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Construction and Validation of Nomograms for Predicting Overall Survival and Cancer-Specific Survival in Nonmetastatic Inflammatory Breast Cancer Patients Receiving Tri-Modality Therapy: A Population-Based Study

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Background: As the most aggressive breast cancer, inflammatory breast cancer (IBC) has a poor prognosis. However, analyzing the prognostic factors of IBC is challenging due to its rarity. We identified the prognostic factors to establish predictive tools for survival in nonmetastatic IBC patients who received tri-modality therapy.

Material/Methods: The data of 893 nonmetastatic IBC patients were acquired from the Surveillance, Epidemiology, and End Results (SEER) database. IBC was identified by "ICD-O-3=8530" or "AJCC T, 7th=T4d"). Patients were randomized to the training (n=668) and validation (n=225) cohorts. Prognostic factors were identified in the training cohort. Factors in the nomogram for overall survival (OS) were filtered by the least absolute shrinkage selection operator (LASSO) regression model. Factors selected by the competing-risk models were integrated to construct nomograms for breast cancer-specific survival (BCSS). Nomogram validation was performed in both cohorts.

Results: The number of positive lymph nodes contributed the most to both nomograms. In the validation cohort, the C-indexes for OS and BCSS were 0.724 and 0.727, respectively. Calibration curves demonstrated acceptable agreement between predicted and actual survival. Risk scores were calculated from the nomograms and used to split patients into the low-risk and high-risk groups. Smooth hazard ratio (HR) curves and Kaplan-Meier curves showed a statistically significant difference in prognosis between the high-risk group and low-risk group (log-rank P<0.001).

Conclusions: We unveiled the prognostic factors of nonmetastatic IBC and formulated nomograms to predict survival. In these models, the likelihood of individual survival can be easily calculated, which may assist clinicians in selecting treatment regimens.

MeSH Keywords: **Inflammatory Breast Neoplasms • Nomograms • SEER Program**

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Background

Inflammatory breast cancer (IBC) has specific characteristics, including diffuse erythema and edema, which has a peau d'orange appearance that involves most of the breast [1]. IBC is the most aggressive breast cancer, with a historical median survival of less than 15 months [2,3]. The survival of IBC patients has appeared to improve due to advancements in systemic therapy. At present, the guidelines for nonmetastatic IBC management recommend neoadjuvant chemotherapy followed by mastectomy and adjuvant radiotherapy (so-called tri-modality therapy) [4,5]. However, the prognosis of IBC remains unsatisfactory [3].

Studies have suggested that IBC differs from noninflammatory breast cancer (NIBC) in clinicopathological features. For example, more patients with IBC lack hormone receptor expression [6,7]. Since IBC accounts for only 2.5% of breast cancers [8], the characteristics associated with poor prognosis are not well defined. Generally, the breast cancer molecular subtype is correlated with patient survival [9]; however, different prognoses have also been observed among patients with the same subtype. These differences may be due to other features, such as age, race, and the number of positive lymph nodes (LNs). To assist clinicians in assessing patient prognosis and selecting a treatment regimen, a survival estimation tool is required to identify high-risk patients. Nomograms have been reported as a predictive tool for clinical outcome. Using a nomogram, the likelihood of individual survival can be easily calculated by adding the scores of each variable [10,11].

Studies have reported that survival in IBC patients undergoing breast-conservative surgery is similar to that in patients receiving a mastectomy [12,13]. However, these studies were from single centers, and the small sample sizes limited the findings. Thus, the relationship between surgical extent and patient prognosis remains controversial. In the present study, we identified prognostic factors of nonmetastatic IBC based on a relatively large cohort from the Surveillance, Epidemiology, and End Results (SEER) database (<http://seer.cancer.gov/>). This database collects data from 18 population-based registries, which covers approximately 28% of the US population. Furthermore, we formulated and validated nomograms to predict the survival of patients with nonmetastatic IBC.

Material and Methods

Data source and patient selection

We extracted relevant data of nonmetastatic IBC patients using SEER*Stat software version 8.3.5. IBC was identified by "ICD-O-3=8530" or "AJCC T, 7th=T4d".

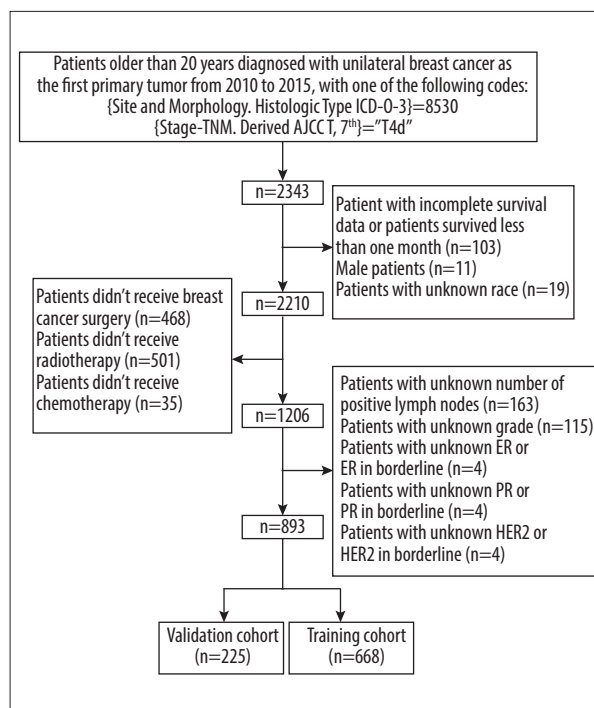


Figure 1. Patient selection process.

