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 (MBC) 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 MBC.

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 1129 patients were collected and divided into the training (753) and validation (376) groups. The multivariate Cox model identified age, stage_ajcc, T stage, chemotherapy and radiotherapy as independent covariates associated with OS, while age, race, stage_ajcc, T stage, and radiotherapy 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 0.744 (95% CI, 0.701-0.787) for OS and 0.746 (95% CI, 0.695-0.797) for CSS in the training cohort. In the validation cohort, the nomogram-predicted C-index was in OS and 0.818 for OS (95% CI, 0.775-0.861) and 0.800 (95% CI, 0.747-0.853) for CSS. All calibration curves exhibited good consistency between predicted and actual survival.

Conclusions

These nomogram models established in this study can help to 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 carcinoma (MBC) is a relatively rare form of breast cancer with worse clinical outcomes and resistance to neoadjuvant systemic chemotherapies[1], accounting for 0.2-5% of all breast cancers [1]. The incidence of MBC is increasing since it was recognized as a distinct pathological diagnosis in 2000[3]. Histologically, MBC is classified into several subtypes, including spindle, squamous, chondroid, osseous and/or rhabdomyoid MBC[4]. MBC commonly shows a triple negative breast cancer (TNBC) phenotype, due to the lack of expression of the ER, PR and HER2 [5], and is managed with

surgical resection in combination with radiotherapy and chemotherapy [1]. However, only radiotherapy shows improvement on overall survival (OS) in MBC patients[6]. Compared with invasive ductal carcinoma, the 5-year survival rate for MBC remains poor owing to its rapid tumor growth rate and chemoresistance [7, 8]. The Surveillance, Epidemiology, and End Results database (SEER database) is a well-constructed database from multiple institutions in the United States (US), covering about 30% of the US population. It has become 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 nomogram to forecast individualized survival of MBC depended on the personalized demographic, pathologic and therapeutic information from the SEER database based on our previous works posted on Research Square as preprints [9, 10].

Materials And Methods

Patient population

The SEER database supported by the National Cancer Institute (NCI) is a population-based cancer registry covering approximately 30% of the United States population[12]. Date of patients with MBC diagnosed between 1973 and 2015 was obtained from the SEER program of the National Cancer Institute. The variables of interest extracted from the SEER database included age at diagnosis, race, tumor size, grade, status of ER, PR and HER2, American Joint Committee on Cancer (AJCC) tumor stage, T stage, N stage, and treatment information including (record of chemotherapy and adjuvant radiotherapy). 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. Patients with unknown race and marital status, unavailable pathological or survival data were excluded. Figure 1 illustrates the detailed flow diagram for patients screening. Overall survival and cancer-specific survival (CSS) were chosen as endpoints. OS was defined as the time from original diagnosis to death from any cause or to the time of the last follow-up. CSS was defined as the time between the date of diagnosis and cancer-related death.

Nomogram Construction And Conformation

Patients were randomly divided into the training set and validation set with a ratio of 2:1. X-tile tool was used to set the optimized cut-off points for continuous variable. 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 by the forward stepwise selection method using the multivariate Cox proportional hazards models. 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 using the “rms” R package (cran.rproject.org/web/packages/rms). The Harrell’s concordance index (C-index) was used to access the discrimination, and calibration curves were applied to estimate the consistency between the actual prognosis and the nomogram-predicted survival probability of the model.

Statistical analysis

IBM SPSS statistics 22 software (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analysis. 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 was used to develop survival models. The two-tailed *P*-value < 0.05 was assumed statistically significant.

