

Established and Validated a Novel Nomogram for Predicting Prognosis of Post-mastectomy pN0-1 Breast Cancer Without Adjuvant Radiotherapy

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Research

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Abstract

Background

The present study aims to establish and validate a nomogram for predicting prognosis of breast cancer with pN0-1 who are treated with mastectomy and without adjuvant radiotherapy.

Material and methods

Between Jan 2009 and Dec 2015, a total of 1879 breast cancer without adjuvant radiotherapy were used for nomogram development. The model was externally validated in an independent cohort of 1356 patients from one phase III trial (NCT00041119). The least absolute shrinkage and selection operator (LASSO) regression were performed to identify predictors of breast cancer specific survival (BCSS), local regional recurrence (LRR), and distant metastasis (DM).

Results

The 5-year BCSS, LRR and DM rates for the entire cohort was 98% ,2% and 4%, respectively. LASSO regression analysis found that pathological T stage, number of positive LN, grade and Ki-67 were significant predictors for both BCSS and DM-free survival in post-mastectomy breast cancer with pN0-1, while number of resected LN and PR status were predictors for DM-free survival. In addition, number of positive LN was the only significant predictor for developing LRR. The C-indexes for the 5-year BCSS and DM nomograms were 0.81 and 0.78 in the training data set, 0.65 and 0.70 in the testing set, and 0.72 and 0.69 in the external validation set, respectively. Calibration plots illustrated excellent agreement between the nomogram predictions and actual observations for 5-year BCSS and DM-free survival.

Conclusion

Our prognostic nomograms could accurately predict 5-year BCSS and DM-free survival in post-mastectomy early stage breast cancer without adjuvant radiotherapy, which provide a useful tool to identify high-risk patients who could benefit from additional adjuvant therapy.

Introduction

According to the report of GLOBOCAN 2018, female breast cancer remains the most frequent cancer among women in the worldwide with 2.1 million newly diagnosed, which accounts for almost 1 in 4 cancer cases among woman[1]. In China, breast cancer is also the most common diagnosed among woman, with an upward stable trend in both incidence and mortality[2]. During the past decades, the prognosis of early stage breast cancer has been remarkably improved due to the great advances in cancer treatments[3, 4]. However, the optimal adjuvant treatment for this patient population (pN0-1) remains to be clearly determined.

Recently, two large phase III randomized controlled trials, National Cancer Institute of Canada Clinical Trials Group MA20[5] and the European Organization for Research and Treatment of Cancer (EORTC) 22922-10925[6], reported the 10 year followed-up results, and both of them indicated that there was an improved disease-free survival with the addition of regional lymph node irradiation to whole-breast RT for early-stage breast cancers, which suggested that adjuvant radiotherapy in early stage breast cancer not only decreased the risk of local regional recurrence(LRR), but also the risk of developing distant metastasis(DM). However, only 24% of patients in the EORTC trial were treated with mastectomy, and all of enrolled patients in MA20 were treated with lumpectomy. In consistent with these two trials, a large individual patient data meta-analysis of 8,135 from 22 randomized trials showed that PMRT could reduce locoregional recurrence($p<0.001$) and breast cancer mortality (RR 0.80, $p=0.01$) among BC patients with axillary dissection and one to three positive nodes[7].

However, early stage breast cancers is a heterogeneous disease, it has been reported that the LRR rates could increase to 20% in patients with multiple risk factors, including young age, large tumor size, lymph vascular invasion, medial/central tumor location or high nuclear grade[8, 9]. In addition, in a recently retrospective study published by Muhsen S. et al, the authors found that nearly 85% of patients with T1-2N1 could spare PMRT due to the low incidence of LRR[10], As a result, the role of adjuvant post-mastectomy radiotherapy (PMRT) in early stage breast cancer remains controversial, and an accurate prognostic indicator to identify patients who at high risk for recurrence is clearly needed for physicians when giving individualized clinical decision making. Nomograms are frequently used not only for predicting survival in patients with all types of cancer but also for successfully quantifying risk prediction according to clinicopathological variables[11-14]. Although many of the available decision tools, such as CancerMath [15], PREDICT[16] and the ipsilateral breast tumor recurrence program (IBTR)[17, 18], have been established to predict survival probability in breast cancer patients, none of these tools are established specially based on the post-mastectomy breast cancer with pN0-1 without adjuvant radiotherapy. As a result, we perform the present study to establish and validate a nomogram based on a large sample size for predicting prognosis of post-mastectomy breast cancer with pN0-1, but without adjuvant radiotherapy, which could be used for adjuvant treatment counseling after mastectomy.