Since information on human epidermal growth factor receptor 2 (HER2) status was not recorded in the database until 2010, only patients diagnosed after 2010 were included in this study. We restricted the search criteria to female patients over 20 years old who had been histologically diagnosed with unilateral breast cancer as the first primary tumor. Only patients treated with surgery, radiation therapy, and chemotherapy were included. Patients who were diagnosed at autopsy only, patients who survived less than 1 month, and patients with unclear information were excluded.

Eventually, 893 patients were eligible for analysis. The patient selection process is presented in the flow chart (Figure 1). Even though 313 patients were excluded from analysis because of a lack of data, patients eventually included in this study accounted for approximately 75% (893/1206) of patients who met the inclusion criteria. The following information was collected: race, age, tumor laterality, grade, the number of positive LNs, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, and the extent of surgery. Surgical procedure codes 20–24 were considered to identify patients who received a partial mastectomy, while codes 30–80 were considered to identify patients who underwent a mastectomy.

Identification of prognostic factors in the training cohort

All patients were randomized at a 3: 1 ratio to the training (n=668) and validation (n=225) cohorts ("caret" package in R software). A chi-square analysis was performed for

the comparisons of the clinicopathological features of the 2 cohorts. OS and BCSS were defined as the study endpoints, and prognostic factors were identified in the training cohort.

OS was measured from the time when patients were diagnosed with IBC to the time of the last follow-up or the time of deaths from any cause. The independent prognostic factors for OS were identified by Cox proportional hazards models, which were performed to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs).

BCSS was calculated from the date when patients were diagnosed with IBC to the date of last follow-up or the date of death from breast cancer. The cumulative incidences of breast cancer-specific (BCS) deaths were calculated based on competing-risk models, and the differences among groups were assessed using Gray's test ("cmprsk" package in R software) [14]. In the competing-risk regression model, deaths from non-BCS causes were considered as competing risks.

Model construction in the training cohort

Two nomograms were constructed to predict survival in the training cohort ("rms" package in R software) [15]. Least absolute shrinkage and selection operator (LASSO) regression was implemented to filter factors for the OS nomogram ("glmnet" package in R software) [16]. Compared with the Cox analysis, the main advantage of the LASSO regression model was that the selection of important prognostic factors for the OS nomogram did not depend on statistical significance. In the LASSO regression model, variables were assigned to different penalties: more important variables got smaller penalties, making them more likely to be retained in the model, whereas unimportant variables received larger penalties and tended to be discarded. Therefore, this method could select the most significant prognostic factors to establish a model for predicting survival [16–18]. Factors associated with the cumulative incidences of BCS deaths in the competing-risk models were used to build the BCSS nomogram. The BCSS nomogram was also constructed based on the Cox regression model, in which patients who died from non-BCS causes were considered as censored.

Model validation in both cohorts

The nomograms were validated in both cohorts in 5 ways. First, the predictive accuracy of the nomograms was validated by bootstrapping with 1000 resamples, and the discrimination was quantified using the concordance index (C-index). Second, calibration curves were generated to plot the nomogram-predicted survival and then compared with the corresponding Kaplan-Meier estimates. Third, using the nomograms, we calculated the risk score for every patient by summing the

respective value of each factor. The predictive precision of the risk scores as a continuous variable was evaluated by time-dependent receiver operating characteristic (ROC) curves, and the areas under the curves (AUCs) were used as the criterion ("survivalROC" package in R software) [19,20]. The ROC curves plotted the predictive sensitivity and specificity; therefore, a larger AUC (range 0.5–1.0) reflected a more accurate prediction. The cutoff value of the risk score was calculated by ROC curves from the highest Youden index [Youden index=(specificity+sensitivity)–1; true positive rate=sensitivity; false positive rate=1–specificity]. Using the cutoff value as a reference, the relationship of the risk score with the logarithm (in HR) of OS or BCSS was illustrated by the smooth HR curve to demonstrate the prognostic value of the risk score as a continuous variable ("smooth HR" package in R software) [21]. Finally, patients were classified in the low-risk and high-risk groups according to the risk score. Survival curves were depicted by the Kaplan-Meier method, and comparisons were carried out using the log-rank test.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL), and R software version 3.5.0. The instructions for R packages can be found on the website of <https://cran.r-project.org>. Statistical significance was defined as $P < 0.05$.

Results

Clinicopathological features of patients and tumors

Overall, 893 patients were enrolled. Patient features are listed in Table 1. We registered 181 OS events. Most tumors were grade III–IV (66.7%), and most patients (96.9%) received a mastectomy, while only 3.1% received a partial mastectomy. There was no significant difference in the baseline characteristics between the 2 cohorts (all $P > 0.05$).

Prognostic factors for OS in the training cohort

In the univariate Cox analysis, grade, the number of positive LNs, ER status, PR status, and HER2 status were significantly correlated with OS. These factors were included in the multivariate analysis, which revealed that grade, the number of positive LNs, ER status, PR status, and HER2 status were independent prognostic factors. These results are listed in Table 2. There was no statistically significant difference in OS between patients who underwent partial mastectomy surgery and patients who underwent mastectomy surgery (HR=0.969, 95% CI, 0.397–2.369; $P=0.946$).

Table 1. Characteristics of patients and tumors.

