Novel Nomograms to Predict of Overall Survival and Cancer-Specific Survival of Patients of Metaplastic Breast Cancer

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Research

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Abstract

Background

Metaplastic breast cancer (BMC) is a rare type of breast cancer with an increasing incidence, we aim to develop clinical nomograms to predict the overall survival and cancer-specific survival for patients with BMC.

Methods

Patients data were collected from the SEER database between 1973 and 2015. All included patients were randomly assigned into the training and validation sets. Univariate and multivariate Cox analysis were performed to identify independent prognostic factors of MBC. These essential prognostic variables were combined to construct nomogram models to predict overall survival (OS) and cancer-specific survival (CSS) in patients with MBC. Model performance was evaluated by concordance index (C-index) and calibration plots.

Results

A total of 1835 patients were collected and divided into the training (1223) and validation (612) groups. The multivariate Cox model identified age, TNM stage, T stage, and N stage, chemotherapy and radiotherapy as independent covariates associated with OS, while these variables except for age and chemotherapy were independent prognostic factors of CSS. The nomogram constructed based on these covariates demonstrated excellent accuracy in estimating 3-, and 5-year OS and CSS, with a C-index of 0.759(95% CI, 0.746-0.772) for OS and 0.766 (95% CI, 0.751-0.781) for CSS in the training cohort. In the validation cohort, the nomogram-predicted C-index was 0.754 for OS (95%CI, 0.734-0.774) and 0.752 (95%CI, 0.728-0.776) for CSS. All calibration curves exhibited good consistency between predicted and actual survival.

Conclusions

These nomogram models established in this study can help enhance the accuracy of prognostic prediction, which may thereby improve individualized assessment of survival risks and facilitate to provide constructive therapeutic suggestions.

Background

Metaplastic breast cancer (BMC) is a relatively rare type of breast cancer, accounting for less than 1% of all cased of breast cancer[1, 2]. The incidence of MBC is increasing since it was recognized as a distinct pathological diagnosis in 2000[3]. An estimated 249,260 new cases of breast cancer will be diagnosed among women in the United States in 2016[4]. Histologically, MBC is classified into several subtypes, including spindle, squamous, chondroid, osseous and/or rhabdomyoid MBC[5]The Surveillance, Epidemiology, and End Results database (SEER database) is an annually updated and population-based

database, covering about 30% of the US population. It has became a distinctive resource to investigate special malignancies, such as MBC, by taking advantages of its wide range of data on cancer.

Nomograms have been proposed as a novel and dependable tool to incorporate demographic and clinicopathologic factors for accurate prognostic prediction of many cancers. They were generated from regression analysis and showed to compare favorably to the standard TNM staging systems. Currently, to our knowledge, there was no available nomograms for individual MBC patients derived from population-based data. Herein, we aim to establish a novel prognostic nomogram to forecast individualized survival of MBC depended on the personalized demographic, pathologic and therapeutic information from the SEER database.

Materials And Methods

Study population

A total of 3927 patients with MBC between 1973 and 2015 were retrospectively gathered from the SEER program of the National Cancer Institute, which was publicly available for registered users without informed patient consent. Covariates of interest extracted for each case included age at diagnosis, race, marital status, grade, status of ER and PR, American Joint Committee on Cancer (AJCC) tumor stage, T stage, N stage, and treatment information including (surgery for the primary site, record of chemotherapy and adjuvant radiotherapy). We selected patients with positive histology of MBC (International Classification of Diseases for Oncology, the following SEER ICD-0-3 codes, including 8052, 8070-8072, 8074, 8560, 8571, 8572, 8575, and 8980 were adopted to identify cases of MBC. The exclusion criteria were as follows: patients with unknown race; inaccessible pathological data including AJCC tumor stage and tumor size; surgical information of primary site and regional lymph node were unclear; and unavailable information about survival data and marital status. The Overall survival (OS) and cancer-specific survival (CSS) were considered as the endpoints. After screening, 1835 eligible patients were included and made up the primary cohort of MBC. Then it was randomly allocated into a training group (n=1223) and a validation group (n=612). The detailed process for patients screening is presented in Figure 1.