Materials And Methods

Study cohorts and data collection

Between Jan 2009 and Dec 2015, a total of 2128 newly diagnosed invasive breast cancer patients undergoing a modified radical mastectomy or total mastectomy and sentinel lymph node biopsy with pathological(p) N0-1, who did not treated with adjuvant radiotherapy, were identified at our institution. Two hundreds and forty-nine patients were excluded from the present analysis for the following reasons: (1) neoadjuvant chemotherapy or radiotherapy; (2) bilateral breast cancers; (3) lack of information about tumor size, Ki-67 and hormonal receptor status;(4) the pathologic diagnosis was Ductal Carcinoma In Situ (DCIS), or Paget's disease. Patients with positive surgical margin were also excluded for analysis in the present study. Finally, the remaining 1879 patients were included for analysis in the present study

(figure 1). The present study procedures were approved by the Ethical Committee of RuiJin Hospital affiliated medicine school of Shanghai Jiao Tong University.

Initially, a total of 3871 patients from one phase III trial (NCT00041119)[19], which aimed to compare the efficacy difference of adjuvant chemotherapy of doxorubicin and cyclophosphamide versus single-agent paclitaxel for breast cancer in women with pN0-1. Among them, 1359 patients treated with mastectomy were included. Subsequently, 3 patients with more than 3 positive lymph node metastasis were excluded. Finally, a total of 1356 patients were used as an externally validated cohort in the preset study. The primary findings of this trial had been previously published. Informed consent was obtained from all included participants in the clinical trial.

Outcomes definitions

The primary endpoints of the current analysis were breast cancer specific survival (BCSS), which is defined as the time from surgery till death from breast cancer. Local regional recurrence (LRR)-free survival was defined as the time from surgery to the time of a first recurrence in the ipsilateral breast or in axillary, supraclavicular or internal mammary nodes. Distant metastases (DM)-free survival was defined as the time from surgery to the time of a recurrence at a distant site.

Statistical analysis

Statistical analyses were conducted through R version 3.6.1 software (The R Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org>) and NCSS 11.0 software. Continuous variables were summarized by median and range, and categorical variables were summarized by frequency and proportion. The study population was randomly dichotomized into 2 groups: 70% in the training (1315) and 30% (564) in the testing group, respectively. Comparisons of baseline characteristics between training and testing groups were performed with c test. Time-dependent variables were assessed through Kaplan–Meier analysis.

Nomogram development

The training data set (n=1315) was used for initial nomogram development. The least absolute shrinkage and selection operator (LASSO) was employed for variable selection to refine the model structures for BCSS, DM-free survival, and LRR-free survival, with the optimal LASSO penalty determined using a 10-fold cross validation. The variables used in the analysis were age (20–29, 30–39, 40–49, 50–59, 60–69, or ≥ 70 years), Charlson Comorbidity Index (CCI) score, Ki-67, ER status (positive or negative), PR status (positive or negative), HER-2 status (positive or negative), grade (grade 1, grade 2 or grade 3), pathological T stage (pT1, pT2 and pT3), number of positive lymph node (LN), number of resected LN, positive LN ratio, tumor location (medial or lateral), molecular types of breast cancer (luminal A, luminal B, Her-2 overexpression and triple negative breast cancer), and adjuvant systematic therapy including chemotherapy (yes or no), endocrine therapy (yes or no) and anti-HER2 therapy (yes or no). The breast cancer subtypes were classified based on the St Gallen consensus 2013[20], luminal A type was defined

as ER and PR positive, HER-2 negative, and Ki-67<14%; luminal B type (HER-2 negative) was defined as ER positive, HER-2 negative, PR negative and/or Ki-67 \geq 14% luminal B type (HER-2 positive) was defined as ER positive, HER-2 positive, any ki-67 and any PR status; HER-2 positive was defined as HER-2 over-expression or amplified, ER and PR negative; triple-negative was defined as ER negative, PR negative and HER-2 negative; A nomogram for possible prognostic factors associated with BCSS, and DM-free survival was established by R software.

Nomogram validation

Calibration curves were plotted to assess the agreement between the actual rate of BCSS and DM-free survival and the predicted probabilities of BCSS and DM-free survival. To obtain a relatively unbiased estimate, bootstrapping method was used with 1000 re-samplings to produce the calibration plot. A calibration curve of 45 ° indicates a perfect prognostic prediction. In addition, the predictive accuracy was evaluated by Harrell's concordance index (c-index), which ranges from 0.5 (random chance) to 1 (perfect prediction). If the C-index exceeds 0.7, the model is generally considered as good, and excellent if the C-index is more than 0.8. Finally, the prediction model was validated using external data set from one phase III trial mentioned above.