Characteristics	All patients N	Training cohort N	Validation cohort N	P value
Race				0.607
White	720 (80.6%)	540 (80.8%)	180 (80.0%)	
Black	109 (12.2%)	78 (11.7%)	31 (13.8%)	
Others	64 (7.2%)	50 (7.5%)	14 (6.2%)	
Age				0.354
<40	111 (12.4%)	87 (13.0%)	24 (10.7%)	
≥40	782 (87.6%)	581 (87.0%)	201 (89.3%)	
Laterality				0.161
Left	472 (52.9%)	344 (51.5%)	128 (56.9%)	
Right	421 (47.1%)	324 (48.5%)	97 (43.1%)	
Grade				0.531
I–II	297 (33.3%)	226 (33.8%)	71 (31.6%)	
III–IV	596 (66.7%)	442 (66.2%)	154 (68.4%)	
No. of positive LNs				0.312
0	255 (28.6%)	200 (29.9%)	55 (24.4%)	
1–3	276 (30.9%)	197 (29.5%)	79 (35.1%)	
4–9	227 (25.4%)	171 (25.6%)	56 (24.9%)	
≥10	135 (15.1%)	100 (15.0%)	35 (15.6%)	
ER status				0.559
Negative	380 (42.6%)	288 (43.1%)	92 (40.9%)	
Positive	513 (57.4%)	380 (56.9%)	133 (59.1%)	
PR status				0.469
Negative	479 (53.6%)	363 (54.3%)	116 (51.6%)	
Positive	414 (46.4%)	305 (45.7%)	109 (48.4%)	
HER2 status				0.587
Negative	566 (63.4%)	420 (62.9%)	146 (64.9%)	
Positive	327 (36.6%)	248 (37.1%)	79 (35.1%)	
Surgery				0.363
Mastectomy	865 (96.9%)	645 (96.6%)	220 (97.8%)	
Partial mastectomy	28 (3.1%)	23 (3.4%)	5 (2.2%)	

ER – estrogen receptor; No. of positive LNs – number of positive lymph nodes; PR – progesterone receptor; HER2 – human epidermal growth factor 2.

Table 2. Association between clinicopathological features and OS.

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		P Value	HR	95% CI		P Value
		Lower	Upper			Lower	Upper	
Race				0.123				
White	Reference							
Black	1.274	0.783	2.074	0.329				
Others	0.489	0.215	1.112	0.088				
Age				0.582				
<40	Reference							
≥40	1.158	0.687	1.952	0.582				
Laterality				0.271				
Left	Reference							
Right	0.827	0.589	1.160	0.271				
Grade				0.001				0.025
I–II	Reference				Reference			
III–IV	2.030	1.351	3.048	0.001	1.633	1.064	2.506	0.025
No. of positive LNs				<0.001				<0.001
0	Reference				Reference			
1–3	1.929	1.067	3.485	0.030	2.185	1.206	3.959	0.010
4–9	3.747	2.164	6.488	<0.001	4.508	2.580	7.877	<0.001
≥10	5.016	2.814	8.943	<0.001	6.001	3.331	10.812	<0.001
ER status				<0.001				0.020
Negative	Reference				Reference			
Positive	0.529	0.376	0.744	<0.001	0.571	0.357	0.914	0.020
PR status				<0.001				0.031
Negative	Reference				Reference			
Positive	0.472	0.327	0.682	<0.001	0.575	0.348	0.950	0.031
HER2 status				<0.001				<0.001
Negative	Reference				Reference			
Positive	0.422	0.278	0.639	<0.001	0.406	0.266	0.619	<0.001
Surgery				0.946				
Mastectomy	Reference							
Partial mastectomy	0.969	0.397	2.369	0.946				

ER – estrogen receptor; No. of positive LNs – number of positive lymph nodes; PR – progesterone receptor; HER2 – human epidermal growth factor 2; 95% CI – 95% confidence interval.

Table 3. Association between clinicopathological features and BCSS.

Variable	Cumulative incidence of breast cancer specific-death			Cumulative incidence of non-breast cancer specific-death		
	3-year	5-year	P value	3-year	5-year	P value
Race			0.048			0.781
White	0.216	0.292		0.025	0.039	
Black	0.219	0.289		0.018	0.018	
Others	0.056	0.146		0.046	0.046	
Age			0.819			0.394
<40	0.182	0.235		0.020	0.020	
≥40	0.207	0.287		0.027	0.039	
Laterality			0.326			0.676
Left	0.228	0.263		0.031	0.040	
Right	0.177	0.297		0.020	0.034	
Grade			0.004			0.065
I-II	0.125	0.200		0.014	0.014	
III-IV	0.243	0.323		0.031	0.049	
No. of positive LNs			<0.001			0.374
0	0.090	0.129		0.011	0.037	
1-3	0.150	0.248		0.014	0.014	
4-9	0.269	0.357		0.034	0.049	
≥10	0.398	0.473		0.055	0.055	
ER status			<0.001			0.630
Negative	0.267	0.378		0.024	0.048	
Positive	0.155	0.199		0.027	0.027	
PR status			0.001			0.032
Negative	0.256	0.348		0.038	0.058	
Positive	0.140	0.196		0.010	0.010	
HER2 status			<0.001			0.375
Negative	0.262	0.351		0.029	0.040	
Positive	0.098	0.151		0.020	0.032	
Surgery			0.763			0.599
Mastectomy	0.207	0.278		0.025	0.036	
Partial mastectomy	0.130	0.335		0.048	0.048	

ER – estrogen receptor; No. of positive LNs – number of positive lymph nodes; PR – progesterone receptor; HER2 – human epidermal growth factor 2.

Prognostic factors for BCSS in the training cohort

To identify factors associated with BCSS, we calculated the cumulative incidences of BCS deaths based on the competing-risk regression models. The cumulative incidences of BCS deaths and non-BCS deaths according to the clinicopathological characteristics are listed in Table 3. Race, grade, ER status, PR status, HER2 status, and the number of positive LNs were significantly associated with BCS deaths. Notably, we also observed no significant difference in the cumulative incidences of BCS deaths between patients who received a partial mastectomy and patients who received a mastectomy ($P=0.763$).

