the time of initial diagnosis with breast cancer. Some scholars have identified the need to reassess the biomolecular status at metastatic sites because the receptor status is not always in concordance between primary and metastatic breast cancer lesions.[32] Indeed, the rates of discordance in HER2 expression are as high as 63%.[33]

For MPE therapy, the official ATS/STS/STR Clinical Practice Guideline recommends therapeutic pleural interventions only for symptomatic patients with two main types of treatment, ie, indwelling pleural catheterization (IPC) and pleural fixation.[4,15] No guideline specifies which is the most appropriate for each individual. However, for a shorter length of hospital stay and fewer pleural procedures, clinicians are more willing to choose IPC.[34] At the time of admission, all patients in our study displayed respiratory symptoms, including dyspnea, cough, and chest pain. After patients were treated with thoracentesis and drainage of 700–1000 mL per day, their clinical symptoms were alleviated to varying degrees. Nevertheless, it needs to be noted that both IPC and pleural fixation are palliative treatments aimed at relieving symptoms. Systemic therapy is still recommended for patients with expected long-term survival. Our study revealed a significant survival benefit for MPE patients treated with systemic or intrapleural chemotherapy in the high-risk group. Therefore, we recommend more aggressive chemotherapy for patients in the high-risk group and cautious use of chemotherapy for patients in the low-risk group.

Our study has several notable strengths. First, our model is specific to the metastatic breast cancer population. Second, the variables in the model are derived from routine laboratory indicators at general hospitals. Third, after the external data were verified, the model proved to predict survival well. Nevertheless, there are also several limitations. First, the sample size was relatively low for a prediction model study, resulting in a certain degree of overfitting. Second, our study was a retrospective study. Patient retrospective bias in the recall of physical activity level can lead to inaccuracy of the ECOG score. Therefore, the ECOG score, which has been shown to be significantly relevant to the survival of MPE patients, was not included in our analysis but has been included in other models of MPE.[9,23] The absence of this information in our model limits comparison with other models. Third, while we have entered a new era of molecularly targeted therapy, currently, MPE still lacks efficient targeted drugs, and the current study is still at the clinical level. Our prediction model does not include biomarkers that may help to improve the performance of the nomogram model, and more biomarkers need to be further investigated.

Conclusion

Our model provides clinically convenient and reliable predictions of 3-, 6-, and 12-month survival probabilities for breast cancer patients with MPE, offering valuable guidance for follow-up treatment. This may help us to strike a better balance between treatment efficacy and side effects. We also provide a web calculator to calculate the risk score (https://mpenomogram.shinyapps.io/MPE_Nomogram/). However, more cohort or prospective studies will still be required to confirm our results and credibility of the model in the future.

Ethics Approval

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University. All patients gave informed consent to the study and voluntarily signed the informed consent form.

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Disclosure

The authors report no conflicts of interest in this work.

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