Results

Baseline characteristics

From Jan 2009 to Dec 2015, a total of 1879 consecutively breast cancer with pN0-1 who treated with mastectomy were included for analysis. Firstly, we randomly divided into a training cohort and a testing cohort (7:3), with 1,316 patients in the training cohort and 563 in the validation cohort. No variables were significantly different between the two cohorts. The median age at diagnosis was 56 years (range, 28–92 years) in the training set and 58 years (range, 23-92 years) in the testing set. The median tumor size was 2 cm in both cohorts. The majority of our cohorts (1,590 patients, 84.6%) did not have lymph node (LN) metastasis. A total of 1731 patients (92.1%) treated with adjuvant systematic therapy, and 623 patients (33%) treated with both adjuvant chemotherapy and hormonal therapy. Adjuvant chemotherapy was received by 785 patients (60%) in the training cohort and 311 (55.2%) in the validation cohort. Among 1096 patients received chemotherapy, 537 patients (49%) treated with doxorubicin, cyclophosphamide, and paclitaxel; 511 patients (46.6%) treated with doxorubicin-containing or taxanes-containing regimens, and the remaining 48 patients (4.4%) treated with other regimens. Adjuvant hormonal therapy was received by 868 patients (66.0%) in the training cohort and 383 patients (68%) in the validation cohort. Among 1251 patients treated with hormonal therapy, 698 patients (55.8%) treated with aromatase inhibitors (AIs); and 549 patients (43.9%) treated with Selective Estrogen Receptor Modulators (SERMs). Detailed baseline characteristics are listed in Table 1.

Survival outcomes

By the latest follow-up of Oct 2019, with a median followed-up of 60 months, a total of 101 (5.37%) patients died in the entire cohorts, with 55 (2.93%) patients deaths attribute to breast cancer and the remaining 46 (2.45%) deaths due to other reasons. The survival outcomes of the entire cohort was excellent. The 5- and 10-year breast cancer specific survival (BCSS) was 98% and 95%, respectively (supplemental figure 1A and 1B). The 5- and 10-year overall survival (OS) was 97% and 91%, respectively (figure 1C and 1D). A total of 44 patients developed local regional recurrences, with the 5- and 10-year cumulate LRR rate was 2% and 3% (supplemental figure 2), respectively. In addition, a total of 90 patients developed distant metastasis (DM), and the 5- and 10-year cumulate DM rate was 4% and 6%, respectively (supplemental figure 2). In the external validation cohort, the 5-year OS and BCSS was 95% and 97%, respectively (supplemental figure 3). And the cumulative incidence of 5-year LRR and DM was 3% and 6%, respectively (supplemental figure 3).

Factors associated with BCSS,LRR and DM

A total of 16 variables were considered as potential predictors. We used a lasso regression algorithm based on each variable for predictor selection in the training cohort. As showed in the figure 3, when the partial likelihood deviance reached its minimum value, the appropriate tuning parameter g was 0.0059 and $\log g$ is -5.14; and five variables with nonzero coefficients were obtained from the LASSO analysis (figure 2).

As for LRR-free survival, LASSO regression showed that only number of positive LN was the significant predictor. And univariate Cox-analysis also found that number of positive LN was a significant risk factors for LRR (HR 1.71, 95%CI: 1.13-2.60, $p=0.027$, table 2); Additionally, ten variables with nonzero coefficients, including tumor location, age, number of positive LN, pathological T stage, Ki-67, PR status, grade, number of resected LN, adjuvant hormonal therapy and anti-HER-2 therapy, were obtained from the LASSO analysis.

Construction of the nomogram

Univariate analysis showed that all of the five variables were significant predictors for BCSS (all $p<0.05$). Multivariate Cox-regression analysis showed that four variables of age ($p=0.052$) number of positive LN ($p<0.001$), pathological T stage ($p=0.021$ and $p<0.001$), Ki-67 ($p=0.005$, table 2) have independent prognostic significance for BCSS. All of these five variables were selected for the construction of nomogram of BCSS (figure 3A). The newly developed predictive model showed good discrimination with a C-index of 0.81. And an excellent concordance between the predicted and observed 5-year BCSS probabilities was observed in calibration plot (figure 4A).

Additionally, univariate analysis showed that six of the ten variables were significant predictors for DM-free survival (number of positive LN, pathological T stage, Ki-67, number of resected LN, grade and PR status, $p<0.05$); Multivariate Cox-regression analysis showed that four variables of number of positive LN ($p=0.002$), pathological T stage ($p=0.01$ and $p=0.002$), Ki-67 ($p=0.018$) and total of resected LN ($p=0.037$) had independent prognostic significance for DM (table 2). Finally, six variables were selected for the

construction of nomogram of DM-free survival (figure 3B). The C-index of nomogram in the testing data set was 0.77, and calibration plot indicated that there was a good concordance between the predicted and observed 5-year DM-free survival probabilities (figure 4D).

Internal validation of nomogram

In the internal validation data set of 563 patients, The C-index of the internal test data set for BCSS and DM-free survival was 0.65 and 0.70, respectively. Calibration plot was used to compare the difference between predicted 5-year BCSS and DM-free survival probabilities and the actual 5-year survival probabilities. Our result showed that the calibration curve revealed good concordance between the predicted and observed probabilities (figure 4B and Figure 4E).