Model construction in the training cohort

In the LASSO regression model, 7 factors were selected: race, tumor laterality, grade, the number of positive LNs, ER status, PR status, and HER2 status. The respective coefficients of these 7 factors were calculated when $\log \lambda = -4.42$ (Figure 2A, 2B).

Based on the Cox regression model, we formulated nomograms to predict 3- and 5-year OS. The OS nomogram that integrated factors selected by the LASSO regression model is shown in Figure 2C. Similarly, factors associated with the cumulative incidences of BCS deaths in the competing-risk models were used to establish a nomogram for BCSS, which included the following variables: race, grade, ER status, PR status, HER2 status, and the number of positive LNs (Figure 2D). The number of positive LNs contributed the most to both the OS and BCSS nomograms. After locating each variable on the point scales, we could obtain the scores of each variable and then calculate the total score for each patient by summing the scores of all variables.

Model validation in both cohorts

In the training cohort, the C-indexes for OS and BCSS were 0.76 and 0.764, respectively. Calibration curves demonstrated that the nomogram-predicted survival closely corresponded with the survival obtained using the Kaplan-Meier method (Figure 3A–3D). The time-dependent ROC curve is shown in Figure 3E. With the risk scores as a continuous variable, the AUCs for the 3- and 5-year OS and BCSS predictions were 0.747, 0.740, 0.770, and 0.774, respectively. The results indicated that nomograms are useful predictors for both OS and BCSS.

We calculated the risk score from the nomograms for every patient to evaluate the performance of the nomograms as a risk stratification tool. The cutoff value obtained from the time-dependent ROC curve for OS was 20. Based on this cutoff value, patients were stratified to low-risk and high-risk groups. In the training cohort, there were 484 patients (72.4%) in the low-risk group and 184 patients (27.5%) in the high-risk group.

Smooth HR curves showed a significant prognostic difference between the 2 prognosis groups (Figure 3F, 3G). The relationship between the risk score and OS was assessed by univariate analysis using the log-rank test. A lower risk score was significantly associated with longer OS (log-rank $P<0.001$, Figure 3H).

The external validation also showed a satisfactory performance of the nomograms (Figure 4). With respect to the validation cohort, the C-indexes for OS and BCSS were 0.724 and 0.727, respectively. There were 150 patients (66.7%) in the low-risk group and 75 patients (33.3%) in the high-risk group (log-rank test $P<0.001$).

Discussion

As the most aggressive breast cancer, IBC has a poor prognosis [3]. However, analysis of the prognostic factors is challenging due to the rarity of IBC. In this population-based study, we extracted 893 nonmetastatic IBC patients from the SEER database. Cox proportional hazards models and competing-risk models were used to investigate the prognostic factors. Then, we formulated nomograms as survival estimation tools, in which we calculated the risk score and estimated the survival for each patient. Next, we applied the risk score to separate patients into the low-risk and high-risk groups. The smooth HR curves displayed a significant prognostic difference between the 2 groups, and the Kaplan-Meier curves showed that a lower score was significantly associated with a longer OS. C-indexes, time-dependent ROC curves, and calibration curves also demonstrated the satisfactory performance of our nomograms. Therefore, in addition to the molecular subtypes, clinicians can assess patient prognosis and select treatment regimens using our nomograms, which integrated factors such as age, race, and the number of positive LNs. Consistent with other studies [22,23], molecular markers ER, PR, and HER2 were used directly in our nomograms instead of molecular subtypes, which would be more convenient for clinical use.

In the study of 82 IBC patients at the Instituto Nacional de Cancerología (INCan) in Mexico City, 60% of IBC patients had poorly differentiated tumors [24]; in agreement with previous studies, most of the tumors in our study were grade III–IV (66.7%). Consistent with the research from Li et al., we found a negative impact of the number of positive LNs on both BCSS and OS [25]. Moreover, the number of positive LNs was the largest contributor to the nomograms. Regarding race, Lisa et al. performed a meta-analysis of 14 studies involving over 40 000 white American and 10 000 African American breast cancer patients and found that African Americans had worse breast cancer survival than white Americans did [26]. Our study demonstrated that African American IBC patients had worse survival outcomes than white patients did.