Nomogram construction

All the categorical variables were presented as frequencies and proportions. Univariate and multivariate analyses were carried out by employing the Cox proportional hazard regression models to determine the hazard ratio (HR) along with corresponding 95% confidence interval (CI) for all possible risk factors. All independent risk factors were identified through the forward stepwise selection method using the Cox proportional hazard regression model. The nomogram was established by combing all independent risk factors prognostic factors for the prediction of the 3-year and 5-year OS and CSS.

Nomogram confirmation

The predictive performance of nomogram model was evaluated by discrimination and calibration. Using the Harrell's concordance index (C-index) to access the Discrimination. Calibration plot was used to visualize the variance between nomogram-predicted prognosis and actual prognosis.

Statistical analysis

IBM SPSS statistics 22 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Survival-related variables were identified using the Kaplan-Meier method and Cox proportional hazards regression model. We explored the variables that remarkably related to survival by univariate or multivariate analyses. R software v 3.6.1 (http://www.r-project.org) was adopted to construct nomograms based on the multivariate results and the "RMS" package (cran.rproject.org/web/packages/rms) was used to develop survival models. The bilateral *P*-value <0.05 was considered statistically significant.

Results

Patients baseline characteristics

The demographic and clinical characteristics of included patients were shown in Table 1. In general, a total of 1835 patients with MBC were collected in this study with 1223 patients randomly assigned to the training set and 612 patients to the validation set. Of these patients, 908 (50.5%) patients were diagnosed at the age more than 60 years, most patients (77.1%) were white, and 85.4% were married. For the degree of cancer differentiation, poorly differentiated (Grade III) was the most type1425 (77.7%). 1504 (82.0%) and 1591 (86.7%) patients were observed to negatively express ER and PR, respectively. According to the AJCC7 system, stage III was the most type (61.1%), follow by stage I (23.3%) and stage III (15.5%). Most patients (58.0%) received mastectomy and were categorized as T2 stage (52.3%). Meanwhile, most patients (75.9%) were categorized as N0 stage. More than half of patients (67.6%) had undergone chemotherapy, while 48.8% patients had undergone radiotherapy.

Prognostic factors for OS and CSS

Univariate and multivariate analyses were conducted to identify predictors of OS and CSS among the 1223 patients in the training cohort. The results showed that age, grade, TNM stage, T stage, N stage, surgery for the primary site, chemotherapy and radiotherapy were significantly associated with OS in the univariable analysis. Meanwhile, those variables, except for age and chemotherapy, were also found significantly associated with CSS. Further multivariate analysis indicated that age, TNM stage, T stage, N stage, chemotherapy and radiotherapy were identified as independent prognostic factors of OS. Moreover, TNM stage, T stage, N stage and radiotherapy were also identified as independent prognostic factors of CSS, as shown in Table 2 and Table 3.

Construction and validation of OS and CSS

All remarkable independent prognostic factors of the Cox proportional hazards regression in the training set were incorporated to create the prognostic nomogram for estimating 3- and 5- year OS and CSS of

patients with MBC. Figure 2(a) shows the OS nomogram at the third year and the fifth year, and Figure 2(b) presents the CSS nomogram at the third and fifth year. We can predict the 3- and 5-year OS and CSS by adding these scores to the total on the bottom scale. By integrating the scores related to each variable and projecting the overall scores to the bottom scale, the possibility of OS and CSS at 2, 3, and 5 years can be predicted. With the help of the nomogram, prognoses can be efectively predicted based on personal patient features.

The predictive accuracy of the nomograms was evaluated by C-index. Our nomogram displayed better accuracy in predicting survival in training set and validation sets. The internal validation was performed via the training set with the C-index as 0.759 (95% CI, 0.746-0.772) in OS and 0.766 (95% CI,0.751-0.781) in CSS, respectively (Table 4). The external validation was performed via the validation set with the C-index as 0.754 (95% CI, 0.734-0.774) in OS and 0.752 (95% CI, 0.728-0.776) in CSS, respectively. Calibration curve showed good agreement between prediction and observation in the probability of 5- and 10-year OS and CSS in both training and validation cohort (Figure 3).