External validation of nomogram

The model was externally validated in an independent cohort of 1356 breast patients from one phase III trial (NCT00041119). As the Ki-67 data could not be obtained from the phase III trial, we constructed a modified nomogram based on four variables including age, number of positive LN, pathological T stage and grade. The C-index for the modified model for BCSS in the training and external validation data set was 0.79 and 0.72, respectively. Calibration plot also revealed good concordance between the predicted and observed probabilities in the external data set (figure 4C).

In addition, ki-67 and total resected LN could not be obtained from the trial, thus a modified nomogram for DM-free survival based on four variables of pathological T stage, number of positive LN, grade and PR status was established in the external validation cohort, The C-index for the modified model for DM-free survival in the training and external validation data set was 0.72 and 0.69, respectively. a good concordance between the predicted and observed 5-year DM-free survival probabilities in the external data set was observed (figure 4F).

Discussion

To our best knowledge, this is the first to establish and externally validating a novel nomogram to predict individualized 5-year BCSS and DM-free survival for early stage post-mastectomy breast cancer with pN0-1, but without adjuvant radiotherapy. In the present study, a total of 1879 post-mastectomy breast cancer with pN0-1 without adjuvant radiotherapy from our single institute were enrolled. In our patient population, 84.6% of them present with lymph node negative disease, and 58.7% of the patients receives adjuvant chemotherapy. Initially, a total of 16 variables, including age, CCI score, Ki-67, ER status, PR status, HER-2 status, grade, pathological T stage, number of positive lymph node (LN), number of resected LN, positive LN ratio, tumor location (medial or lateral), molecular types of breast cancer, and adjuvant systematic therapy including chemotherapy (yes or no), endocrine therapy (yes or no) and anti-HER2 therapy (yes or no), are identified for LASSO regression analysis, which effectively process the demographic and clinical feature selection as a statistical method for high-dimensional data [21, 22]. Finally, five variables, including age, grade, pathological T stage, number of positive lymph node (LN), and

Ki-67 with nonzero coefficients were distinguished for predictors of BCSS, one risk factor of number of positive LN for developing LRR, and six of ten variables with nonzero coefficients, including number of positive LN, pathological T stage, Ki-67, PR status, grade, number of resected LN, were predictors for DM. We included these risk factors in the construction of nomograms for BCSS and DM-free survival, and both the C-index values and the calibration diagrams showed satisfactory robustness when applied to both internal and external validation cohorts.

Prior to the present study, several retrospective studies have been published to investigate the risk factors for developing LRR in early stage breast cancer[23-26]. Sharma et al. found that young age was an independent risk factor for developing LRR in patients with pT1-2 with 0 to 3 positive LN of 1019 patients during 1997-2002. The overall 5- and 10-year LRR rates was 1.6% and 2.7%[27]. Then, Pauline T Truong et al. analyzed 1505 T1-2N0 breast cancer between 1989 and 1999, without adjuvant radiotherapy, logistic regression analysis indicated that grade, lympho-vascular invasion (LVI), T stage and systematic therapy are predictors for LRR[26]. More recently, Mamtani et al[8] performed a retrospective analysis of 657 patients with pT1-2N0 post-mastectomy breast cancer treated with modern systematic therapy, and found that only tumor size was the risk factor for developing LRR ($p=0.006$), and the crude LRR rates in the overall population was 4.7%. In our population, the crude LRR rate was 2.3%, and the only risk factor for LRR is the number of positive LN, although tumor size has a tendency to increase the risk of developing LRR (1.15, 95%CI: 0.98-1.35, $p=0.097$). One possible reason for this finding is that the patients received adjuvant systematic therapy in our population is higher than Mamtani et al's study (92.1% vs. 86%). In the external validation cohort, the cumulated incidence of 5-year LRR and DM is 3% and 6%, respectively, which is comparable to our cohorts.

Since the publication of MA20 and EORTC study, more and more oncologists agree that adjuvant radiotherapy in early stage breast cancer not only decrease the LRR risk, but also the risk of distant metastasis. As a result, we also investigate the predictors for BCSS and DM-free survival in this patients cohort. Our analysis find that pathological T stage, number of positive LN, grade and Ki-67 are significant predictors for both BCSS and DM-free survival in post-mastectomy breast cancer with pN0-1, while number of resected LN and PR status are also predictors for DM-free survival. In our nomogram, Ki-67 is identified as a risk factor for both BCSS and DM. This finding is supported by previous studies, which indicates Ki-67 overexpression as an independent predictor for poor prognosis. Matsubara N. et al[28] retrospectively analyzed 1,166 early stage patients and found that Ki-67 overexpression ($Ki-67 \geq 10\%$) was identified as an independent prognostic factor for distant-metastatic-free survival (DFS) and overall survival (OS) by univariate and multivariate analysis. Regrading other four prognostic factors for BCSS, including age, pathological T stage, number of positive LN and grade, multiple studies have reported these three factors as predictor for survival.