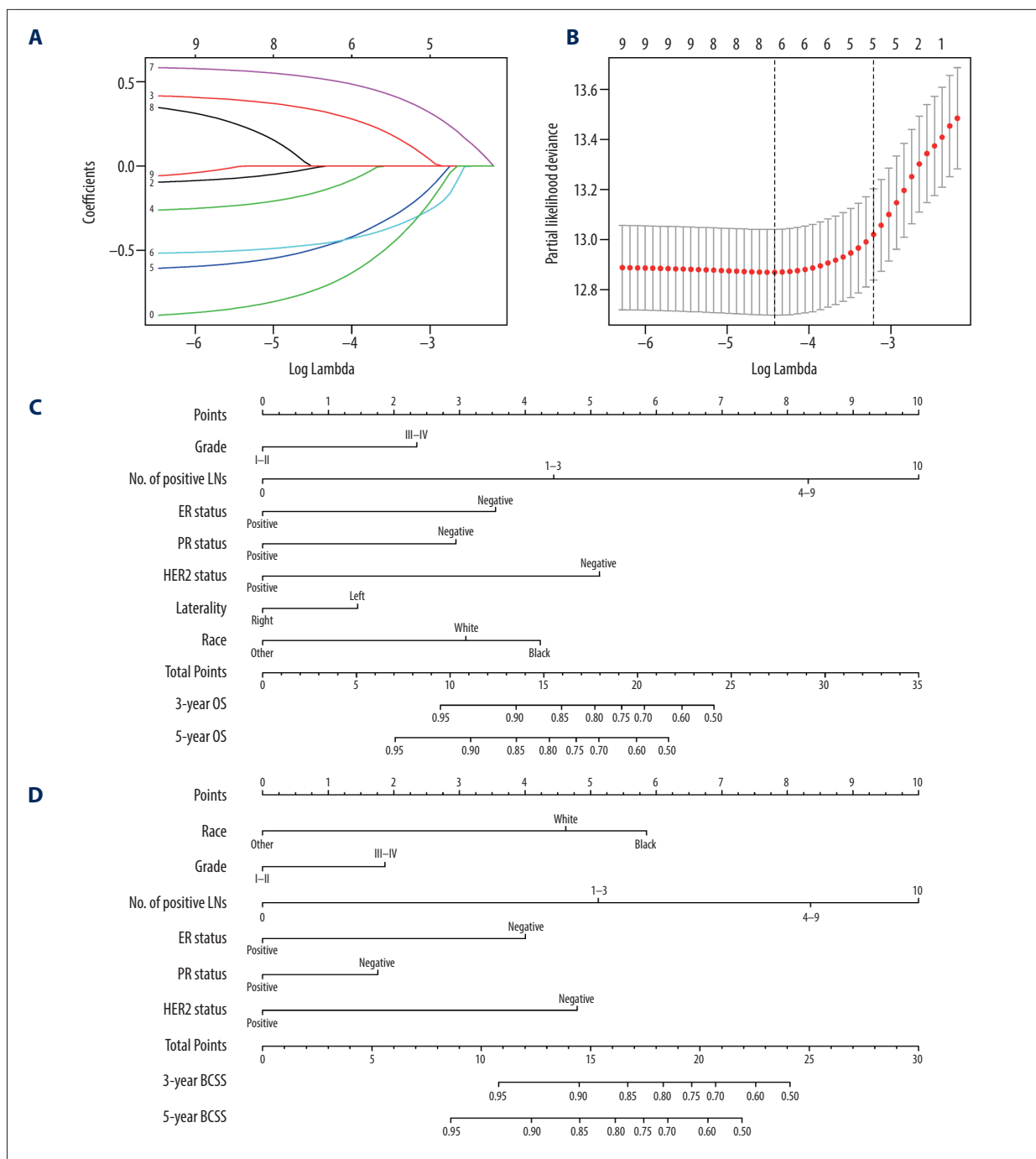


Figure 2. Model construction in the training cohort. **(A)** LASSO coefficient profiles of the prognostic factors. This analysis resulted in the selection of 7 factors – race, grade, laterality, ER status, PR status, HER2 status, and the number of positive LNs – with respective coefficients of -0.005 , 0.328 , -0.151 , -0.485 , -0.462 , -0.726 and 0.520 , in the LASSO regression model. **(B)** Selection of the optimal tuning parameter (lambda) in the LASSO model. The left and right dotted vertical lines represent the optimal values selected by the minimum criteria and the 1-SE criteria, respectively. The optimal lambda=0.012 with log lambda=-4.42 was determined by the minimum criteria. Nomograms for predicting the probabilities of 3- and 5-year **(C)** OS and **(D)** BCSS. Locate a patient’s variable and draw a line up to the Points axis to find the point value for each variable. Calculate the total point value by summing the scores of each variable. Then, locate the total point value on the Total Points axis and draw a line down to the 3-year survival axis or the 5-year survival axis to obtain the likelihood of 3- or 5-year survival. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; No. of positive LNs, the number of positive lymph nodes.