Discussion

Metaplastic breast cancer (MBC) is a kind of heterogenous breast cancer, which is relatively rare in clinical practice. Although some studies have reported the risk factors related to the survival of MBC patients[6-8], there is no recognized prognostic factors to predict the prognosis of MBC. Paul Wright et al. [9] found that for patients with positive or negative hormone receptors, there was no significant difference in the 5-year survival rate of MBC, which indicated that the status of hormone receptors could not be considered as a prognostic factor of MBC. Additionally, previous study demonstrated that the subtype of MBC could be an independent predictor of its prognosis[3]. Several studies revealed that the prognosis of MBC patients with larger tumor and lymph node metastasis are generally poor[6, 10]. In recent years, some studies have also focused on the relationship between gene signatures and prognosis of MBC patients, such as the high expression of RPL39[6, 10] and the mutation of the colony stimulating factor 1 receptor (CSF1R)[11], all of which can indicate poor prognosis. However, single prognostic factors play a limited role in predicting individual survival probability. Nomograms are graphical display of mathematical models for predicting cancer risk, prevention and therapeutic outcomes, which becomes increasingly popular clinical decision aids due to their ability to handle complexity in a systematic, unbiased manner[12-14]. It has been revealed that nomograms exhibited more excellent prediction precision and prognostic value in diverse malignancies than the existing tumor system[15, 16]To construct a prognostic nomogram, we performed univariate and multivariate Cox proportional-hazards regression analyses to find clinical characteristics that correlated with the OS and CSS of MBC patients on the basis of a large data set from the SEER database. We demonstrated that several clinicopathological characteristics were independent prognostic factors for OS, including age, grade, TNM stage, T stage, N stage, surg_prim_site, chemotherapy and radiotherapy. Furthermore, age, TNM stage, T stage, N stage, chemotherapy and radiotherapy were identified as independent prognostic factors for OS via multivariate analysis. In addition, grade, TNM stage, T stage, N stage, surg_prim_site and radiotherapy were found to be associated with CSS via univariate analysis, and further multivariate analysis confirmed

that TNM stage, T stage, N stage and radiotherapy were independent prognostic factors for CSS of MBC patients. The nomograms established in this study showed favorable discrimination and calibration for 3-year and 5-year OS and CSS of MBC patients and offered a more accurate and personalized clinical tool for prognosis evaluation of MBC patients.

Most of the prognostic studies of MBC have been small and with conflicting results or included non-validated cases from population based databases[15, 16]. In this large cases of MBC we have critically assessed the prognostic value of known prognostic variables. The clinical significance of age, TNM stage, T stage, N stage, chemotherapy, radiotherapy in MBC patients were highlighted in nomogram models. The result demonstrated that half of patients were >60 years of age, who suffered worst survival and poor OS. Of note, age showed no significant influence on CSS. Patients with older age generally accompanied a higher-risk histological phenotype[28], which has been identified as an independent risk factor and may eventually result in lower survival [28]. In this study, surgical resection of the primary site remained the mainstay of therapy, with mastectomy more than lumpectomy, which was consistent with previous study[32]In addition, we found that chemotherapy is an independent prognostic factor for OS in MBC patients. Although it is correlated with CSS in univariate analysis, it is not an independent prognostic factor for CSS. It may results from the lower response rates to chemotherapy regimens in MBC[18, 22, 24, 33, 34]. Several studies have concluded that radiotherapy, as part of a multimodal treatment, could improve survival of MBC patients. Similarly, our multivariate results demonstrated that radiation was independently associated with lower HR in patients who received radiotherapy[25, 35, 36]. Moreover, radiotherapy was revealed to be able to reduce the risk of local recurrence[37]. T stage represents the tumor size and extrathyroidal extension, and our results demonstrated that T4 have an impact on OS and CSS in MBC patients, which was in line with previous population-based studies of MBC [35]. LNM has been identified as a key prognostic indicator for a variety of malignancies, and the number of LNM has been included into the N-staging. Previous studies reported that lymph node status was significantly correlated with survival endpoints in patients with MBC [38, 39]There were several potential shortcomings in this study. First, retrospective data retrieved from the same database was used in the construction and validation of the nomograms, which may result in the risk of potential selection bias. Therefore, it would be more reliable to validate the nomograms in another dataset. Second, in this study, we only included two endpoints: 3- and 5-year survival. However, the assessment of recurrence risk is believed to be more meaningful than death because of the rare specific mortality of MBC, which was not performed in this study owing to the lack of data with respect to recurrence in SEER database. Moreover, several other crucial prognostic factors, such as RET mutation status and calcitonin doubling times, were also unavailable in the SEER database