There are some limitations needed to be concerned in our study. First, LVI status has been reported as a risk for poor survival in previous studies[29], however, LVI status was not reported in our institute until Jan 2012, thus, we could not assess the prognostic role of LVI status in this patient population. Second, our study is a retrospective study, Inherent biases are also unavoidable in any retrospective study, and thus, a

large prospective investigation are still needed to confirm our results. Thirdly, although the nomogram models are validated by an external cohort of 1356 patients from a phase III trial, radiation information of these patients are unavailable. we do not know the percentage of patients received with radiation therapy. Thus the external validation set could be potentially compromised by including radiated patients. Further studies externally validating the models in this patients population are recommended. Finally, applying these nomogram models in the setting of particularly large tumors (>5 cm) should be cautious, because the limited number of such patients (n=35) within our study population.

Conclusion

In summary, we established and validated a novel nomogram for predicting survival of early stage post-mastectomy pN0-1 breast cancer without adjuvant radiotherapy. This nomogram could help physicians to accurately evaluate the individual BCSS and DM-free survival in this patient population, and distinguish potential high-risk patients who could benefit from additional treatment.

Abbreviations

LASSO, least absolute shrinkage and selection operator; BCSS, breast cancer specific survival; LRR, local regional recurrence; DM, distant metastasis; EORTC, European Organization for Research and Treatment of Cancer; PMRT, post-mastectomy radiotherapy; IBTR, ipsilateral breast tumor recurrence; P, pathological; DCIS, Ductal Carcinoma In Situ; CCI, Charlson Comorbidity Index; LN, lymph node; OS, overall survival; LVI, lympho-vascular invasion;

Declarations

Ethical Approval and Consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study procedures were approved by the Ethical Committee of RuiJin Hospital affiliated medicine school of Shanghai Jiao Tong University. The information is coded and the patients are deidentified. Consent was not required to be obtained.

Consent for publication

Not applicable.

Availability of supporting data

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

Conceptualization: J.C. and W.X.Q.; Project administration: C.X. and L.C.. Methodology: W.X.Q., S.G.Z., J.C., S.Z. Data Curation: J.C. and C.X. Formal analysis: W.X.Q.. Manuscript preparation: W.X.Q., C.X., J.C., L.C. Final approval of manuscript: all authors.

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Tables

Table 1. baseline characteristics of included patients

Group	Training set (1316)	Validation set (n=563)	P value
Age (median, range)	56(28-92) years	58(23-92) years	
N stage			
pN0	1115	475	0.90
pN1	201	88	
CCI score	1(0-8)	2(0-7)	
Location			
Medial	409	191	0.25
Lateral	907	372	
T size (median, range)	2(0.01-14) cm	2(0.02-12.5) cm	
T stage			
T1mic	36	11	0.65
T1a	77	26	
T1b	172	72	
T1c	521	221	
T2	484	224	
T3	26	9	
Grade			
1	119	58	0.57
2	742	321	
3	455	184	
Adjuvant chemotherapy			
Yes	790	313	0.08
No	526	250	
Adjuvant anti-HER-2 therapy			
Yes	171	70	0.80
No	1145	493	
Number of positive LN			
0	1115	475	0.28

1	133	56	
2	49	17	
3	19	15	
Number of resected LN	13 (1-46)	13 (1-38)	
ER status			
Positive	857	376	0.52
Negative	459	187	
PR status			
Positive	539	235	0.79
Negative	777	328	
HER-2 status			
Positive	294	123	0.79
Negative	1022	440	
Adjuvant hormonal therapy			
Yes	868	383	0.41
No	448	180	
HR/HER-2 status			
ER-positive/HER-2 negative	743	329	0.86
ER-negative/HER-2 negative	279	111	
ER positive/HER-2 positive	114	47	
ER negative/HER-2 positive	180	76	
Molecular types			
Luminal A	457	186	0.60
Luminal B	413	194	
HER-2 positive	178	76	
Triple-negative	268	107	

Table 2. multi-variable cox regression of selected variables in the nomogram.

Group	BCSS	LRR	DM
	HR (95%CI), <i>p</i> value	HR (95%CI), <i>p</i> value	HR (95%CI), <i>p</i> value
Age	1.03 (1.00-1.05), <i>p</i> =0.052	-	-
Number of positive LN	1.77(1.29-2.46), <i>p</i> <0.001	1.71 (1.13-2.60), <i>p</i> =0.027	1.55 (1.17-2.06), <i>p</i> =0.002
T stage			
pT1	Reference	-	Reference
pT2	2.25(1.13-4.52), <i>p</i> =0.021	-	1.98(1.18-3.32), <i>p</i> =0.01
pT3	13.04(4.61-36.88), <i>p</i> <0.001	-	4.99(1.77-14.06), <i>p</i> =0.002
Grade			
1-2	Reference	-	Reference
3	1.38 (0.68-2.79), <i>p</i> =0.37	-	1.17 (0.68-2.04), <i>p</i> =0.55
Ki-67	1.02(1.00-1.033), <i>p</i> =0.005	-	1.01 (1.00-1.02), <i>p</i> =0.020
Number of resected LN	-	-	1.04 (1.00-1.07), <i>p</i> =0.039
PR status			
Positive	-	-	Reference
Negative	-	-	0.68 (0.37-1.23), <i>p</i> =0.20