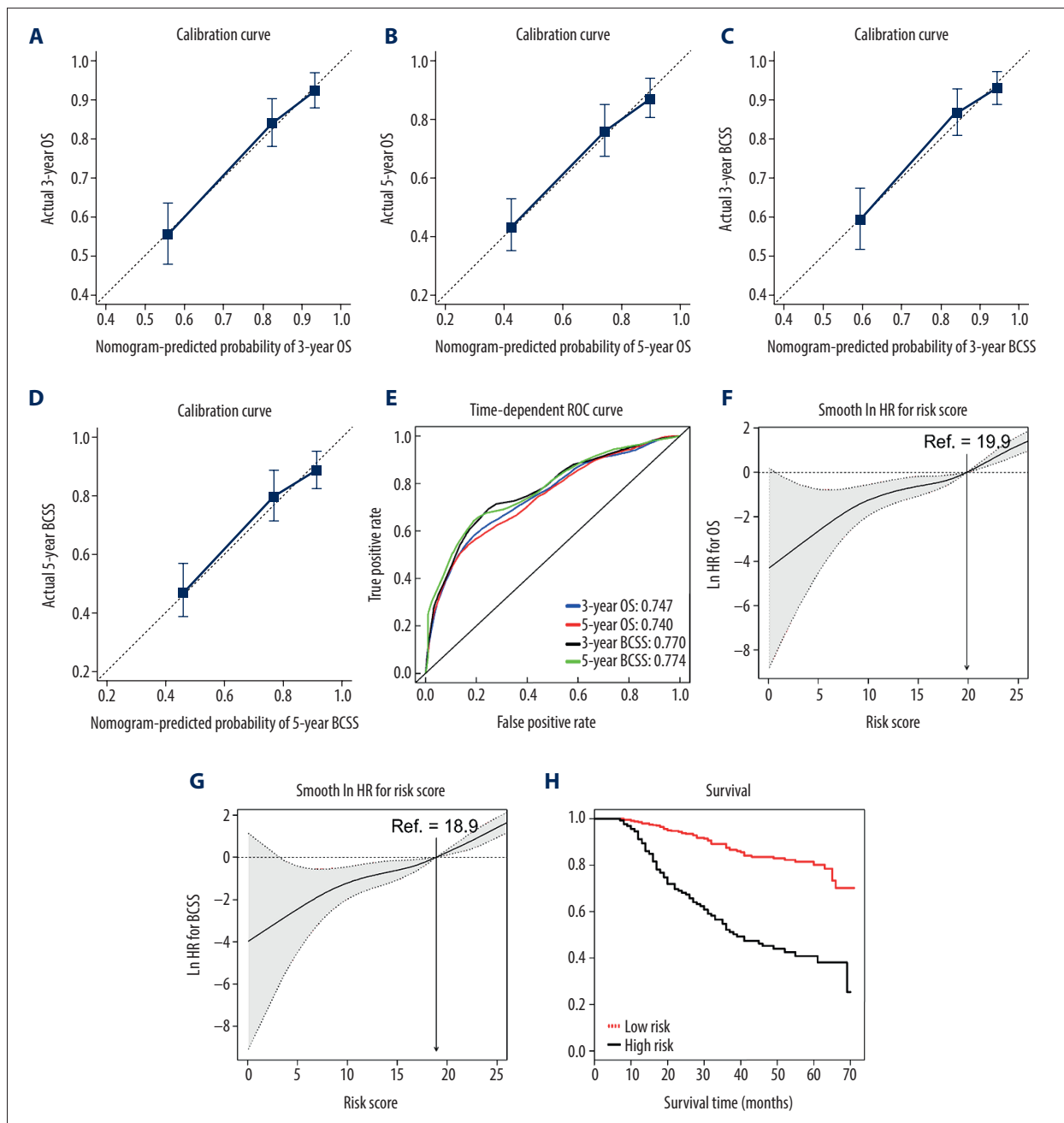


Figure 3. Model validation in the training cohort. Calibration curves for predicting (A) 3-year OS and (B) 5-year OS and (C) 3-year BCSS and (D) 5-year BCSS. The X-axis plots the nomogram-predicted survival; the Y-axis plots the actual survival. (E) Time-dependent ROC curves for predicting 3-year and 5-year OS and 3-year and 5-year BCSS. (F, G) With the cutoff value obtained from the ROC curves as a reference, smooth HR curves displayed a significant prognostic difference between the high-risk group and low-risk group. (H) Kaplan-Meier estimates of survival for patients in the high-risk group versus the low-risk group. Ln HR – logarithm hazard ratio; OS – overall survival; BCSS – breast cancer-specific survival.

IBC is characterized by a lack of hormone receptor expression and a high proportion of HER2-positivity [6,7,27]. The positive rate of HER2 and hormone receptor expression in our study were similar to those in previous studies. In concordance with the report from Dawood et al., ER-positive status

was independently associated with improved survival in IBC patients [28]. Interestingly, HER2 positivity was significantly associated with longer OS and BCSS in our study, presumably the result of trastuzumab treatment. Dawood et al. reported that in the absence of trastuzumab, there was no

