A nomogram for determining the disease-specific survival in invasive lobular carcinoma of the breast

A population study

Rong Fu, BDa,b,c, Jin Yang, BDa,b, Hui Wang, BDa,b, Lin Li, MDc, Yuzhi Kang, MDc, Rahel Elishilia Kaaya, BDb, ShengPeng Wang, MD, PhDd,e,*, Jun Lyu, MD, PhDa,*

Abstract

We aimed to establish and validate a nomogram for predicting the disease-specific survival of invasive lobular carcinoma (ILC) patients.

The Surveillance, Epidemiology, and End Results program database was used to identify ILC from 2010 to 2015, in which the data was extracted from 18 registries in the US. Multivariate Cox regression analysis was performed to identify independent prognostic factors and a nomogram was constructed to predict the 3-year and 5-year survival rates of ILC patients based on Cox regression. Predictive values were compared between the new model and the American Joint Committee on Cancer staging system using the concordance index, calibration plots, integrated discrimination improvement, net reclassification improvement, and decision-curve analyses.

In total, 4155 patients were identified. After multivariate Cox regression analysis, nomogram was established based on a new model containing the predictive variables of age, the primary tumor site, histology grade, American Joint Committee on Cancer TNM (tumor node metastasis) stages II, III, and IV, breast cancer subtype, therapy modality (surgery and chemotherapy). The concordance index for the training and validation cohorts were higher for the new model (0.781 and 0.832, respectively) than for the old model (0.733 and 0.779). The new model had good performance in the calibration plots. Net reclassification improvement and integrated discrimination improvement were also improved. Finally, decision-curve analyses demonstrated that the nomogram was clinically useful.

We have developed a reliable nomogram for determining the prognosis and treatment outcomes of ILC. The new model facilitates the choosing of superior medical examinations and the optimizing of therapeutic regimens with cooperation among oncologists.

Abbreviations: AJCC = American Joint Committee on Cancer, AUC = area under the time-dependent receiver operating characteristic curve, CI = confidence interval, C-index = concordance index, DCA = decision-curve analyses, HR = hazard ratio, IDI = integrated discrimination improvement, ILC = invasive lobular carcinoma, NRI = net reclassification improvement, SEER = surveillance, epidemiology, and end results.

Keywords: invasive lobular carcinoma, nomogram, prognosis, survival

1. Introduction

Breast cancer is a heterogeneous disease with multiple prognoses.[1] Invasive lobular carcinoma (ILC) is the most-common specific type of breast cancer, which accounts for 15% of all cases and presents with a distinct morphology and clinical behavior compared with invasive carcinoma of no special type.[2] ILC has unique clinical, pathological, and radiographic features that suggest it is a distinct clinical entity.[3] Over the last 2 decades ILC has accounted for 25,000 to 30,000 new cases of breast cancer in the USA annually, and its incidence is increasing, especially among postmenopausal women. If considered an independent cancer type, ILC would be the sixth-most-common cancer in women, with an occurrence frequency similar to those of non-Hodgkin's lymphoma and melanoma.[4,5] ILC tumors typically have a good prognosis, low histology grade, and positivity for the estrogen receptor; however, they can be strongly metastatic and are the main cause of cancer deaths among women in many countries worldwide.[2,6] There is increasing evidence that ILC is clinically unique, and that its early diagnosis and prognosis are especially important.

The American Joint Committee on Cancer (AJCC) staging system has been widely used to determine clinical treatment strategies and assess clinical risks. However, there are limitations in using the AJCC staging system alone to predict the prognosis of patients, and the overall outcomes can vary widely for tumors at the same stage. The clinical uniqueness of ILC means that novel prognostic tools are needed to increase the accuracy of predicting the survival of affected patients.[7]

A nomogram is a convenient diagrammatic representation of a mathematical model that combines various important factors to predict a specific endpoint.[8] A nomogram can therefore be an effective visual tool for improving the predictive accuracy of the prognosis in individual patients and for providing individualized prognostic information based on a combination of parameters.[9–11] Nomograms have been found to be helpful for clinicians making decisions and predicting the outcome of an individual, thereby bringing benefits to both clinicians and patients.[12] The aim of this study was to establish a comprehensive prognostic evaluation system for ILC patients and validate its predictive accuracy.