Results

Patients characteristics

A total of 3927 MBC patients were obtained from the SEER database, and 1129 of these patients with available information required for analysis were screened out and used to perform subsequent analysis. The detailed clinicopathologic characteristics of included patients were presented in Table 1. All included patients were allocated randomly into two datasets, including 753 patients randomly assigned to the training set and 376 patients to the validation set. Of these patients, 620 (54.92% patients were diagnosed at the age more than 60 years, most patients (76.62%) were white. The cut-off value was set as 58 mm by X-tile software, and 14.26% patients had a tumor more then 58 mm diameter. For the degree of cancer differentiation, poorly differentiated (Grade III) was the most type 877 (77.68%). 883 (78.21%) 977 (86.54%), and 1065 (94.33%) patients were observed to negatively express ER, PR and HER2, respectively. According to the AJCC7 system, stage II was the most type (61.65%), follow by stage I (23.91%) and stage III (14.44%). Most patients (51.64%) were categorized as T2 stage. Meanwhile, most patients (78.12%) were categorized as N0 stage. More than half of patients (66.43%) had undergone chemotherapy, while 47.03% patients had undergone radiotherapy.

Table 1
Characteristics of the training and validation cohorts.

Variables	All patients (N = 1129)		Training set (n = 753)		Validation set (n = 376)	
	N	%	N	%	N	%
Age						
< 60	509	45.08	344	0.46	165	0.44
≥ 60	620	54.92	409	0.54	211	0.56
Race						
White	865	76.62	580	0.77	284	0.76
Black	180	15.94	120	0.16	60	0.16
Others	84	7.44	53	0.07	31	0.08
Tumor size (mm)						
≤ 58	968	85.74	647	0.86	321	0.85
> 58	161	14.26	106	0.14	55	0.15
Grade						
G1	61	5.40	41	0.05	20	0.05
G2	160	14.17	109	0.14	50	0.13
G3	877	77.68	584	0.78	291	0.77
G4	31	2.75	18	0.02	13	0.03
ER						
negative	883	78.21	601	0.80	282	0.75
positive	246	21.79	152	0.20	94	0.25
PR						
negative	977	86.54	650	0.86	327	0.87
positive	152	13.46	103	0.14	49	0.13
HER2		0.00		0.00		0.00
negative	1065	94.33	714	0.95	351	0.93
positive	64	5.67	39	0.05	25	0.07
Stage ajcc7						

Variables	All patients (N = 1129)		Training set (n = 753)		Validation set (n = 376)	
	N	%	N	%	N	%
I	270	23.91	183	0.24	87	0.23
II	696	61.65	461	0.61	234	0.62
III	163	14.44	109	0.14	54	0.14
Stage_T						
T1	299	26.48	198	0.26	101	0.27
T2	583	51.64	385	0.51	197	0.52
T3	179	15.85	121	0.16	58	0.15
T4	68	6.02	49	0.07	19	0.05
Stage_N						
N0	882	78.12	597	0.79	285	0.76
N1	178	15.77	114	0.15	64	0.17
N2	50	4.43	32	0.04	18	0.05
N3	19	1.68	10	0.01	9	0.02
Chemotherapy						
No/unknown	379	33.57	253	0.34	126	0.34
Yes	750	66.43	500	0.66	250	0.66
Radiation						
No/unknown	598	52.97	395	0.52	203	0.54
Yes	531	47.03	358	0.48	173	0.46

Prognostic Factors Of Os And Css

According to univariate analysis performed among the training cohort, nine variables including age, race, tumor size, grade, TNM stage, T stage, N stage, chemotherapy and radiotherapy were significantly associated with OS in patients with MBC. Meanwhile, those variables, except for chemotherapy, were also found to be significantly associated with CSS of MBC patients. Further multivariate analysis indicated that age, TNM stage, T stage, chemotherapy and radiotherapy were identified as independent prognostic

factors of OS of patients with MBC. Moreover, age, race, TNM stage, T stage, and radiotherapy were also identified as independent prognostic factors of CSS of MBC patients, as shown in Table 2 and Table 3.