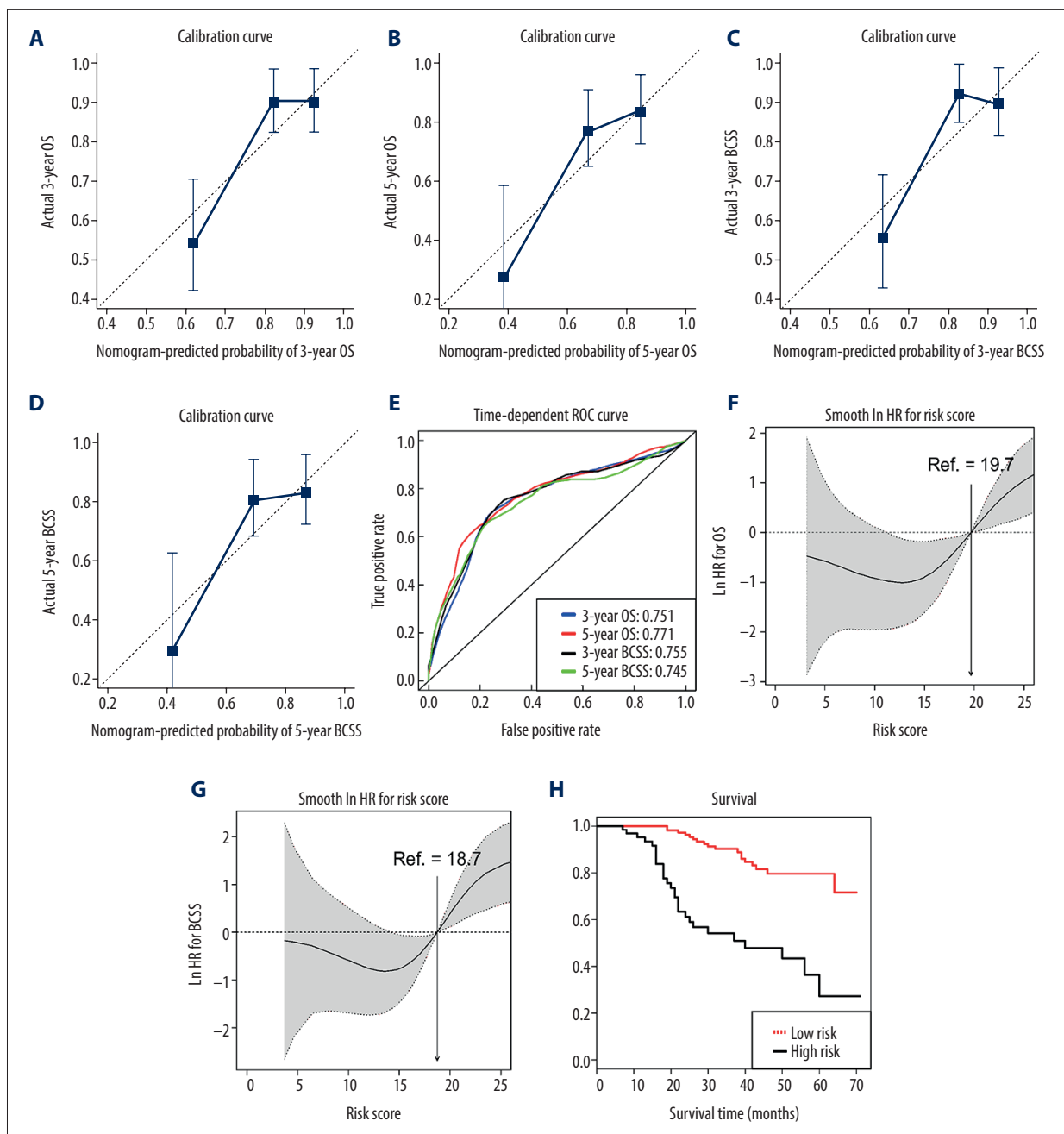


Figure 4. Model validation in the validation cohort. Calibration curves for predicting (A) 3-year OS and (B) 5-year OS and (C) 3-year BCSS and (D) 5-year BCSS. The X-axis plots the nomogram-predicted survival; the Y-axis plots the actual survival. (E) Time-dependent ROC curves for predicting 3-year and 5-year OS and 3-year and 5-year BCSS. (F, G) With the cutoff value obtained from the ROC curves as a reference, smooth HR curves displayed a significant prognostic difference between the high-risk group and low-risk group. (H) Kaplan-Meier estimates of survival for patients in the high-risk group versus the low-risk group. Ln HR – logarithm hazard ratio; OS – overall survival; BCSS – breast cancer-specific survival.

significant association between HER2 status and recurrence-free survival. Then, trastuzumab was added to the treatment regimens of HER2-positive patients who experienced recurrence. Trastuzumab significantly improved the survival of HER2-positive patients, and trastuzumab-treated

HER2-positive patients had a survival rate that even surpassed that of HER2-negative patients (HR of 0.56; 95% CI, 0.34–0.93 [P=0.024]) [28]. In the NOAH trial, compared with neoadjuvant chemotherapy alone, the addition of trastuzumab improved survival in HER2-positive locally advanced breast cancer,

including IBC [29]. Prospective trials have also suggested that trastuzumab is useful in the treatment of IBC [30–32].

In non-IBC, the survival of patients undergoing a breast-conservative surgery has been similar to that of patients receiving a mastectomy [33]. With advancements in systemic therapy, the survival of patients with IBC has appeared to improve [3]. A highly debated question is whether IBC remains an absolute contraindication to breast-conservative surgery. Small studies have reported a similar survival of IBC patients undergoing breast-conservative surgery to that of patients receiving a mastectomy [12,13]. Bonev et al. retrospectively analyzed 24 IBC patients at the median follow-up of 60 months and found no significant difference in OS between patients who received a partial mastectomy and patients who received a mastectomy ($P=0.49$) [12]. However, these studies contained limited patient cohorts. In our study, most patients (96.9%) received a mastectomy, while only 3.1% received a partial mastectomy. We found that patients who underwent different types of surgery showed similar BCSS and OS. Chen et al. published a similar result from a population-based study analysis of over 3000 patients; using a Cox proportional hazards model, they recognized that patients who underwent a breast-conservative surgery had a similar BCSS to those who received a mastectomy. Their findings are consistent with our results from the competing-risks model. They proposed that a mastectomy should not be the only surgical method for IBC [34]. Nevertheless, Muzaffar et al. found that a partial mastectomy was correlated with poor survival in nonmetastatic IBC. One possible explanation for this contradictory result is the differences in patient populations [35]. For example, only some patients in their analysis were treated with radiotherapy, but all patients in our analysis received radiation therapy. Therefore, breast-conservative surgery may be an acceptable alternative to a mastectomy for IBC patients receiving radiotherapy and systemic therapy.

There are some limitations to our study. First, we excluded patients with missing data, which might have resulted in a bias. Second, HER2 status data were not recorded in this database

References:

1. Frederick LG, David LP, Irvin DF et al: AJCC Cancer Staging Manual. 2010. Springer
2. Bozzetti F, Saccozzi R, De Lena M, Salvadori B: Inflammatory cancer of the breast: Analysis of 114 cases. *J Surg Oncol*, 2010; 18(4): 355–61
3. Yamauchi H, Woodward WA, Valero V et al: Inflammatory breast cancer: What we know and what we need to learn. *Oncologist*, 2012; 17(7): 891–99
4. Dawood S, Merajver SD, Viens P et al: International expert panel on inflammatory breast cancer: Consensus statement for standardized diagnosis and treatment. *Ann Oncol*, 2011; 22(3): 515–23
5. Network NCC (2017). NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines): Breast cancer version 2. 2017. https://www.nccn.org/professionals/physician_gls/pdf/breastpdf
6. Cabioglu N, Gong Y, Islam R et al: Expression of growth factor and chemokine receptors: new insights in the biology of inflammatory breast cancer. *Ann Oncol*, 2007; 18(6): 1021–29
7. Zell JA, Tsang WY, Taylor TH et al: Prognostic impact of human epidermal growth factor-like receptor 2 and hormone receptor status in inflammatory breast cancer (IBC): Analysis of 2,014 IBC patient cases from the California Cancer Registry. *Breast Cancer Res*, 2009; 11(1): R9
8. Hance KW, Anderson WF, Devesa SS et al: Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst*, 2005; 97(13): 966–75