2. Meterials and methods

2.1. Data source

Patient information was collected from the Surveillance, Epidemiology, and End Results (SEER) database, which covers approximately 30% of the population of the USA and includes cases from 18 registries. Informed patient consent is unnecessary when utilizing data from the SEER program that does not include personal identifying information. We searched for ILC patients using the ICD-O-3 (third revision of the International Classification of Diseases for Oncology) histological subtype code 8520/3. We used the sixth edition of the AJCC staging system and restricted our search to between 2010 and 2015.

2.2. Variable selection

The analyzed demographic variables of the patients included age at diagnosis, race, sex, marital status, primary tumor site, histology grade, laterality, AJCC tumor node metastasis (TNM) stage, AJCC T stage, AJCC N stage, AJCC M stage, treatment status (surgery, radiation, and chemotherapy), bone metastasis, and breast cancer subtype.

Age was classified into <40, 40 to 59, 60 to 79, and $\geq$80 years. Race was classified into white, black, and other. Sex was classified into female and male. Marital status was classified into married, unmarried, and unknown. The primary tumor site was classified into the axillary tail, central portion, lower-inner quadrant, lower-outer quadrant, upper-inner quadrant, and upper-outer quadrant of the breast. The histology grade was classified into grades I, II, and III. Laterality was classified into left primary origin, right primary origin, and only 1 side. The AJCC TNM stage was classified into stages II, III and IV. The AJCC T stage was classified into stages T1, T2, T3, and T4. The AJCC N stage was classified into stages N1, N2, and N3. The AJCC M stage was classified into stages M0 and M1. Surgery, radiation, and chemotherapy were classified into receiving and not receiving/unknown. Bone metastasis was classified into yes and no/unknown. The breast cancer subtype was classified into luminal A, luminal B, HER2 enriched, and triple negative. Patients with missing or unknown survival time were excluded.

2.3. Statistical analysis

Continuous variables that conformed to a normal distribution were expressed as mean $\pm$ SD values, while categorical variables were expressed as frequencies and percentages. Multivariate Cox proportional-hazards regression models were applied to determine the factors associated with survival. Based on the predictive model with the identified prognostic factors, a nomogram was constructed for predicting the 3-year and 5-year survival rates of ILC patients.

The nomogram was tested by measuring discrimination and calibration curves in both a training cohort (internally) and a validation cohort (externally). The predictive accuracy of the nomogram was evaluated using the concordance index (C-index) and the area under the time-dependent receiver operating characteristic curve (AUC). The C-index quantified the predictive ability of the model, and ranged from 0.5 to 1.0. Calibration plotting was used to evaluate the agreement between the predicted probabilities and the actual outcomes. Bootstrapping with 500 resamples was used to evaluate both discrimination and calibration. The relative integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) were calculated to estimate the accuracy of the model in predicting outcomes with and without the application of prognostic therapies. Decision-curve analyses (DCAs) were used to assess the clinical value of the predictive models. All statistical analyses were performed using SPSS (version 25.0, SPSS, Chicago, IL) and R software (version 3.6.1), with a 2-sided probability value of $P < .05$ considered to be indicative of statistical significance.

2.4. Ethical review

Because of cancer is a reportable disease in every state of the USA, informed patient consent is not required. Once the data use agreement is signed, data on cancer research is freely available to the public.