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	1.871(1.396–2.507)	< 0.001	1.663(1.197–2.310)	0.002
Race		0.031		
White	Reference			
Black	0.869(0.595–1.268)	0.466		
Others	1.564(0.918–2.664)	0.100		
Tumor size (mm)				
≤ 58	Reference			
> 58	4.069(3.047–5.432)	< 0.001		
Grade		0.002		
G1	Reference			
G2	1.913(0.730–5.013)	0.187		
G3	2.526(1.037–6.151)	0.041		
G4	5.935(2.091–16.850)	0.001		
ER				
negative	Reference			
positive	0.886(0.629–1.248)	0.488		
PR				
negative	Reference			
positive	0.782(0.510–1.197)	0.257		
HER2				
negative	Reference			
positive	0.886(0.482–1.627)	0.696		
Stage ajcc7		< 0.001		0.001
I	Reference			

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
II	2.726(1.657–4.482)	< 0.001	2.577(0.858–7.619)	0.092
III	8.312(4.950–13.955)	< 0.01	5.194(1.683–16.032)	0.004
Stage_T		< 0.001		< 0.001
T1	Reference			
T2	1.999(1.249–3.199)	0.004	0.890(0.325–2.440)	0.820
T3	6.480(3.990–10.525)	< 0.001	2.627(0.954–7.235)	0.062
T4	9.776(5.711–16.736)	< 0.001	2.469(0.838–7.273)	0.101
Stage_N		< 0.001		
N0	Reference			
N1	1.648(1.164–2.334)	0.005		
N2	2.811(1.737–4.551)	< 0.001		
N3	3.546(1.864–6.746)	< 0.001		
Chemotherapy				
No/unknown	Reference			
Yes	0.578(0.445–0.774)	< 0.001	0.665(0.486–0.911)	0.011
Radiation				
No/unknown	Reference			
Yes	0.534(0.401–0.710)	< 0.001	0.511(0.377–0.693)	< 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	1.477(1.073–2.034)	0.017	1.560(1.111–2.190)	0.010
Race		0.002		0.027
White	Reference			
Black	0.881(0.571–1.359)	0.566	0.891(0.572–1.388)	0.609
Others	1.977(1.115–3.506)	0.020	1.673(0.934–2.995)	0.084
Tumor size (mm)				
≤ 58	Reference			
> 58	4.571(3.315–6.303)	< 0.001		
Grade		0.003		
G1	Reference			
G2	1.990(0.576–6.873)	0.277		
G3	3.423(1.090–10.751)	0.035		
G4	7.381(1.998–27.269)	0.003		
ER				
negative	Reference			
positive	0.920(0.627–1.350)	0.670		
PR				
negative	Reference			
positive	0.935(0.596–1.467)	0.771		
HER2				
negative	Reference			
positive	1.036(0.546–1.965)	0.914		
Stage ajcc7		< 0.001		0.001
I	Reference			

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
II	2.989(1.632–5.475)	< 0.001	2.436(0.681–8.715)	0.171
III	10.936(5.893–20.293)	< 0.01	5.443(1.462–20.267)	0.012
Stage_T		< 0.001		< 0.001
T1	Reference			
T2	2.177(1.238–3.827)	0.007	0.939(0.293–3.009)	0.915
T3	7.814(4.402–13.870)	< 0.001	2.863(0.889–9.222)	0.078
T4	12.081(6.469–22.562)	< 0.001	2.692(0.778–9.319)	0.118
Stage_N		< 0.001		
N0	Reference			
N1	2.037(1.398–2.967)	< 0.001		
N2	3.439(2.052–5.764)	< 0.001		
N3	3.869(1.880–7.962)	< 0.001		
Chemotherapy				
No/unknown	Reference			
Yes	0.962(0.691–1.340)	0.819		
Radiation				
No/unknown	Reference			
Yes	0.633(0.461–0.869)	0.005	0.518(0.373–0.720)	< 0.001

Construction And Validation Of Os And Css

According to the results of multivariate analysis, all independent prognostic factors in the training set were incorporated to create the nomograms for estimating 3- and 5- year OS and CSS of patients with MBC. Figure 2**(A)** and Fig. 2**(B)** showed the prediction of the 3- and 5-year OS and CSS in the nomogram, respectively. Each factor was allocated a score on the points scale in the nomogram, and we can estimate the 3- and 5-year survival probability of patients with MBC by calculating the total score via adding up all points on the basis of personal patients features.

Nomograms were validated using C-index in the training set and validation set, respectively. The results showed sufficient accuracy in forecasting the prognosis of MBC in training set and validation set. The C-index of the nomogram for OS and CSS is 0.744 (95% CI, 0.701–0.787) and 0.746 (95% CI, 0.695–0.797) in the training set, respectively (Table 4). The C-index calculated from the validation set is 0.818 (95% CI, 0.775–0.861) in OS and 0.800 (95% CI, 0.747–0.853) in CSS, respectively. The calibration plots showed good coordination between prediction by nomogram models and observed outcomes in the probability of 3- and 5-year OS and CSS of patients with MBC in both training cohort and validation set (Fig. 3).

Discussion

- Metaplastic breast cancer is a kind of heterogenous breast cancer, which is relatively rare in clinical practice. Despite several studies have found risk factors related to the clinical outcomes of MBC patients[11–13], there is no recognized prognostic factors to predict the prognosis of MBC. Paul Wright et al.[14] 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[11, 15]. 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 60S ribosomal protein L39 (RPL39)[13] and the mutation of the colony stimulating factor 1 receptor (CSF1R)[16], 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 thanks to their ability to deal with complex problems in a systematic and unbiased manner[17–19]. It has been revealed that nomograms exhibited more excellent prediction precision and prognostic value in diverse malignancies than the existing tumor system[20, 21]. To construct a prognostic nomogram, we conducted univariate and multivariate 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, stage_ajcc, T stage, chemotherapy and radiotherapy. In addition, multivariate analysis confirmed that age, race, stage_ajcc, T 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.
- Prognostic studies have given conflicting results regarding factors associated with prognosis and survival [22–32]. In the present study, we critically evaluated the prognostic value of various factors based on a large cases of MBC recorded on the SEER. The clinical significance of age, stage_ajcc, T stage, chemotherapy, and radiotherapy in MBC patients were highlighted in nomogram models. The

result demonstrated that half of patients were older then 60 years, who suffered worst survival and poor OS. Patients with older age generally accompanied a higher-risk histological phenotype[33], which has been considered as an independent risk factor and may eventually result in lower survival [34–36]. Of note, race was defined as a independent prognostic factor for CSS but not for OS. 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 result from the worse response to chemotherapy regimens in MBC[23, 27, 29, 37, 38]. Previous studies have concluded that radiotherapy was able to improve the survival of patients with MBC [8, 28, 38], and our data also demonstrated that radiation was independently prognostic factors associated with survival probability of patients with MBC[8, 30, 39]. Moreover, radiotherapy was revealed to be able to reduce the risk of local recurrence[40]. T stage is closely related prognosis of cancers and previous study based on US population found that T stage was a is a independent prognostic factor for the OS and CSS of MBC patients[8]. Similarly our results also identified T stage as a independent prognostic factor of MBC patients. Lymph nodes metastasis (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[41, 42]. However, N-stage was not identified as a independent prognostic factor for MBC patients in this study.

- There were several potential shortcomings in this study. First, retrospective data retrieved from the same database was used in the generation and validation of the nomogram models, which may lead to 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 considered as a more meaningful endpoint than OS or CSS 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

- In the present study, we identified the independent prognostic factors for the OS and CSS of MBC patients, and the nomograms reliably predicted 3- and 5-year OS and CSS of MBC patients were successfully established and well-validated on the basis of large population from SEER. The nomograms established in this study are expected to assist clinicians to conduct individual prognostic assessments and to formulate reasonable treatment strategies. However, further external validation using external data in the future is required to increase model reliability and generalize the applicability of these nomogram model in clinical practice.

Abbreviations

MBC: Metaplastic breast cancer; US: United States; OS: overall survival; TNBC: triple negative breast cancer; NCI: National Cancer Institute; CSS: cancer-specific survival; AJCC: American Joint Committee on Cancer; CI: confidence interval; C-index: concordance index; SEER: the Surveillance, Epidemiology, and End Results ; RPL39: 60S ribosomal protein L39 CSF1R: colony stimulating factor 1 receptor; LNM: Lymph nodes metastasis

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 interests.

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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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Figures

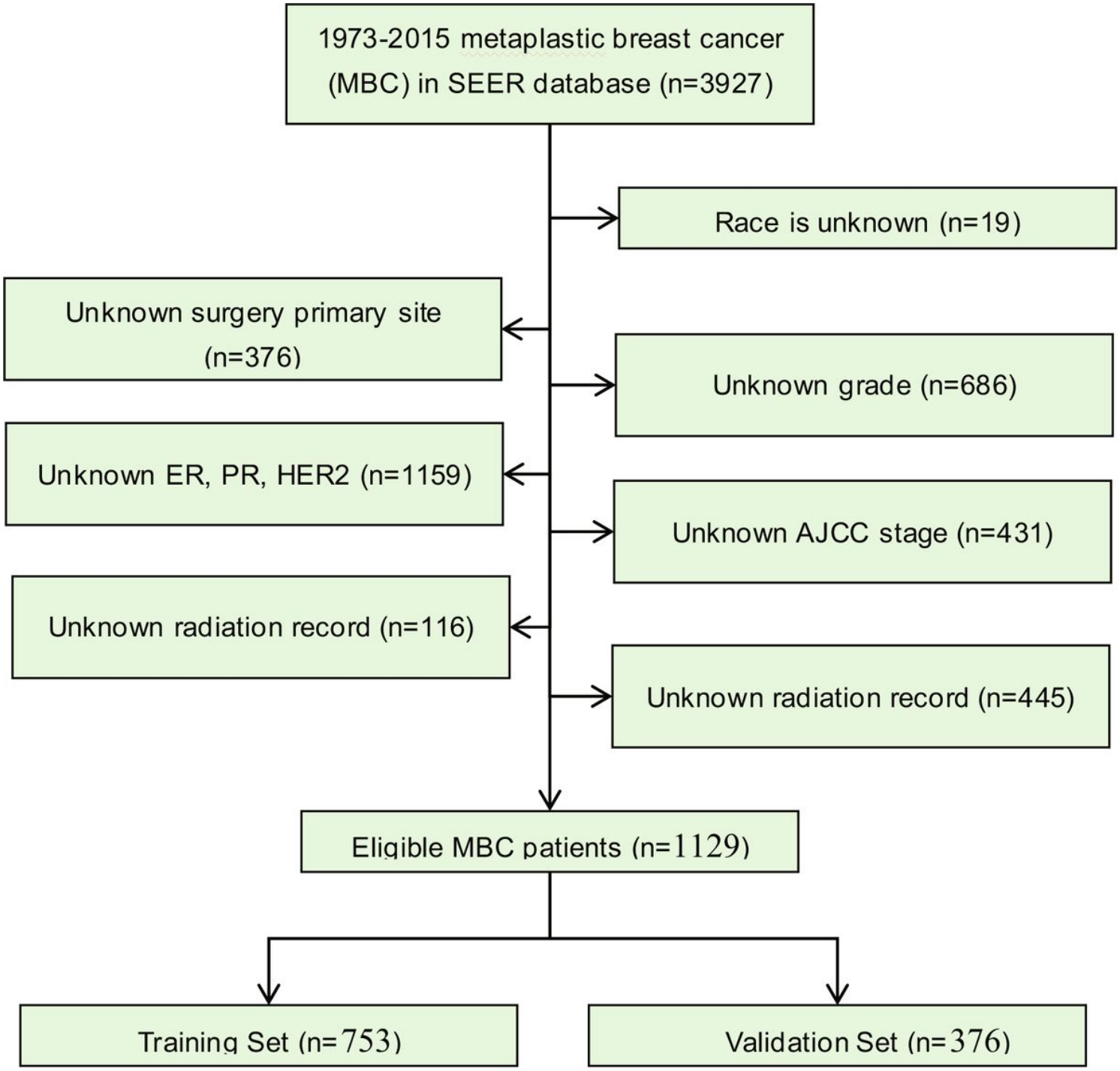

Figure 1

Flow chart of patient selection.