until 2010; therefore, only patients diagnosed after 2010 were included in this study, which resulted in a short follow-up. Third, when comparing the prognosis of patients receiving different types of surgery, the propensity score matching (PSM) method may be more appropriate and is commonly used for such comparisons. However, since the percentage of patients who received a partial mastectomy was small, after matching, the statistical power for comparison might have been insufficient. Fourth, the lack of information regarding treatment details and some prognostic markers, such as multigene panel status and Ki67 index, might also have weakened the effectiveness of the nomograms. Therefore, a prospective trial would be ideal for validating these nomograms before clinical application.

Conclusions

Based on a relatively large cohort from the SEER database, we identified prognostic factors of nonmetastatic IBC patients who received tri-modality therapy. Further, we formulated nomograms as survival estimation tools, in which we can calculate the risk score and estimate survival for each patient. Using the risk score, patients can be split into low-risk and high-risk groups, which can assist clinicians in selecting treatment regimens.

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Data availability

The datasets analyzed during the current study are available on the SEER database, <http://seer.cancer.gov/>.

Conflict of interest

None.

9. Wu SG, Zhang WW, Wang J et al: Inflammatory breast cancer outcomes by breast cancer subtype: A population-based study. *Future Oncol*, 2019; 15(5): 507–16
10. Sternberg CN: Are nomograms better than currently available stage groupings for bladder cancer? *J Clin Oncol*, 2006; 24(24): 3819–20
11. Wang Y, Li J, Xia Y et al: Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol*, 2013; 31(9): 1188–95
12. Bonev V, Evangelista M, Chen JH et al: Long-term follow-up of breast-conserving therapy in patients with inflammatory breast cancer treated with neoadjuvant chemotherapy. *Am Surg*, 2014; 80(10): 940–43
13. Brzezinska M, Williams LJ, Thomas J, Michael Dixon J: Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. *Breast Cancer Res Treat*, 2016; 160(3): 387–91
14. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics*, 1988; 16(3): 1141–54
15. Alexia I, Deborah S, Raj GV, Panageas KS: How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*, 2008; 26(8): 1364–70
16. Tibshirani R: The lasso method for variable selection in the Cox model. *Stat Med*, 1997; 16(4): 385–95
17. Halabi S, Lin CY, Kelly WK et al: Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*, 2014; 32(7): 671–77
18. Hao HZ, Lu W: Adaptive Lasso for Cox's proportional hazards model. *Biometrika*, 2007; 94(3): 691–703
19. Heagerty PJ, Lumley T, Pepe MS: Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*, 2000; 56(2): 337–44
20. Heagerty PJ, Yingye Z: Survival model predictive accuracy and ROC curves. *Biometrics*, 2005; 61(1): 92–105
21. Meiramachado L, Cadarsosuárez C, Gude F, Araújo A: smoothHR: An R package for pointwise nonparametric estimation of Hazard ratio curves of continuous predictors. *Comput Math Methods Med*, 2013; 4: 745742
22. T. J Overall Survival and Cause-Specific Mortality of Patients With Stage T1a,bN0M0 Breast Carcinoma. *Yearbook of Surgery*
23. Gong Y, Ji P, Jiang Y et al: Development and validation of nomograms for predicting overall and disease-specific survival in young women with breast cancer. *Eur J Cancer*, 2018; 92: S42
24. Garza-Salazar JGDL, Meneses-García A, Arce-Salinas C: *Inflammatory Breast Cancer*. 2013. Springer, London
25. Li J, Gonzalezangulo AM, Allen PK et al: Triple-negative subtype predicts poor overall survival and high locoregional relapse in inflammatory breast cancer. *Oncologist*, 2011; 16(12): 1675–83
26. Lisa AN, James M, David C et al: African American ethnicity, socioeconomic status, and breast cancer survival. *Cancer*, 2010; 94(11): 2844–54
27. Parton M, Dowsett M, Ashley S et al: High incidence of HER-2 positivity in inflammatory breast cancer. *Breast*, 2004; 13(2): 97–103
28. Dawood S, Broglio K, Gong Y et al: Prognostic significance of HER-2 status in women with inflammatory breast cancer. *Cancer*, 2008; 112(9): 1905–11
29. Gianni L, Eiermann W, Semiglazov V et al: Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2. *Lancet*, 2010; 375(9712): 377–84
30. Hurley J, Doliny P, Reis I et al: Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol*, 2006; 24(12): 1831–38
31. Burstein HJ, Harris LN, Gelman R et al: Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study. *J Clin Oncol*, 2003; 21(1): 46–53
32. Pelt AEV, Mohsin S, Elledge RM et al: Neoadjuvant trastuzumab and docetaxel in patients with breast cancer: preliminary results. *Clinical Breast Cancer*, 2004; 4(5): 348–53
33. Fisher B, Anderson S, Bryant J et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*, 2002; 347(16): 1233–41
34. Chen H, Wu K, Wang M et al: A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End Results database 18. *Breast*, 2017; 35: 48–54
35. Muzaffar M, Johnson HM, Vohra NA et al: The impact of locoregional therapy in nonmetastatic inflammatory breast cancer: A population-based study. *Int J Breast Cancer*, 2018; 2018: 6438635