Figures

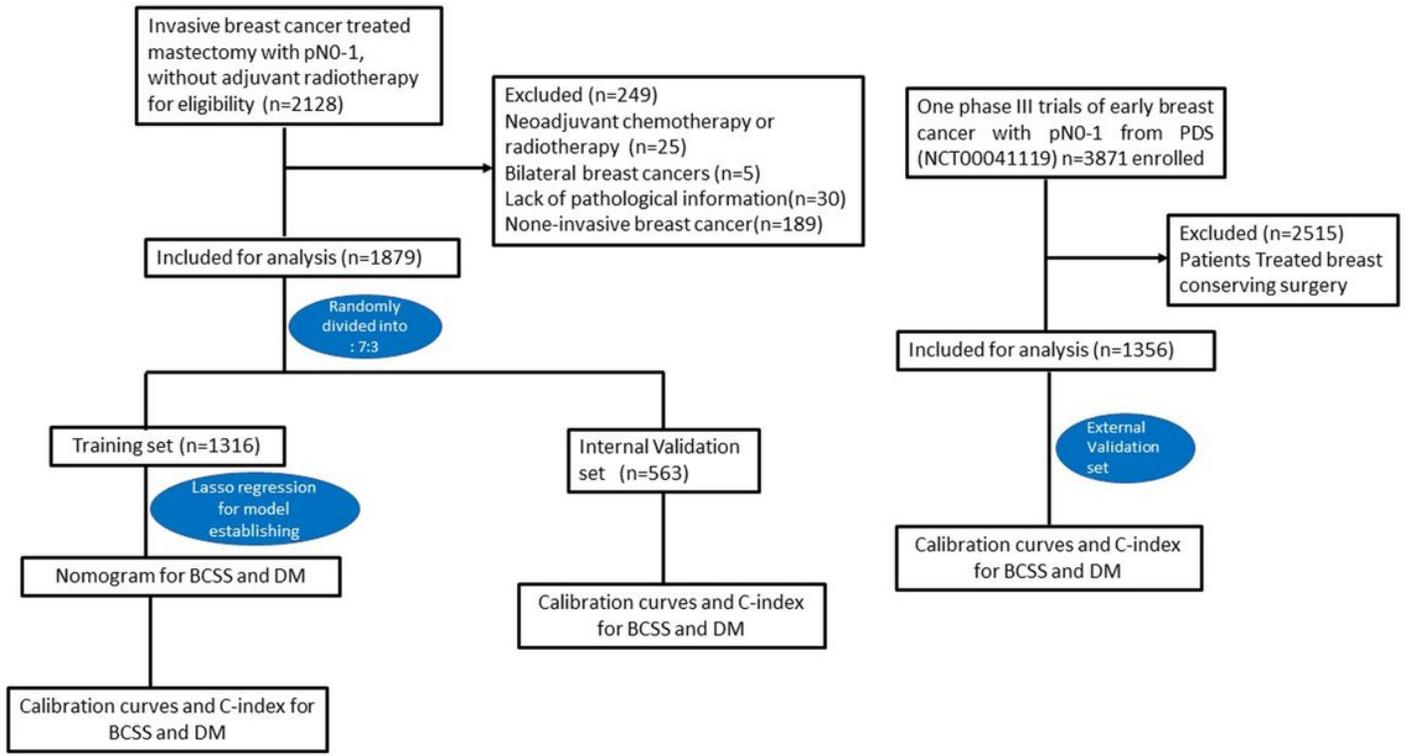


Figure 1

Flow of patient selection and external validation.

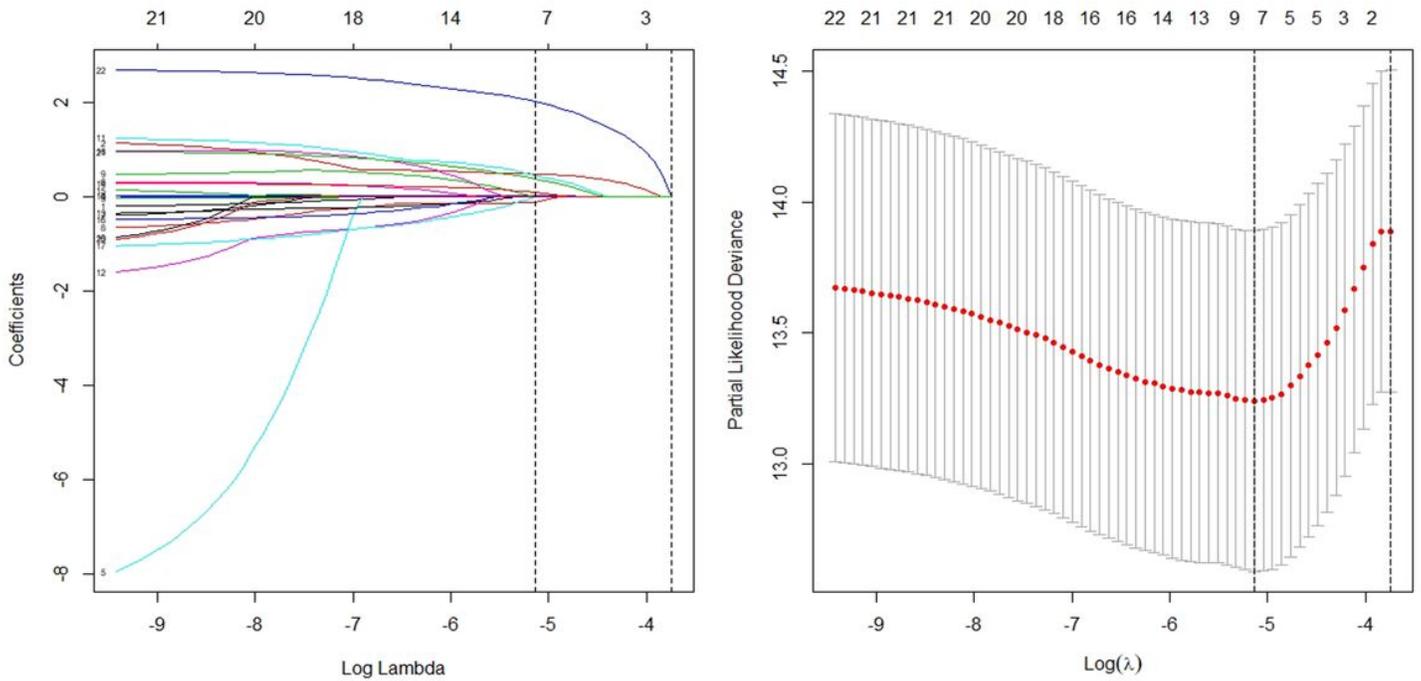


Figure 2

Feature selection using least absolute shrinkage and selection operator (LASSO) Cox regression for BCSS: (A) LASSO coefficients profiles for clinical features; (B) selection of tuning parameter(λ) in the LASSO regression using 10-fold cross-validation via minimum criterial.

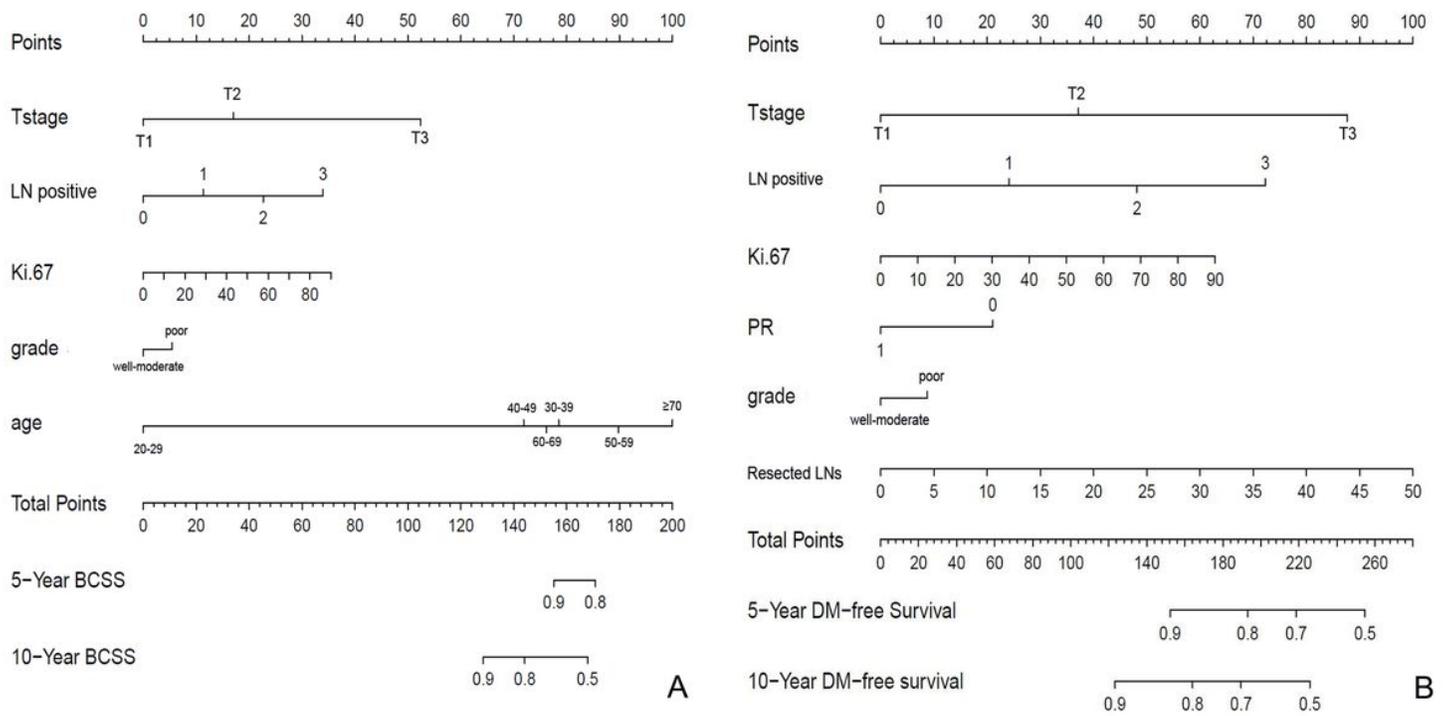


Figure 3

Nomogram for predicting 5-year BCSS(A) and 5-year DM-free survival(B)

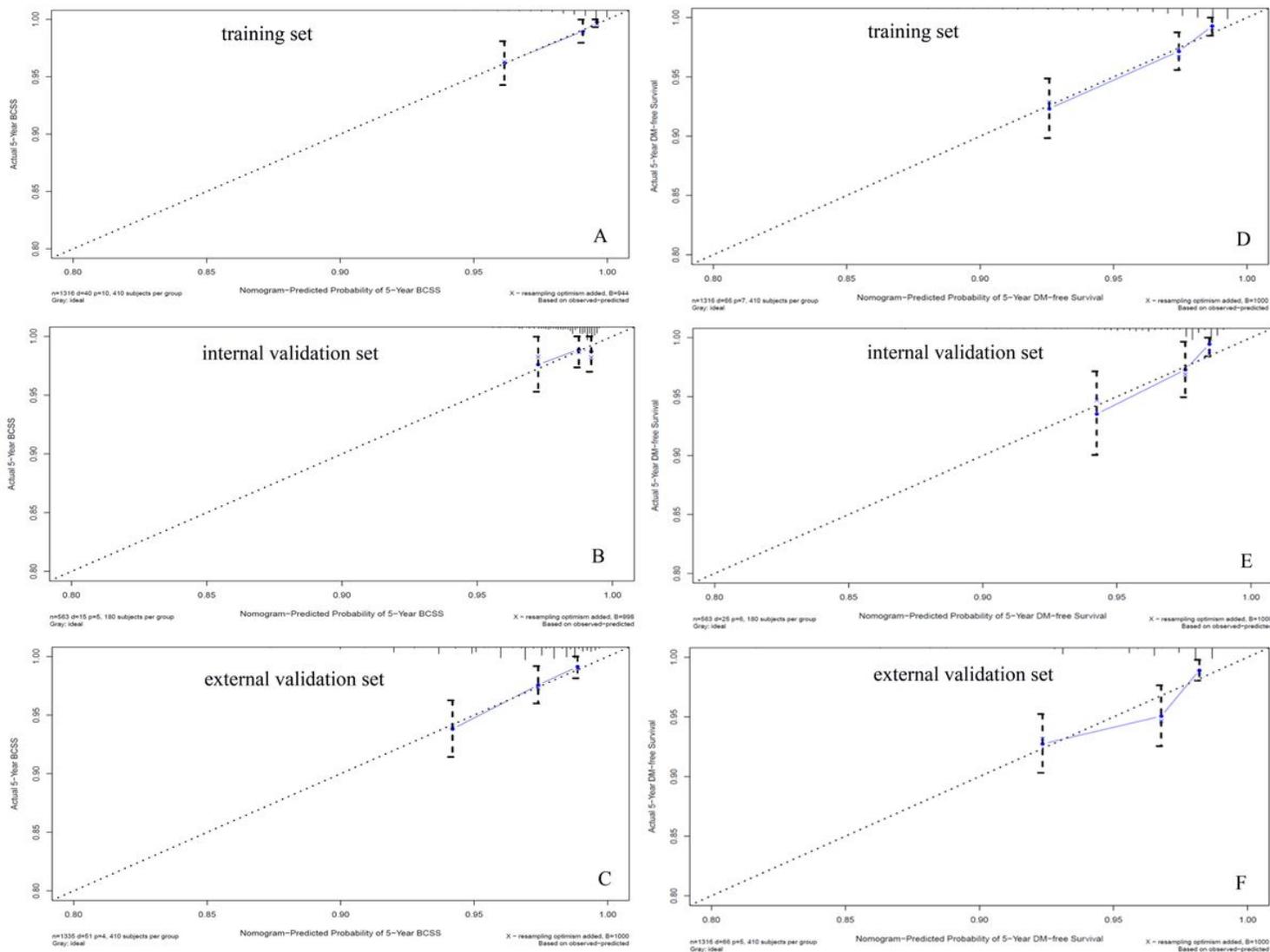


Figure 4

Calibration curves for 5-year BCSS and 5-year DM-free survival in the training, internal validation and external validation cohort

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementalfigure3.jpg](#)
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