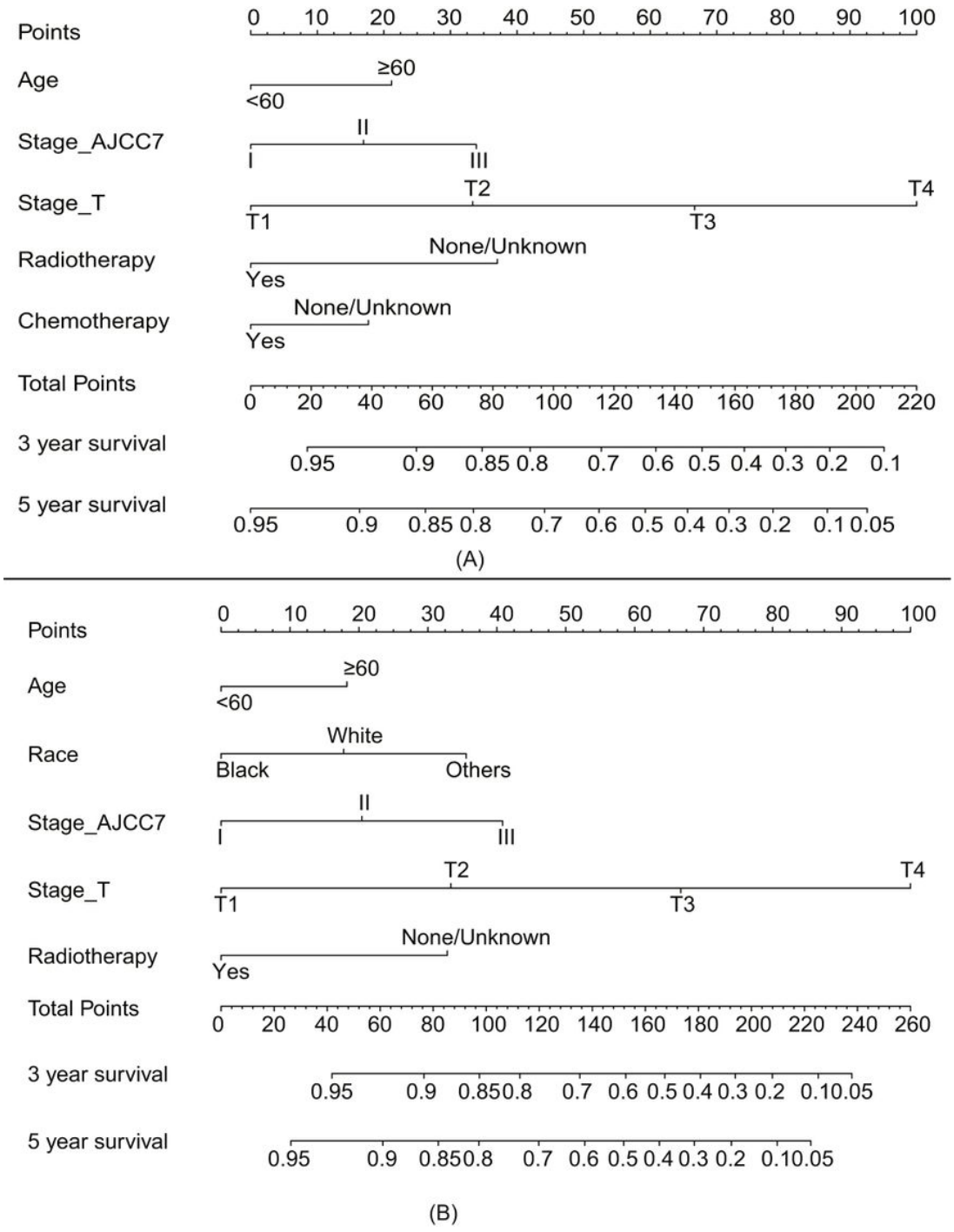

Figure 2

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

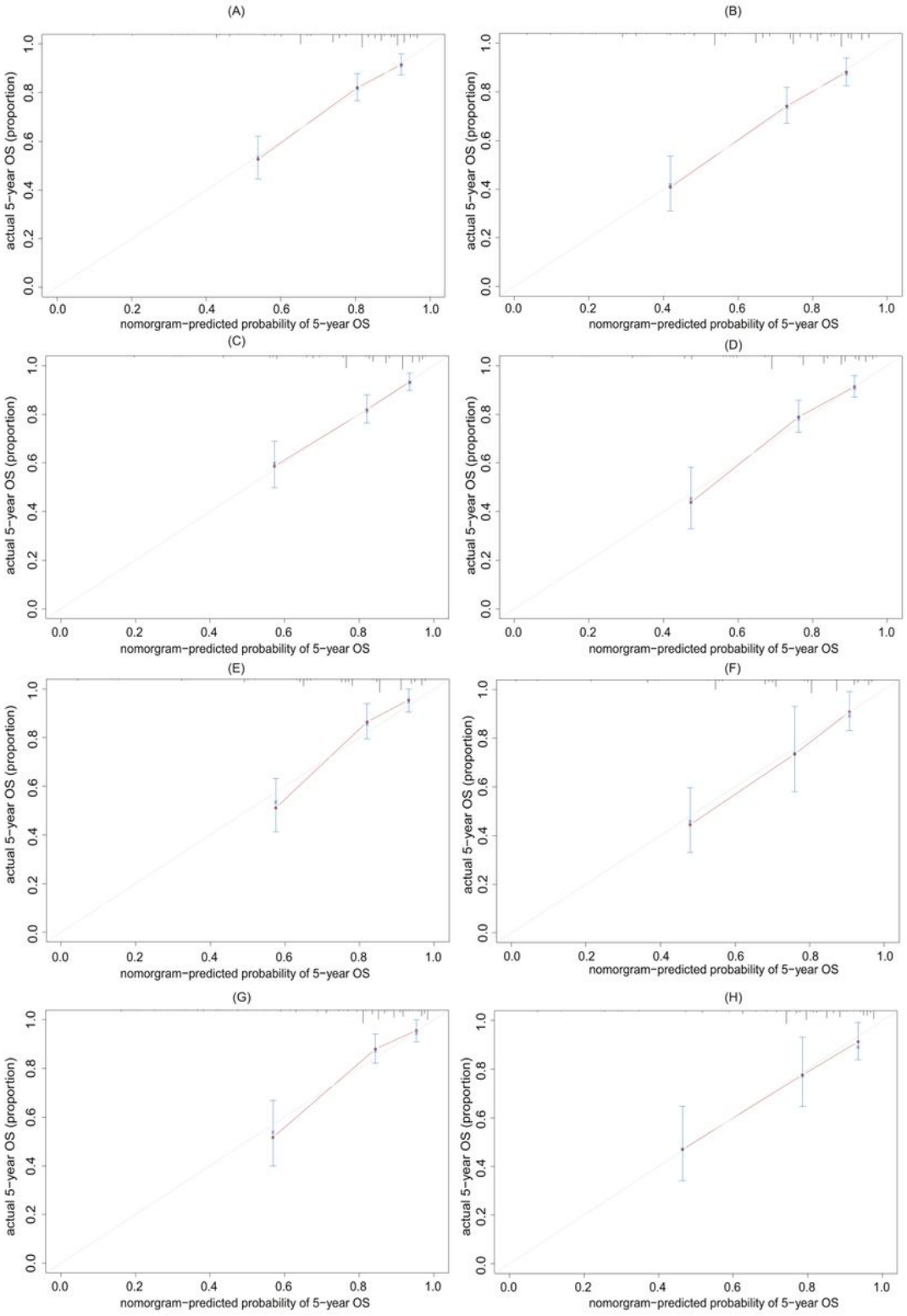

Figure 3

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.