3. Results

3.1. Baseline characteristics

There were 4155 eligible ILC patients identified in the SEER database. For nomogram construction and validation, we randomly assigned 70% of the patients to the training cohort

(n=2908) and 30% to the validation cohort (n=1247). The survival period was known for all of the patients included in this study. The largest proportions of the patients were aged 60 to 79 years (49.1% and 49.2% in the training and validation cohorts, respectively), white (83.5% and 83.1%), female (both 99.9%), married (82.6% and 80.0%), and had a primary tumor site in the upper-outer quadrant of the breast (57.2% and 57.3%). Many patients were histology grade II, AJCC TNM stage II, AJCC stage T2, AJCC stage N1, AJCC stage M0, and luminal-A breast cancer subtype. About 94% of patients had undergone surgery. More than half of the patients had received both radiation and chemotherapy. Table 1 lists the clinicopathological characteristics of all of the included patients.

3.2. Multivariate cox regression analysis

Several independent prognostic variables were identified by analyzing the multivariate model. Data on the age at diagnosis, primary tumor site, histology grade, AJCC stage, surgery status, chemotherapy status, and breast cancer subtype were entered into multivariate Cox regression analyses, which demonstrated that AJCC TNM stage III (hazard ratio [HR] = 3.280 vs AJCC TNM stage II, $P < .001$), AJCC TNM stage IV (HR = 12.932 vs AJCC TNM stage II, $P < .001$), no surgery (HR = 2.338, $P < .001$), no chemotherapy (HR = 1.435, $P < .05$), and triple-negative breast cancer subtype were independent risk factors for the survival of ILC patients (Table 2).

3.3. Nomogram construction

The data from the logistic regression model were used to construct a nomogram. Each variable included in the nomogram was assigned a value related to the degree to which it influenced the outcome variable in the model. Each predictive factor was scored according to a set scale. The total summation score (in points) on this nomogram was then converted into the probabilities of 3-year and 5-year survival. The nomogram showed that the AJCC stage was the most important contributor to the prognosis, followed by the breast cancer subtype, surgery status, primary tumor site, age, histology grade, and chemotherapy status (Fig. 1).

3.4. Performance of the nomogram

The C-indexes were higher for the nomogram (0.781 and 0.832 for the cohort and validation cohorts, respectively) than for the AJCC staging system (0.733 and 0.779). For the nomogram, the AUCs of the training cohort (0.793 at 3 years and 0.772 at 5 years) and validation cohort (0.83 and 0.824, respectively) indicated that the model had better discriminative ability than the 6 edition of the AJCC staging system (Fig. 2). Calibration plots of the nomogram showed that the predicted 3-year and 5-year survival probabilities for the training and validation cohorts were almost identical to the actual observations (Fig. 3).

3.5. Validation of the nomogram

The NRI values were 0.202 (95% confidence interval [CI] = 0.119 to 0.332) and 0.117 (95% CI = 0.074–0.278) for 3 years and 5 years of follow-up examinations, respectively, in the training cohort; the corresponding values in the validation cohort were 0.269 (95% CI = 0.110 to 0.446) and 0.180 (95%

Table 1

Patient characteristics in the study.

Variable n (%)	Training cohort (n = 2908)	Validation cohort (n = 1974)
Age		
<40 yr	67 (2.3)	17 (1.4)
40–59 yr	1378 (47.4)	595 (47.7)
60–79 yr	1427 (49.1)	613 (49.2)
≥80 yr	36 (1.2)	22 (1.8)
Race		
White	2429 (83.5)	1036 (83.1)
Black	298 (10.2)	136 (10.9)
Other	181 (6.2)	75 (6.0)
Sex		
Female	2905 (99.9)	1246 (99.9)
Male	3 (.1)	1 (.1)
Marital status		
Married	2403 (82.6)	998 (80.0)
Unmarried	390 (13.4)	196 (15.7)
Unknown	115 (4.0)	53 (4.3)
Site		
Axillary tail of breast	15 (.5)	9 (.7)
Central portion of breast	348 (12.0)	137 (11.0)
Lower-inner quadrant of breast	154 (5.3)	62 (5.0)
Lower-outer quadrant of breast	341 (11.7)	151 (12.1)
Upper-inner quadrant of breast	388 (13.3)	174 (14.0)
Upper-outer quadrant of breast	1662 (57.2)	714 (57.3)
Grade		
I	697 (24.0)	282 (22.6)
II	1886 (64.9)	826 (66.2)
III	325 (11.2)	139 (11.1)
Later		
Left - origin of primary	1468 (50.5)	622 (49.9)
Right - origin of primary	1440 (49.5)	624 (50.0)
Only one side	0 (0)	1 (.1)
AJCC		
II	1418 (48.8)	612 (49.1)
III	1299 (44.7)	551 (44.2)
IV	191 (6.6)	84 (6.7)
T		
T1	730 (25.1)	345 (27.7)
T2	1361 (46.8)	545 (43.7)
T3	716 (24.6)	324 (26.0)
T4	101 (3.5)	33 (2.6)
N		
N1	1903 (65.4)	822 (65.9)
N2	530 (18.2)	233 (18.7)
N3	475 (16.3)	192 (15.4)
M		
M0	2717 (93.4)	1163 (93.3)
M1	191 (6.6)	84 (6.7)
Surgery		
Yes	2742 (94.3)	1174 (94.1)
No/Unknown	166 (5.7)	73 (5.9)
Radiotherapy		
Yes	1679 (57.7)	725 (58.1)
No/Unknown	1229 (42.3)	522 (41.9)
Chemotherapy		
Yes	1978 (68.0)	841 (67.4)
No/Unknown	930 (32.0)	406 (32.6)
Bone		
Yes	153 (5.3)	65 (5.2)
No/Unknown	2755 (94.7)	1182 (94.8)
Subtype		
Luminal A	2703 (93.0)	1154 (92.5)
Luminal B	135 (4.6)	66 (5.3)
HER2 enriched	17 (.6)	8 (.6)
Triple Negative	53 (1.8)	19 (1.5)

AJCC = American Joint Committee on Cancer, Later = laterality.

Selected variables by multivariate Cox regression analysis in the training cohort.

Variable	Multivariate analysis		
	HR	95%CI	*P*-value
Age at diagnosis	0.833	0.675–1.028	.089
Site			
Axillary tail of breast	1.157	0.278–4.811	.810
Central portion of breast Reference			
Lower-inner quadrant of breast	0.536	0.266–1.080	.081
Lower-outer quadrant of breast	0.880	0.551–1.406	.593
Upper-inner quadrant of breast	0.951	0.600–1.510	.834
Upper-outer quadrant of breast	0.851	0.605–1.198	.356
Grade			
I	Reference		
II	1.204	0.894–1.622	.222
III	1.438	0.967–2.137	.073
AJCC			
II	Reference		
III	3.280	2.341–4.596	<.001
IV	12.932	8.495–19.686	<.001
Surgery			
Yes	Reference		
No/Unknown	2.338	1.576–3.469	<.001
Chemotherapy			
Yes	Reference		
No/Unknown	1.435	1.100–1.870	.008
Subtype			
Luminal A	Reference		
Luminal B	0.935	0.548–1.595	.805
HER2 enriched	0.815	0.198–3.345	.776
Triple Negative	4.595	2.876–7.342	<.001

AJCC=American Joint Committee on Cancer, CI=confidence interval, HR=hazard ratio.

CI=−0.024 to 0.345). These values indicate that the nomogram represented a great improvement. Similarly, the IDI values for 3 years and 5 years of follow-up were 0.028 and 0.030 in the training cohort, respectively, and 0.040 and 0.033 in the validation cohort, which indicate that the new model had superior predictive performance.

3.6. Decision-curve analysis

The results of the DCA graphically showed that the new model yielded greater net benefits for the 3-year and 5-year survival than the traditional AJCC staging system, which indicates that the model is clinical useful and can play a useful practical role in decision-making.
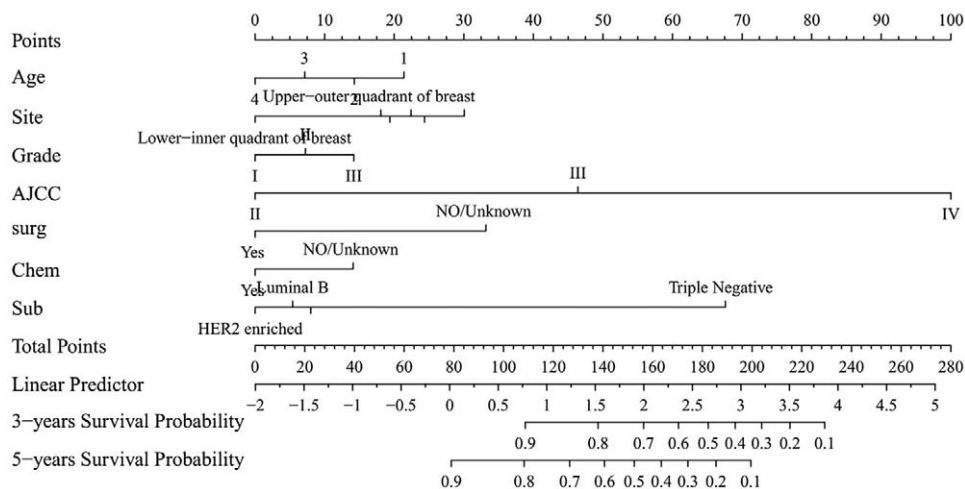

Figure 1. Nomogram predicting 3- and 5-year survival, AJCC=area under the time-dependent receiver operating characteristic curve, Chem=chemotherapy, Sub=breast cancer subtype, surg=surgery.
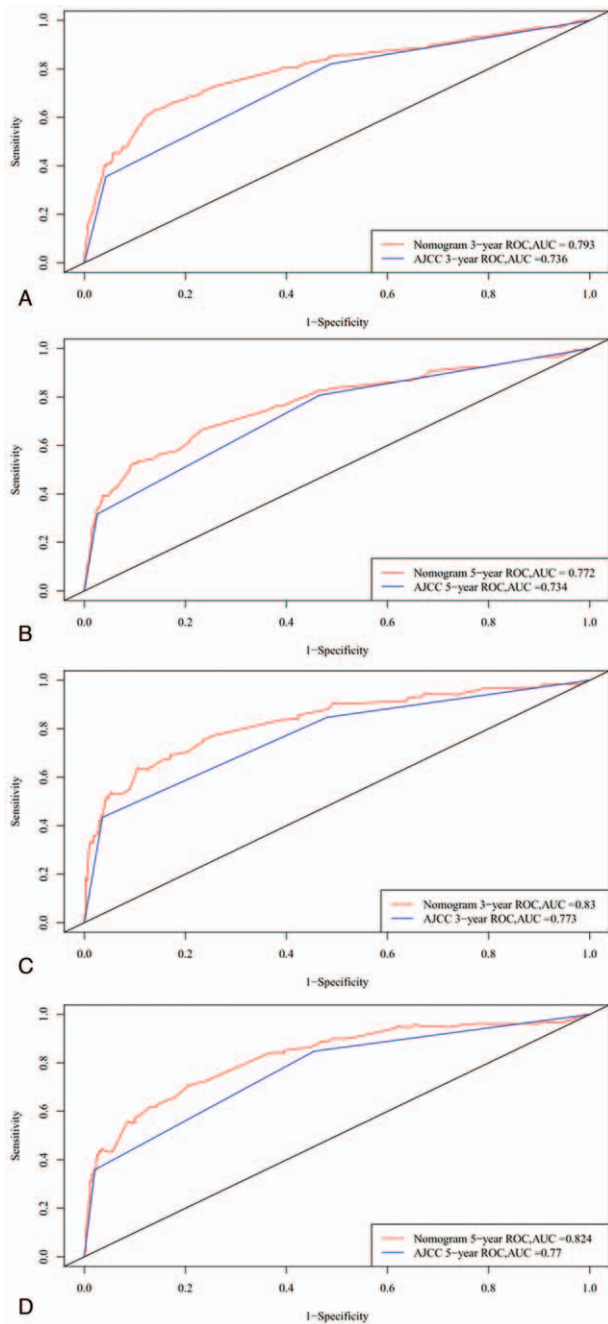
Figure 2. ROC curves. The ability of the model to be measured by the C index. A and B came from the training set, and C and D came from the validation set. ROC = receiver operating characteristic.

Figure 3. Calibration plots. Show the relationship between the predicted probabilities base on the nomogram and actual values of the train set (A and B) and validation set (C and D).

4. Discussion

ILC, which is also known as infiltrating lobular carcinoma, is the second-most-common histological type of breast cancer, and its incidence is increasing.[13] Although ILC is less common than invasive ductal breast cancer (IDC), the proportion of cases with ILC is gradually increasing.[14,15] ILC tumors have a better long-term outlook and tend to be less aggressive than IDC tumors, but they are inclined to metastasize to the genital tracts, the gastrointestinal system, and meninges, and additional more commonly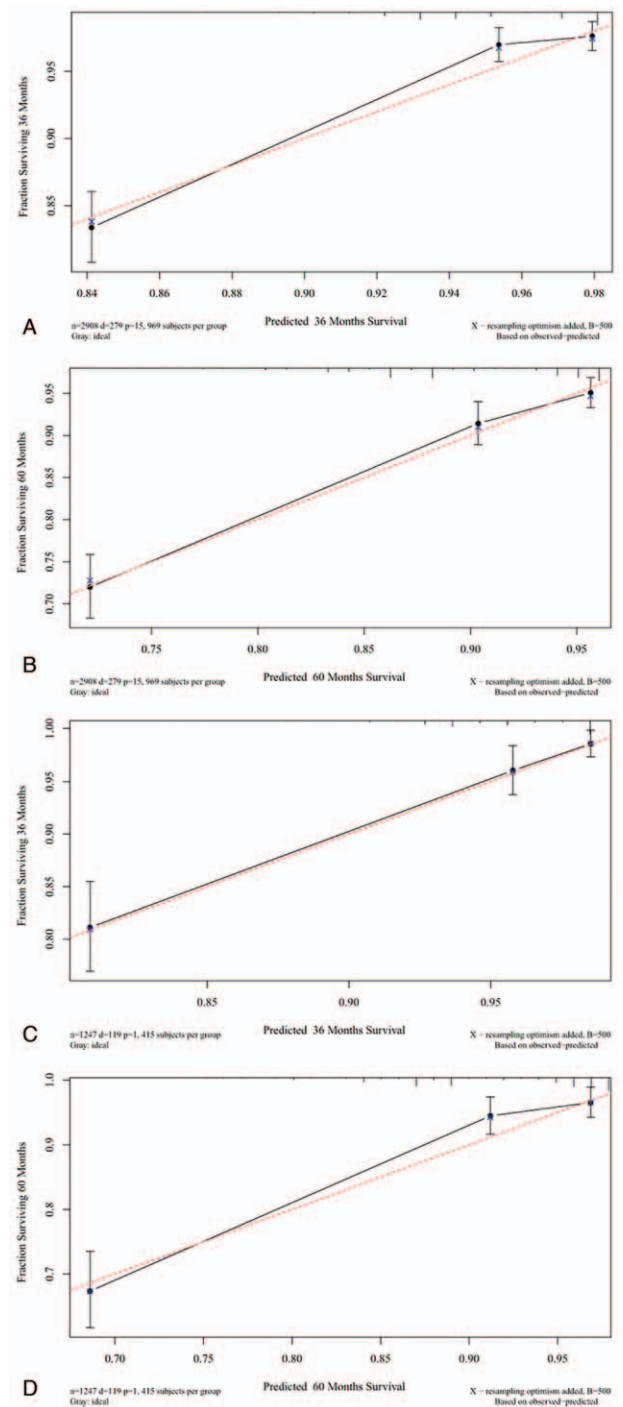 transfer to atypical sites.[16–20] This situation indicates the need for further research into the prognosis of ILC. The early identification of high-risk ILC patients is helpful for providing adjuvant treatment or trials. Although the existing clinical AJCC staging system provides meaningful predictions of the prognosis of ILC patients, it has limitations in estimating the clinical risk of ILC. We have therefore developed a comprehensive predictive model that includes not only the patient demographics but also therapies and other clinical parameters. Our novel model can

provide an independent data set for ensuring fairer model assessments.

This study was based on the large-sample database of the SEER program, which started with 8 registries in 1973 and has continuously increased with the addition of other participating sites over time. Currently the database includes 18 geographically diverse areas representing 30% of the USA population, with efforts made to accurately reflect the racial, economic, and social diversity of the country.[21–23] In order to obtain reliable research results, we identified 4155 patients with ILC from 2010 to 2015 in the SEER database.

Table 1 indicates that most of the patients in our study tended to be older, white, female, and married, had a primary tumor site in the upper-outer quadrant of the breast, and had received treatment with surgery, radiotherapy, and chemotherapy. ILC patients are more likely to have hormone-receptor-positive tumors, which are typically of a lower histology grade, and these results are consistent with previous research findings.[24–27] The results of the multivariate Cox regression presented in Table 2 indicate that surgery and chemotherapy were protective factors. As many studies have shown, selecting surgical treatment for ILC patients is an appropriate and acceptable option and offers superior local control.[28,29] Although ILC often responds poorly or not at all to chemotherapy, there is currently insufficient evidence to support these assumptions.[16,17,30] Moreover, ILC patients exhibit better disease-free survival and overall survival, especially among those at a high risk.[3,31] Similarly, from our nomogram (Fig. 1) it is evident that the prognosis is worse for patients who do not receive chemotherapy, while the probabilities of residual disease and local recurrence decrease after chemotherapy.[32] Although the luminal-B and HER2-enriched breast cancer subtypes accounted for only a small proportion of the tumors in the present study, they exhibited significant responses to chemotherapy.[31,33] Therefore, in view of these objective results, surgery and chemotherapy can be considered to be protective factors for ILC patients.

A nomogram is a graphical representation of a complex statistical formula that includes multiple variables and provides an easy-to-understand answer to a focused question. In this study we developed and validated an easy-to-use nomogram for predicting the 3-year and 5-year survival rates in ILC patients. Our new nomogram model contains a large number of risk factors that are easily collectable from historical records. The nomogram was able to identify a high-risk subgroup of patients who might need intensive therapy. To the best of our knowledge, our nomogram is the first for predicting the 3-year and 5-year survival rates, and we evaluated the performance of the model by using C-indexes, calibration, NRI, IDI, and DCA. This study generated receiver operating characteristic curves to compare the performances of the new nomogram and the traditional AJCC staging system based on AUCs.

The AUC was larger for the nomogram than for the AJCC staging system alone. Our nomogram also showed good discrimination, with C-indexes of 0.781 and 0.832 for the training and validation cohorts, respectively, which are higher than the values for the AJCC staging system. These results indicate that our nomogram model provided a good fit to the randomly allocated training and validation cohorts. To further confirm the good performance of our novel model, we used calibration curves to depict the calibration according to the consistency between the predicted probabilities and observed outcomes. Figure 3 shows that the nomogram predictions were
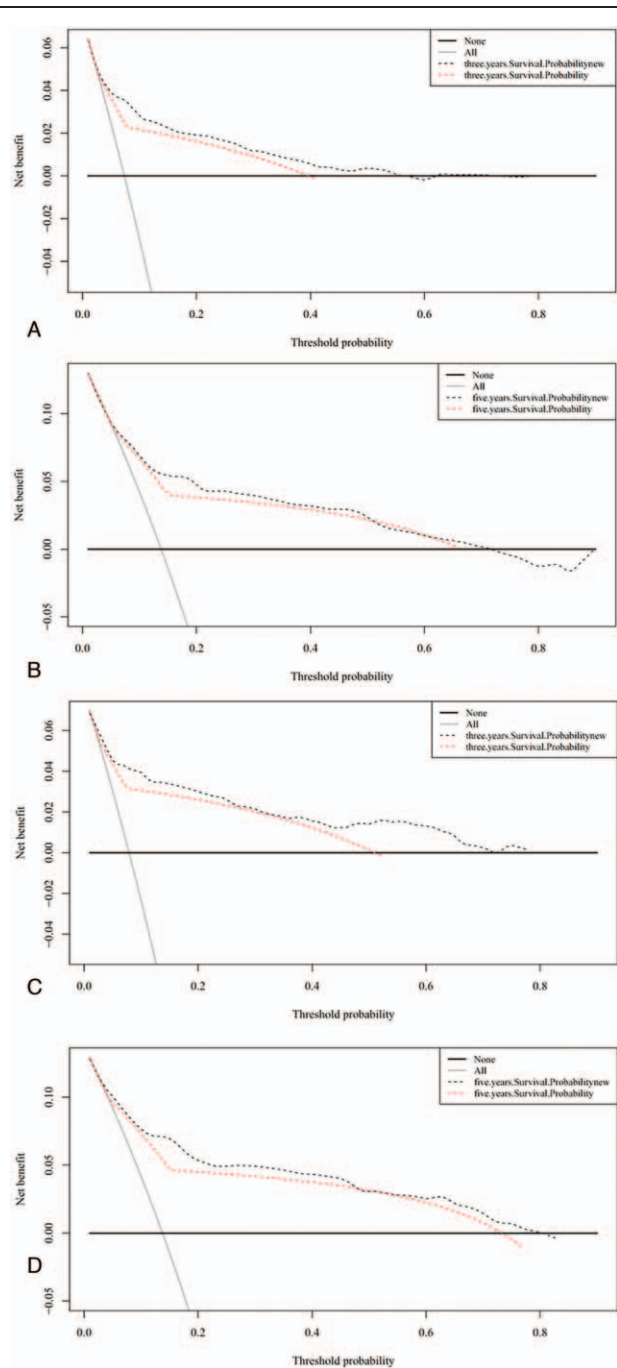

Figure 4. Decision curve analysis. In the figure, the abscissa is the threshold probability, the ordinate is the net benefit rate. The horizontal one indicates that all samples are negative, and all are not treated, with the benefit of 0. The oblique one indicates that all samples are positive. The net benefit is a backslash with a negative slope. A and B came from the training set, C and D came from the validation set.

well calibrated. We also applied IDI and NRI to evaluate the performance of our survival model, with the positive results further demonstrating the superior performance of the nomogram. Figure 4 shows the results of DCAs, with the abscissa corresponding to the threshold probability and the ordinate being the net benefit rate.[34–36] The figure illustrates that the new model yielded net benefits that were superior to those of the traditional

AJCC staging system. These results together demonstrate that our nomogram would provide useful information about the risks and benefits of certain treatment plans, thereby helping clinicians to make good decisions and even provide psychological support.

5. Limitations

This study analyzed a large population from the high-quality SEER database, but the utilization of retrospective data would have introduced unavoidable bias. Second, information was not available for some of the cases, and we only included patients for whom complete information was available, which would have excluded many patients and hence introduced selection bias. Finally, the predicted values calculated by using the nomogram only represent reference information that should be interpreted by clinicians, rather than absolutely accurate prognoses.

6. Conclusion

In summary, nomograms are an important component of modern medical decision-making. We have developed and validated a highly accurate ILC-prognosis nomogram based on the SEER database. