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Development and validation of a nomogram for predicting survival of advanced breast cancer patients in China

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ABSTRACT

Background: There is a lack of prognostic models predicting the overall survival (OS) of advanced breast cancer (ABC) patients in China.

Methods: Data from the China National Cancer Center database that recorded 4039 patients diagnosed with breast cancer between 1987 and 2019 were extracted and a total of 2263 ABC participants were enrolled in this study, which were further randomized 3:1 and divided into training (n = 1706) and validation (n = 557) groups. The nomogram was built based on independent predictors identified by univariate and multivariate cox regression analyses. The discriminatory and predictive capacities of the nomogram were assessed by Harrell's concordance index (C-index) and calibration plots.

Results: Univariate and multivariate analyses found that age, Eastern Cooperative Oncology Group (ECOG) score, T-stage, N-stage, tumor subtype, the presence of distant lymph node (DLN)/liver/brain metastasis, local therapy, efficacy of first-line therapy and metastatic-free interval (MFI) were significantly related to OS (all $P < 0.05$). These variables were incorporated into a nomogram to predict the 2-year and 3-year OS of ABC patients. The C-indexes of the nomogram were 0.700 (95% confidence interval [CI]: 0.683–0.717) for the training set and 0.686 (95% CI: 0.652–0.719) for the validation set. The calibration curves revealed satisfactory consistency between actual survival and nomogram prediction in both the internal and external validations. The nomogram was capable of stratifying patients into different risk cohorts.

Conclusions: We constructed and validated a nomogram that might serve as an efficient tool to provide prognostic prediction for ABC patients and guide the physicians to make personalized treatment decisions.

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1. Introduction

With 1.7 million new patients diagnosed each year, breast cancer becomes a worldwide public health dilemma [1]. Advanced breast cancer (ABC) comprises both locally advanced and de novo metastatic or recurrent breast cancer. About 6%–10% of breast cancer patients are diagnosed with de novo stage IV disease, and over 30% patients with non-metastatic breast cancer will relapse [2].

Most ABC is incurable, with a median overall survival (OS) of only two to three years [3]. The outcome of ABC patients is associated with different prognostic factors, including biological breast cancer subtype, performance status, age, distant metastasis sites, prior therapy and metastatic-free interval (MFI) [4–6]. These prognostic factors may influence the therapeutic strategy and the fully evaluation of individual characteristics may be beneficial when making a personalized choice of treatment. As already reported, several prognostic prediction models have been constructed and widely accepted for early-stage breast cancer [7–11].

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In contrast, until now, only few prognostic models predicting survival of metastatic breast cancer patients have been established [12,13], and have not yet been widely validated.

In this study, we searched the data from the China National Cancer Center to investigate the risk factors of survival in ABC patients. Furthermore, we intended to construct and externally validate a nomogram with helpful clinicopathological features for survival prediction of breast cancer patients after metastasis or recurrence.

2. Methods

2.1. Study population

A total of 2263 female patients diagnosed with breast cancer during 1987 and 2019 who had developed ABC afterwards and were treated in the China National Cancer Center over a period of more than 15 years (from January 2003 to June 2019) were enrolled in our study. The inclusion criteria were as follows: (1) breast cancer confirmed by pathology; (2) female patients with ABC, including metastatic or locoregional recurrent breast cancer, and locally advanced unresectable disease that had relapsed; (3) complete medical information including age at initial diagnosis and relapse, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, distant metastasis sites, local therapy, first-line therapy. Exclusion criteria included: (1) with previous or coexisting cancers except breast cancer; (2) follow-up less than 1 month from the initiate of first-line therapy. All participants were followed up to June 30, 2019 or date of deaths by outpatient visits or telephone follow-up. Seventy-five percent of included patients were randomized as the training group to identify the prognostic factors and to establish the nomogram for prognostic prediction. The rest of the population were selected as the validation group for evaluation of the nomogram.

2.2. Clinical data

The following clinical data were collected for every patient from medical records: age at diagnosis with ABC, Eastern Cooperative Oncology Group (ECOG) score at diagnosis with ABC, pathological type of primary tumor, the initial T-stage, N-stage and M-stage, breast cancer subtype of primary tumor, metastatic sites (distant lymph node [DLN]/liver/lung/bone/brain) or locoregional recurrence, local therapy in first-line treatment (including surgery, radiation, radiofrequency ablation and interventional therapy), first-line therapy, best efficacy of first-line therapy (progressive disease [PD], or no PD), MFI, survival month, and overall survival status. Breast cancer subtypes were classified as: (1) luminal-like subtype (ER/PR+ and HER2+/−), (2) HER2 subtype (ER-, PR- and HER2+), (3) triple-negative subtype (ER-, PR- and HER2-). Hormone receptor status was assessed by routine immunohistochemistry (IHC) and HER2 was determined by either IHC or fluorescent in-situs hybridization (FISH). Cancers with 1%–100% ER IHC staining were considered ER-positive and cancers with 1%–100% PR IHC staining were considered PR-positive. HER2 IHC3+ or gene amplified by FISH were regarded as HER2-positive. DLN was considered as non-regional lymph node for breast cancer. The clinical stages were classified based on the 8th American Joint Committee on Cancer (AJCC) TNM staging system. Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 was used to evaluate treatment responses. MFI was measured as time between initial breast cancer and diagnosis of recurrence or metastasis.

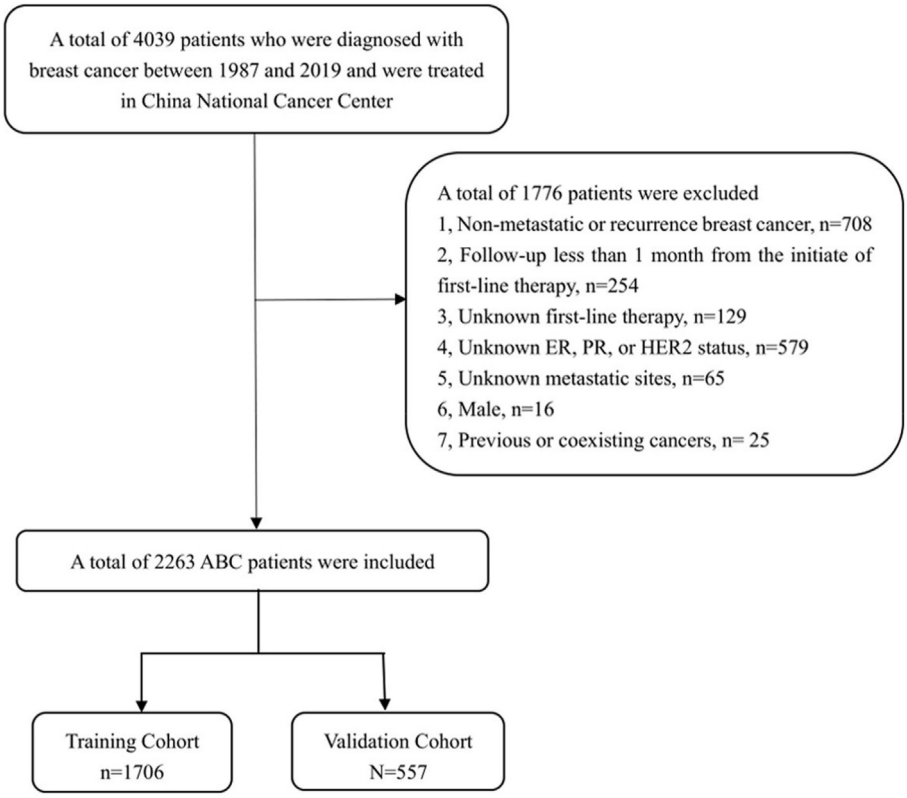

Fig. 1. Flow diagram of enrolled participants. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ABC, advanced breast cancer.

2.3. Statistical analysis

OS was defined as the time between the cancer metastasis or recurrence and death due to any causes or last follow-up. The cumulative OS was estimated using Kaplan-Meier (KM) analysis. Variables significant at $P < 0.05$ level in the univariate analysis were incorporated into the Cox multivariate regression analysis. A prediction nomogram was developed based on the independent risk features identified by the cox multivariate regression analysis. The discrimination power of the nomogram was evaluated by the Harrell's concordance index (C-index) with a 95% confidence interval (CI). The nomogram was applied to the validation set for external validation. The predicted survival was compared with the actual condition by calibration plots in both the training and validation cohorts. SPSS (version 19.0, Chicago, IL, USA) and R software (version 3.6.1) with the survival and *rms* package were used for statistical analysis. A two-sided P value < 0.05 was considered significantly different.

3. Results

3.1. Patient characteristics

A total of 2263 (56.0%) ABC participants were included in this study. Fig. 1 showed the specific screening process. Table 1 listed the clinicopathological features of patients in the training (n = 1706) and validation sets (n = 557). The median age of the study population was 49.0 (range 20.0–83.0) years old and 1158 (51.2%) patients were younger than 50. The median follow-up was 61.6 months and 1210 (53.5%) patients were dead at the end of the follow-up period. With a median OS of 45.4 months, the 2-year and 3-year OS rates were 75.2% and 60.2%, respectively. Three hundred and forty-three (15.2%) patients presented with de novo stage IV breast cancer. Of the whole population, 362 (16.0%) had MFI no less than 5 years. There were 915 (40.4%), 550 (24.3%), 809 (35.7%), 93 (4.1%), 861 (38.0%), 575 (25.4%) patients having DLN, liver, lung, brain, bone metastasis and locoregional recurrence, respectively. Besides, 47.8% (1082) of the enrolled patients had multi-metastatic sites when first diagnosed with stage IV breast cancer. Luminal-like subtype, HER2 subtype and triple-negative subtype comprised 68.3% (1545), 13.2% (300) and 18.5% (418) of total participants, respectively. Local therapy was performed in 42.0% (951) of patients. During the first-line therapy, 111 (4.9%), 1933 (85.4%) and 219 (9.7%) patients were treated with single-agent chemotherapy, combination therapy and endocrine therapy, respectively. As for patients with HER2-positive (n = 665), 44.5% (296) of them received anti-HER2 therapy in first-line treatment. Two hundred and seventy-five (12.2%) patients had PD when they were first evaluated for the first-line therapy.

3.2. Selected prognostic factors for OS

After univariable analysis, the variables of pathological type, M-stage, bone metastasis were not related to survival, and were excluded from further analysis (Table 2). In univariable analysis, some subgroup of patients had similar OS, which were therefore combined as one group in the multivariable analysis, including T1 and Tx, T3 and T4, N0, N1 and Nx, N2 and N3. The multivariable analysis demonstrated that age, ECOG, T-stage, N-stage, subtype, the presence of DLN/liver/brain metastasis, local therapy, best efficacy of first-line therapy and MFI were independent prognostic factors for OS (Table 2).

Table 1
Clinicopathological features of patients in the training and validation cohorts.

Characteristic	Training cohort, N (%)	Validation cohort, N (%)
Age		
<50	873 (51.17)	285 (51.17)
≥50	833 (48.83)	272 (48.83)
ECOG		
0	404 (23.68)	153 (27.47)
1	1230 (72.10)	386 (69.30)
2	72 (4.22)	18 (3.23)
Pathological type		
IDC	1577 (92.44)	513 (92.10)
ILC	69 (4.04)	17 (3.05)
Others	60 (3.52)	27 (4.85)
T-stage		
T1	437 (25.62)	132 (23.70)
T2	714 (41.85)	244 (43.81)
T3	119 (6.98)	45 (8.08)
T4	85 (4.98)	24 (4.31)
Tx	351 (20.57)	112 (20.11)
N-stage		
N0	464 (27.20)	157 (28.19)
N1	431 (25.26)	126 (22.62)
N2	310 (18.17)	100 (17.95)
N3	334 (19.58)	112 (20.11)
Nx	167 (9.79)	62 (11.13)
M-stage		
M0	1452 (85.11)	468 (84.02)
M1	254 (14.89)	89 (15.98)
Subtype		
Luminal-like	1160 (68.00)	385 (69.12)
HER2	219 (12.84)	81 (14.54)
Triple-negative	327 (19.17)	91 (16.34)
DLN metastasis		
No	1023 (59.96)	325 (58.35)
Yes	683 (40.04)	232 (41.65)
Liver metastasis		
No	1302 (76.32)	411 (73.79)
Yes	404 (23.68)	146 (26.21)
Lung metastasis		
No	1106 (64.83)	348 (62.48)
Yes	600 (35.17)	209 (37.52)
Brain metastasis		
No	1634 (95.78)	536 (96.23)
Yes	72 (4.22)	21 (3.77)
Bone metastasis		
No	1063 (62.31)	339 (60.86)
Yes	643 (37.69)	218 (39.14)
Locoregional recurrence		
No	1273 (74.62)	415 (74.51)
Yes	433 (25.38)	142 (25.49)
Local therapy		
No	971 (56.92)	341 (61.22)
Yes	735 (43.08)	216 (38.78)
First-line therapy		
Single-agent chemotherapy	83 (4.87)	28 (5.03)
Combination therapy	1462 (85.70)	471 (84.56)
Endocrine therapy	161 (9.44)	58 (10.41)
Best efficacy of first-line therapy		
No PD	1506 (88.28)	482 (86.54)
PD	200 (11.72)	75 (13.46)
MFI		
<5 years	1431 (83.88)	470 (84.38)
≥5 years	275 (16.12)	87 (15.62)

ECOG Eastern Cooperative Oncology Group, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, HER2 human epidermal growth factor receptor 2, DLN distant lymph node, PD progressive disease, MFI metastatic-free interval.

3.3. Prognostic nomogram for OS

The positive variables in multivariable analysis were integrated into the nomogram scoring system (Fig. 2). The value of each of these variables was given a score on the point scale axis. The estimated probability of 2-year and 3-year OS was calculated by

Table 2
Univariable and multivariable cox regression analyses of overall survival in the training cohort.

Univariable analysis			Multivariable analysis		
Characteristic	HR (95% CI)	*P* value	Characteristic	HR (95% CI)	*P* value
Age			Age		
<50	Reference		<50	Reference	
≥50	1.24 (1.09, 1.41)	0.0014	≥50	1.21 (1.06, 1.38)	0.0048
ECOG			ECOG		
0	Reference		0	Reference	
1	1.40 (1.17, 1.66)	0.0002	1	1.29 (1.08, 1.54)	0.0044
2	2.87 (2.11, 3.88)	<0.0001	2	2.11 (1.54, 2.87)	<0.0001
Pathological type					
IDC	Reference				
ILC	1.06 (0.78, 1.45)	0.7121			
Others	0.74 (0.52, 1.06)	0.1020			
T-stage			T-stage		
T1	Reference		T1/Tx	Reference	
T2	1.28 (1.09, 1.52)	0.0033	T2	1.12 (0.97, 1.29)	0.1362
T3	1.92 (1.48, 2.49)	<0.0001	T3/T4	1.32 (1.07, 1.63)	0.0096
T4	1.90 (1.42, 2.55)	<0.0001			
Tx	1.10 (0.90, 1.34)	0.3381			
N-stage			N-stage		
N0	Reference		N0/N1/Nx	Reference	
N1	1.18 (0.98, 1.42)	0.0866	N2/N3	1.32 (1.14, 1.52)	0.0001
N2	1.59 (1.30, 1.93)	<0.0001			
N3	1.87 (1.55, 2.27)	<0.0001			
Nx	1.25 (0.98, 1.61)	0.0737			
M-stage					
M0	Reference				
M1	1.14 (0.95, 1.37)	0.1719			
Subtype			Subtype		
Luminal-like	Reference		Luminal-like	Reference	
HER2	1.48 (1.22, 1.80)	<0.0001	HER2	1.21 (0.99, 1.48)	0.0597
Triple-negative	1.64 (1.39, 1.93)	<0.0001	Triple-negative	1.64 (1.38, 1.95)	<0.0001
DLN metastasis			DLN metastasis		
No	Reference		No	Reference	
Yes	1.60 (1.40, 1.82)	<0.0001	Yes	1.50 (1.30, 1.72)	<0.0001
Liver metastasis			Liver metastasis		
No	Reference		No	Reference	
Yes	1.84 (1.59, 2.13)	<0.0001	Yes	1.74 (1.49, 2.04)	<0.0001
Lung metastasis			Lung metastasis		
No	Reference		No	Reference	
Yes	1.22 (1.07, 1.40)	0.0035	Yes	0.97 (0.84, 1.13)	0.7079
Brain metastasis			Brain metastasis		
No	Reference		No	Reference	
Yes	2.04 (1.52, 2.73)	<0.0001	Yes	2.53 (1.85, 3.46)	<0.0001
Bone metastasis					
No	Reference				
Yes	1.12 (0.98, 1.28)	0.0872			
Locoregional recurrence			Locoregional recurrence		
No	Reference		No	Reference	
Yes	0.72 (0.62, 0.84)	<0.0001	Yes	1.03 (0.87, 1.21)	0.7284
Local therapy			Local therapy		
No	Reference		No	Reference	
Yes	0.55 (0.48, 0.63)	<0.0001	Yes	0.60 (0.52, 0.70)	<0.0001
First-line therapy			First-line therapy		
Single-agent chemotherapy	Reference		Single-agent chemotherapy	Reference	
Combination therapy	1.40 (1.17, 1.66)	0.0002	Combination therapy	0.76 (0.57, 1.02)	0.0631
Endocrine therapy	2.87 (2.11, 3.88)	<0.0001	Endocrine therapy	0.69 (0.48, 1.00)	0.0475
Best efficacy of first-line therapy			Best efficacy of first-line therapy		
No PD	Reference		No PD	Reference	
PD	2.05 (1.69, 2.47)	<0.0001	PD	2.05 (1.69, 2.50)	<0.0001
MFI			MFI		
<5 years	Reference		<5 years	Reference	
≥5 years	0.62 (0.51, 0.75)	<0.0001	≥5 years	0.75 (0.61, 0.92)	0.0062

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, HER2 human epidermal growth factor receptor 2, DLN distant lymph node, PD progressive disease, MFI metastatic-free interval.

counting the scores and locating on the total point scale. The C-indexes of the nomogram were 0.700 (95% CI: 0.683–0.717) and 0.686 (95% CI: 0.652–0.719) for the training and the validation sets, respectively. The calibration plots revealed satisfactory agreement between actual survival and predicted survival in both the internal (Fig. 3) and external validations (Fig. 4).

3.4. Risk stratifications using the new nomogram

We categorized patients with similar outcome in the training set into three subgroups based on the predicted probability of 3-year OS: low-risk (>0.70), medium-risk (0.40–0.70) and high-risk groups (0–0.40). Three subgroups of the whole population had

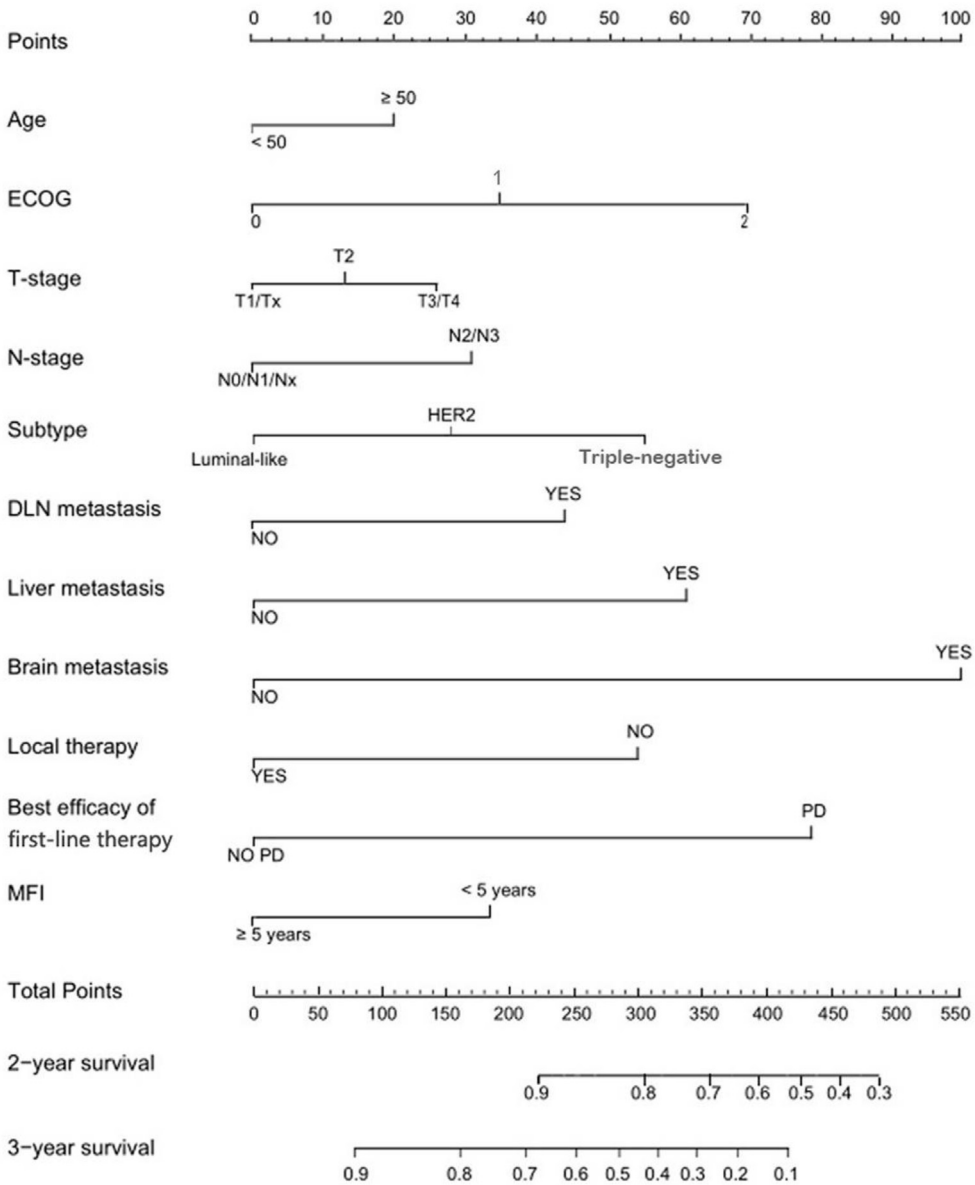

Fig. 2. Nomogram for predicting the 2-year and 3-year overall survival. ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; DLN, distant lymph node; PD, progressive disease; MFI, metastatic-free interval.

significant difference among the KM curves (Fig. 5, all $P < 0.0001$). The low-risk, medium-risk and high-risk subgroups had 84.9%, 55.1% and 27.6% 2-year OS, and 71.3%, 35.8% and 8.4% 3-year OS, respectively. The median OS of patients with low, medium and high risk were 57.0, 26.7 and 16.3 months. In patients with liver metastasis, the low-risk, medium-risk and high-risk subgroups had 78.4%, 53.5% and 28.1% 2-year OS, and 68.3%, 32.6% and 13.0% 3-year OS, respectively (Fig. 6, all $P < 0.0001$). Similarly, in patients with triple-negative disease, the low-risk, medium-risk and high-risk subgroups had 72.7%, 55.3% and 24.1% 2-year OS, and 59.0%, 36.8% and 5.4% 3-year OS, respectively (Fig. 7, all $P < 0.0001$).

4. Discussion

Without a widely accepted consensus on medical treatment, ABC remains incurable [6]. Prognosis of patients with ABC varies greatly on an individual level, even survival times of up to 15 years have been reported [14]. A valid prediction tool to identify ABC patients with promising prognostic factors can help clinicians make more appropriate clinical decisions. However, only limited numbers of prediction models used in advanced/metastatic breast cancer have been reported until now [12,15]. Li et al. [12] developed a model to predict the prognosis of stage IV breast cancer patients based on the data from the National Cancer Database in the United states, but they failed to distinguish the de novo metastatic patients from those who progressed to metastatic diseases after adjuvant treatments. Lee et al. [15] established a nomogram, with a C-index of 0.65 (95%CI: 0.62–0.67), developed from ABC patients administrated with anthracyclines, cyclophosphamide, or capecitabine as first-line chemotherapy, which might be restricted for widely use in patients accepting other treatments including effective cytotoxic agents, endocrine and targeted therapies [16–19]. In our study, we have established a prediction model based on widely available baseline clinicopathological features to predict survival for patients

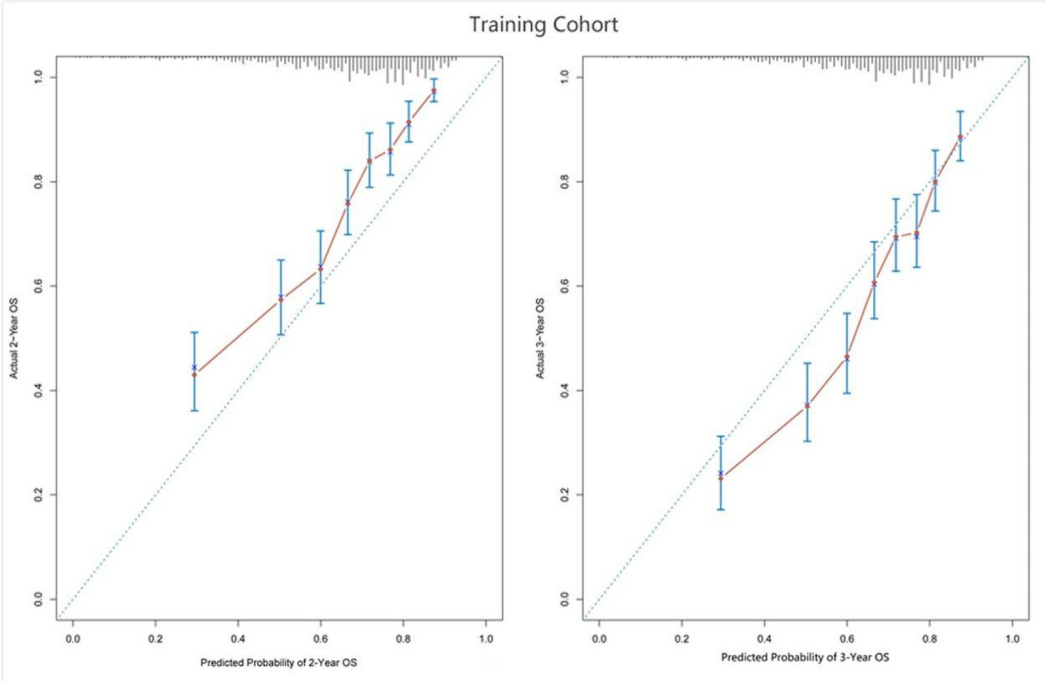

Fig. 3. The calibration curve to predict 2-year and 3-year overall survival (OS) in the training cohort.

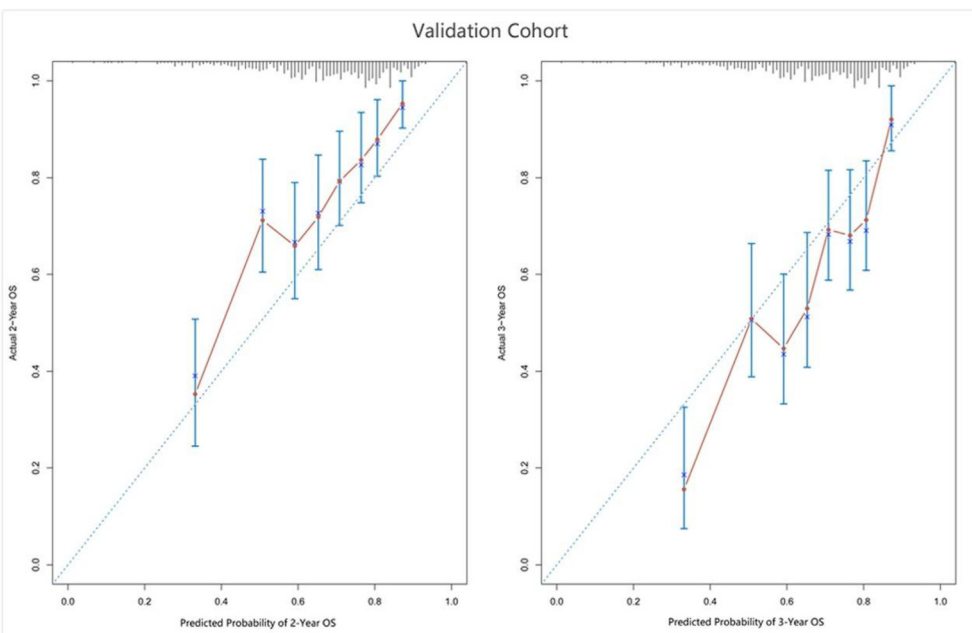

Fig. 4. The calibration curve to predict 2-year and 3-year overall survival (OS) in the validation cohort.

with ABC using data from our center.

One interesting thing we have found was that the initial tumor size and primary axillary lymph node status were related to the survival after relapse, which was consistent with the previous studies [20,21]. We should not neglect the fact that there was a relatively high proportion of patients with unknown T-stage (Tx = 20.57%) and unknown N-stage (Nx = 9.79%), which suggested the results needed further confirmation. The other thing we have found was that there was no significant difference in outcome between de novo and relapsed metastatic breast cancer in our data (M1 vs M0, HR = 1.14, 95% CI = 0.95–1.37, $P = 0.1719$). The prognosis of patients with de novo stage IV breast cancer was reported to be superior compared with those with recurrent diseases [2,22], likely due to the single metastatic site, hormone receptor positive with single bone metastasis, treatment naïve and trastuzumab treatment for HER2+ disease. However, other studies found no difference in outcome between these two cohorts [23,24], which were in accord with our study. The increased efficacy of new agents and the

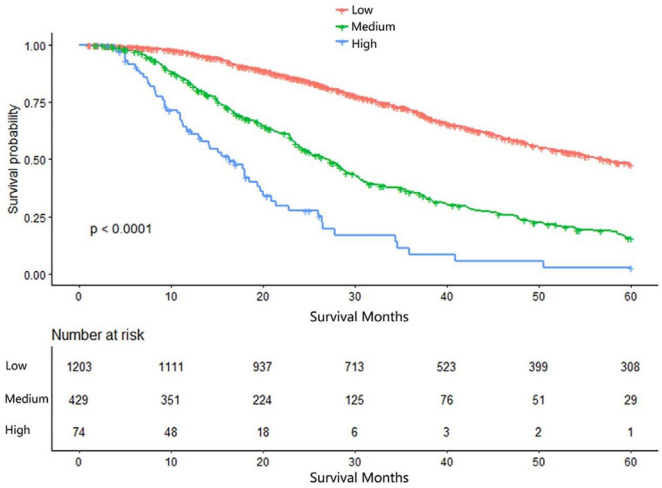

Fig. 5. Survival probability of nomogram-based stratification of overall population.

various metastatic sites might have smoothened the possible overall survival difference. Some researchers demonstrated that the different outcomes between these two cohorts of patients depended on the MFI [2,25]. Compared with de novo stage IV breast cancer patients, relapsed breast cancer patients with longer MFI had similar risk of death. In conclusion, it seemed that the reasons behind the survival distinctions between women with de novo and recurrent metastatic breast cancer came to the different clinicopathological features, including breast cancer subtype, metastatic sites, efficacy of the systemic treatment and MFI. Therefore, we included de novo stage IV breast cancer patients in the study population to build the prediction model, unlike the other studies [15,21] which had excluded patients with distant metastasis at initial diagnosis. We analyzed the features including breast cancer subtype, metastatic sites, efficacy of the systematic treatment and MFI and the multivariate analysis proved that they were positive prognostic factors for OS.

Based on the stratification analysis, the developed nomogram could be applied to identifying patients with different risks. Breast cancer patients with liver metastasis were reported to have an unfavorable prognosis, with a median post-metastasis survival of approximately 18–24 months [26]. Effective local therapy of breast cancer liver metastasis achieved a survival advantage over adequate systemic therapy in a special group of patients [27]. However, how to choose patients with favorable prognostic factors and suitable for the local treatment remained uncertain. This prediction model could identify low-risk patients who might benefit from aggressive local curative treatment of liver metastasis. As for advanced patients with aggressive triple-negative breast cancer (TNBC), treatment remained challenging. The prediction model suggested that the low-risk group of TNBC patients could have relatively better outcome. More intensive attempts, including atezolizumab plus nab-paclitaxel [28] and olaparib [29], were supposed to be recommended for this group of patients to achieve clinical remission. The ability to identify patients with high risk was essential in making personal decisions for the remaining lifetime in addition to the treatment options, since the therapies might not only be less beneficial but also increase unnecessary compromise in quality of life.

There were several limitations of the current study. Firstly, less record of the metastatic tumor receptor status was one of the deficiencies of the model, since phenotype discordance has been found between primary and relapsed breast cancer [30]. Reassessment of the HER2 and hormone receptor expression profile at the time of disease relapse might optimize the prognostic model.

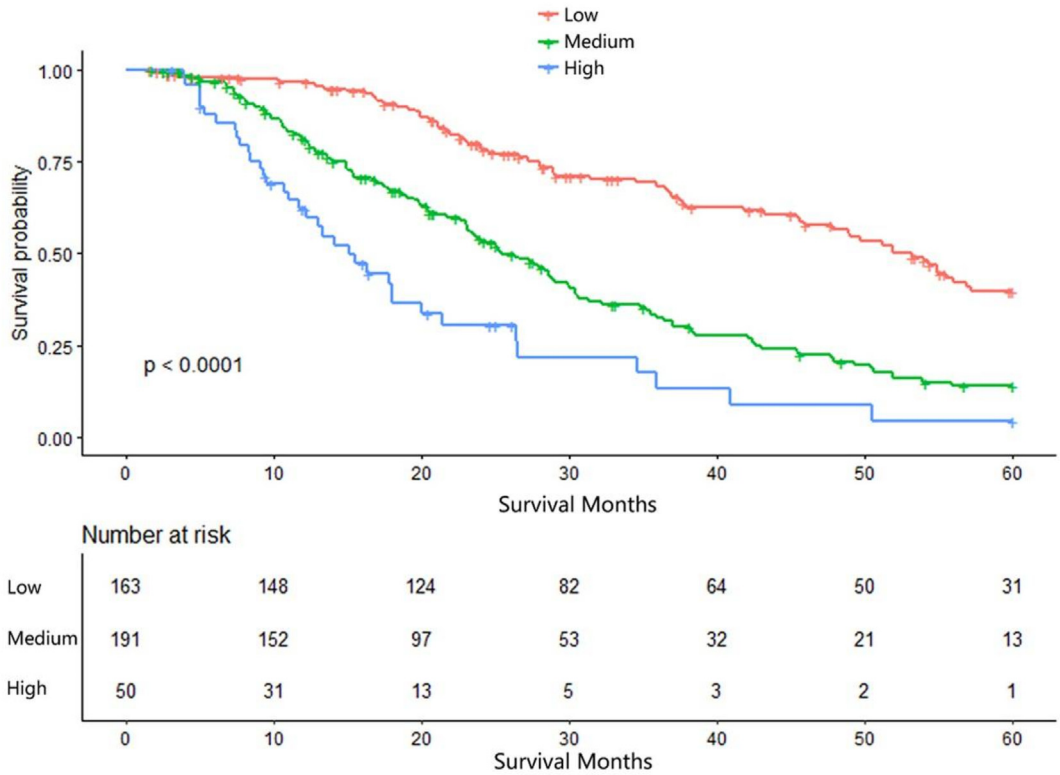

Fig. 6. Survival probability of nomogram-based stratification of patients with liver metastasis.

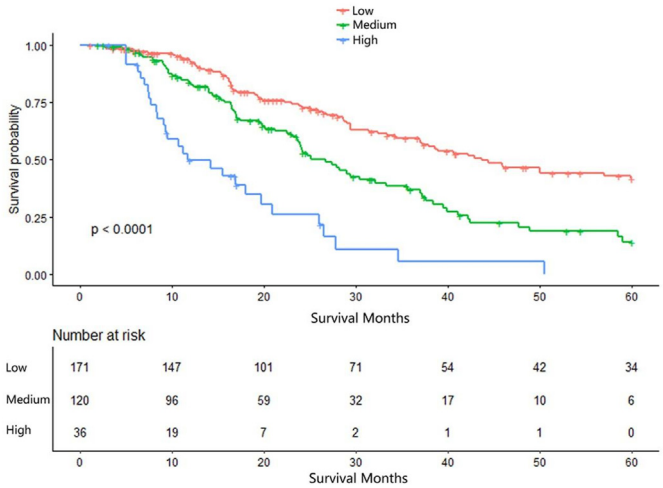

Fig. 7. Survival probability of nomogram-based stratification of patients with triple-negative disease.

Secondly, we need different population from another center to externally validate this prediction model. Finally, the missing clinical data and loss to follow-up of the patients might have some effects on the discriminatory and predictive capacities of the nomogram. We are supposed to design a prospective trial to further validate the model in the future.

5. Conclusions

In summary, we demonstrated important risk factors in ABC patients and incorporated these parameters into a nomogram to predict the outcome of the patients. This prognostic model could help patients better understand their future prognosis and could also guide the physicians to make personalized therapeutic decisions for individual ABC patients.

Contribution

Shaoyan Lin: Assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript. Hongnan Mo: Assembly of data, Manuscript writing, Final approval of manuscript. Yiqun Li: Assembly of data, Manuscript writing, Final approval of manuscript. Xiuwen Guan: Assembly of data, Manuscript writing, Final approval of manuscript. Yimeng Chen: Assembly of data, Manuscript writing, Final approval of manuscript. Zijing Wang: Assembly of data, Manuscript writing, Final approval of manuscript. Peng Yuan: Assembly of data, Manuscript writing, Final approval of manuscript. Jiayu Wang: Assembly of data, Manuscript writing, Final approval of manuscript. Yang Luo: Assembly of data, Manuscript writing, Final approval of manuscript. Ying Fan: Assembly of data, Manuscript writing, Final approval of manuscript. Ruigang Cai: Assembly of data, Manuscript writing, Final approval of manuscript. Qiao Li: Assembly of data, Manuscript writing, Final approval of manuscript. Shanshan Chen: Assembly of data, Manuscript writing, Final approval of manuscript. Pin Zhang: Assembly of data, Manuscript writing, Final approval of manuscript. Qing Li: Assembly of data, Manuscript writing, Final approval of manuscript. Fei Ma: Assembly of data, Manuscript writing, Final approval of manuscript. Binghe Xu: Conception and design, Assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript.

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Ethical approval

The study was approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Declaration of competing interest

The authors declared no competing interests.

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