Conclusion

We successfully established and validated prognostic nomograms to predict 3- and 5-year OS and CSS of MBC patients based on a large study cohort. The nomograms may provide an alternative tool for prognostic prediction, which may help improve survival predictions and facilitate reasonable treatment recommendations, allowing for tailored treatments of MBC.

Abbreviations

BMC: Metaplastic breast cancer; CSS: cancer-specific survival; C-index: concordance index; SEER: the Surveillance, Epidemiology, and End Results ; CSF1R: colony stimulating factor 1 receptor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interes**ts.**

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Authors' contributions

Conceptualization: YFL and DBC.

Data curation: YFL, HJX, MPD and GAC

Formal analysis: MPD and GAC.

Funding acquisition: YFL.

Project administration: HCJ, MC

Methodology:YFL, MPD, GAC and HJY.

Writing-original draft: YFL, MC .

Writing-review&editing: MC and HCJ.

All authors have read and approved the final manuscript.

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Tables

Table 1. Characteristics of the training and validation cohorts.

Variables	All patients (N=1835)		Training set (n=1223)		Validation set (n=612)	
	N	%	N	%	N	%
Age						
<60	908	49.5	617	50.4	291	47.5
≥60	927	50.5	606	49.6	321	52.5
Race						
White	1414	77.1	945	77.3	469	76.6
Black	295	16.1	202	16.5	93	15.2
Others	126	6.9	76	6.2	50	8.2
Marital						
Single	268	14.6	181	14.8	87	14.2
Married	1567	85.4	1042	85.2	525	85.8
Grade						
G1	86	4.7	56	4.6	30	4.9
G2	239	13.0	159	13.0	80	13.1
G3	1425	77.7	945	77.3	480	78.4
G4	85	4.6	63	5.2	22	3.6
ER						
negative	1504	82.0	1014	82.9	490	80.1
positive	331	18.0	209	17.1	122	19.9
PR						
negative	1591	86.7	1069	87.4	522	85.3
positive	244	13.3	154	12.6	90	14.7
Stage ajcc7						
I	428	23.3	298	24.4	130	21.2
II	1122	61.1	732	59.9	390	63.7
III	285	15.5	193	15.8	92	15.0
Stage_T						

T1	478	26.0	325	26.6	153	25.0
T2	960	52.3	636	52.0	324	52.9
T3	285	15.5	186	15.2	99	16.2
T4	112	6.1	76	6.2	36	5.9
Stage_N						
N0	1392	75.9	925	75.6	467	76.3
N1	308	16.8	204	16.7	104	17.0
N2	83	4.5	60	4.9	23	3.8
N3	52	2.8	34	2.8	18	2.9
Surg prim site						
Lumpectomy	771	42.0	514	42.0	257	42.0
Mastectomy	1064	58.0	709	58.0	355	58.0
Chemotherapy						
No/unknown	594	32.4	389	31.8	205	33.5
Yes	1241	67.6	834	68.2	407	66.5
Radiation						
No/unknown	940	51.2	624	51.0	316	51.6
Yes	895	48.8	599	49.0	296	48.4

Table 2. Univariate and multivariate analyses of variables associated with OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age				
<60	Reference			
≥60	1.786(1.436-2.221)	<0.001	1.653(1.307-2.089)	<0.001
Race		0.791		
Black	Reference			
White	0.923(0.684-1.246)	0.601		
Other	1.088(0.705-1.682)	0.703		
Marital				
Married	Reference			
Single	0.842(0.631-1.124)	0.244		
Grade		0.004		
G1	Reference			
G2	2.023(0.904-4.531)	0.087		
G3	2.584(1.220-5.474)	0.013		
G4	3.819(1.677-8.695)	0.001		
ER				
negative	Reference			
positive	0.933(0.689-1.264)	0.656		
PR				
negative	Reference			
positive	0.861(0.612-1.212)	0.392		
Stage ajcc7		<0.001		0.002
I	Reference			
II	2.421(1.686-3.476)	<0.001	3.506(1.731-7.101)	<0.001
III	8.743(5.987-12.767)	<0.01	4.403(1.786-10.855)	0.001
Stage_T		<0.001		<0.001
T1	Reference			

T2	1.776(1.280-2.464)	0.001	0.585(0.316-1.084)	0.088
T3	5.175(3.631-7.376)	<0.001	1.595(0.835-3.047)	0.157
T4	9.686(6.491-14.453)	<0.001	2.467(1.148-5.299)	0.021
Stage_N		<0.001		0.006
N0	Reference			
N1	1.901(1.463-2.469)	<0.001	1.220(0.878-1.695)	0.235
N2	3.767(2.602-5.453)	<0.001	2.265(1.286-3.991)	0.005
N3	5.174(3.433-7.798)	<0.001	2.409(1.396-4.155)	0.002
Surg prim site				
Lumpectomy	Reference			
Mastectomy	2.581(2.020-3.298)	<0.001	1.202(0.899-1.607)	0.213
Chemotherapy				
No/unknown	Reference			
Yes	0.657(0.529-0.816)	<0.001	0.689(0.538-0.882)	0.003
Radiation				
No/unknown	Reference			
Yes	0.656(0.528-0.814)	<0.001	0.666(0.530-0.836)	<0.001

Table 3. Univariate and multivariate analyses of variables associated with CSS

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age				
<60	Reference			
≥60	1.185(0.925-1.517)	0.179		
Race				
Black	Reference			
White	0.916(0.648-1.297)	0.622		
Other	1.054(0.633-1.755)	0.839		
Marital				
Married	Reference			
Single	0.745(0.541-1.026)	0.071		
Grade		0.001		0.409
G1	Reference			
G2	1.495(0.561-3.984)	0.421	1.086(0.405-2.913)	0.870
G3	2.826(1.164-6.863)	0.022	1.438(0.585-3.534)	0.428
G4	3.988(1.510-10.531)	0.005	1.754(0.655-4.698)	0.264
ER				
negative	Reference			
positive	0.923(0.651-1.309)	0.654		
PR				
negative	Reference			
positive	0.870(0.588-1.289)	0.489		
Stage ajcc7		<0.001		0.003
I	Reference			
II	3.306(2.019-5.414)	<0.001	4.240(1.809-9.939)	0.001
III	14.131(8.556-23.339)	<0.001	5.619(1.959-16.115)	0.001
Stage_T		<0.001		<0.001
T1	Reference			

T2	2.137(1.400-3.262)	<0.001	0.582(0.286-1.183)	0.135
T3	7.345(4.727-11.415)	<0.001	1.810(0.866-3.781)	0.115
T4	14.008(8.662-22.654)	<0.001	2.606(1.119-6.066)	0.026
Stage_N		<0.001		<0.001
N0	Reference			
N1	2.423(1.807-3.250)	<0.001	1.299(0.893-1.890)	0.171
N2	4.516(3.000-6.798)	<0.001	2.150(1.163-3.973)	0.015
N3	6.595(4.230-10.283)	<0.001	2.659(1.467-4.820)	0.001
Surg prim site				
Lumpectomy	Reference			
Mastectomy	2.720(2.038-3.630)	<0.001	1.216(0.871-1.698)	0.251
Chemotherapy				
No/unknown	Reference			
Yes	1.041(0.796-1.360)	0.772		
Radiation				
No/unknown	Reference			
Yes	0.757(0.591-0.970)	0.028	0.645(0.501-0.830)	0.001

Table 4. The C-index of nomogram for OS and CSS in patients with MBC

Survival	Training cohort		Validation cohort	
	HR	95% CI	HR	95% CI
OS	0.759	0.746-0.772	0.754	0.734-0.774
CSS	0.766	0.751-0.781	0.752	0.728-0.776

Figures

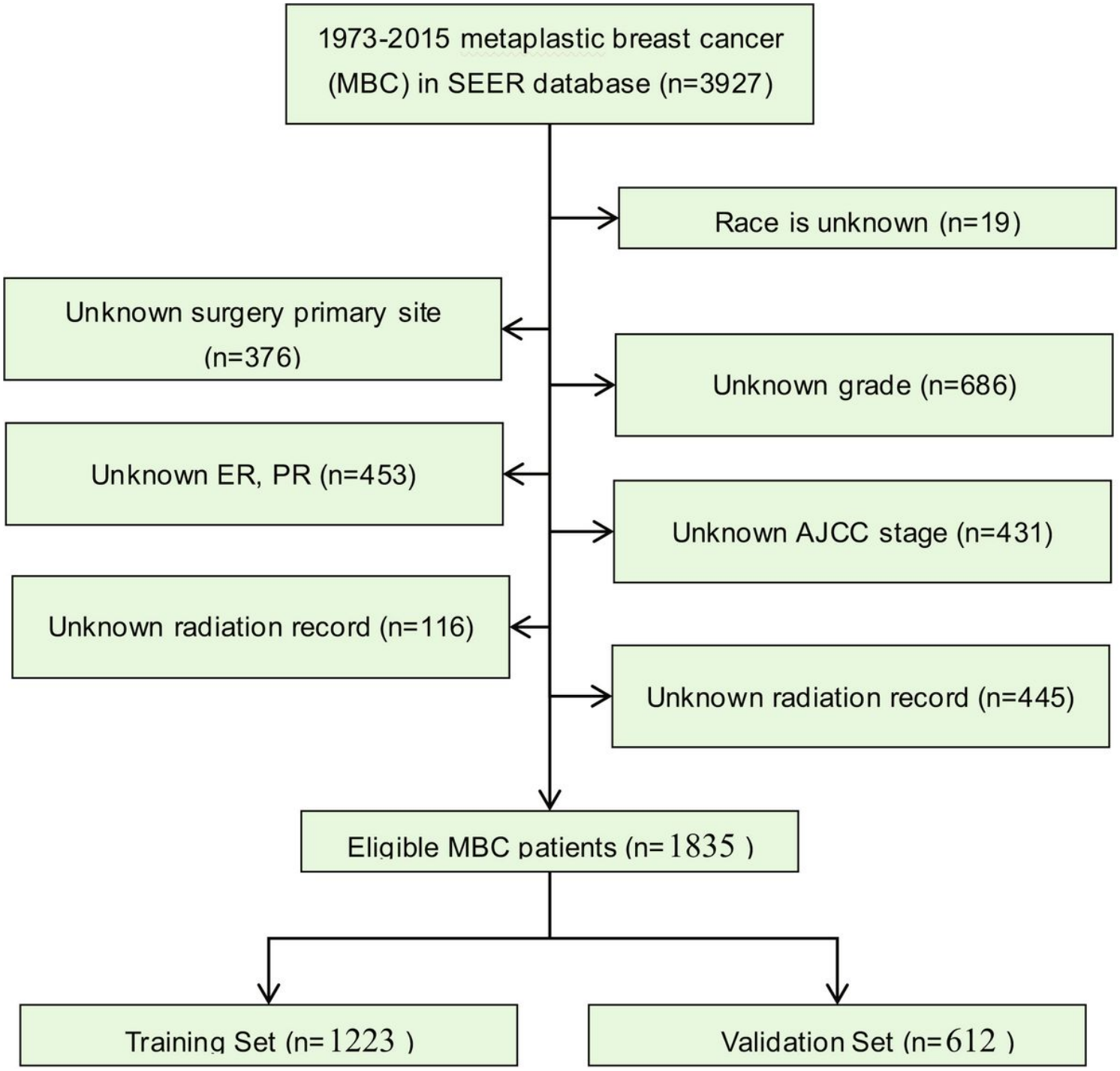

Figure 1

Flow chart of patient selection.

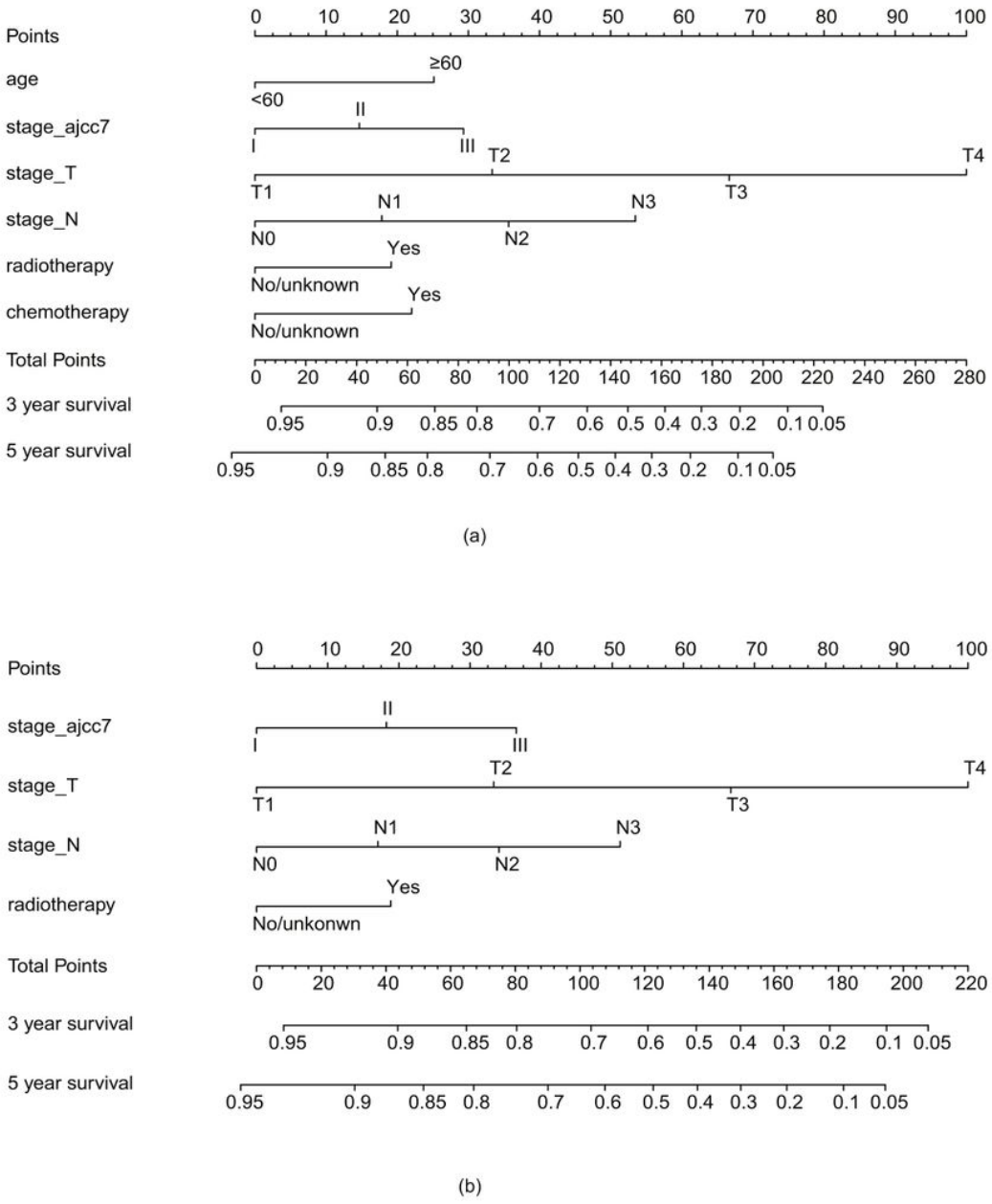

Figure 2

Nomograms for predicting the 3-, and 5-year (a) overall survival and (b) cancer-specifc survival of MBC.

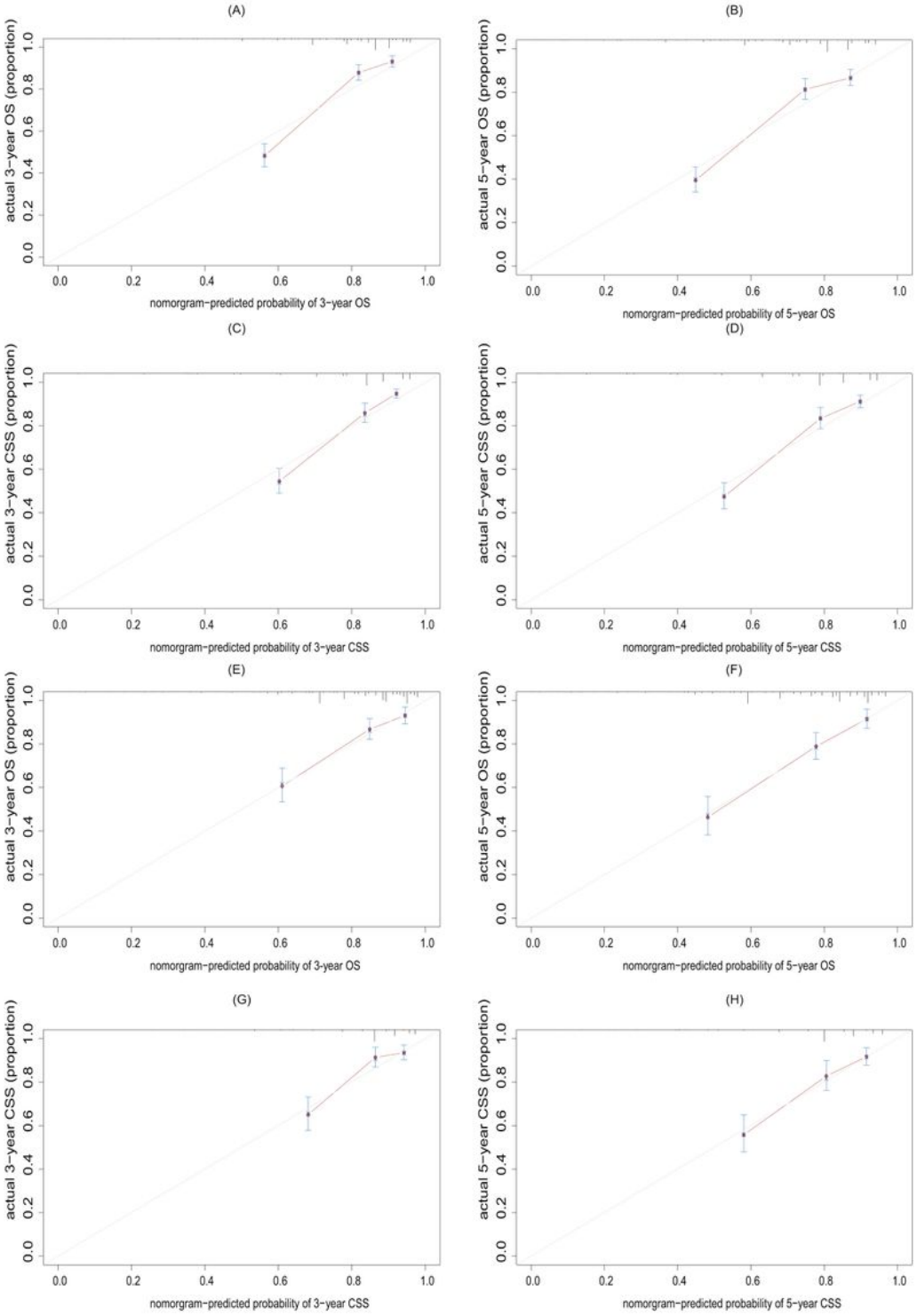

Figure 3

The calibration curves for predictions survival of MBC patients. The overall survival (A, B) and cancer-specifc survival (C, D) in the training cohort at 3 and 5 years after diagnosis, and the overall survival (E, F) and cancer-specifc survival (G, H) in the validation cohort at 3 and 5 years after diagnosis.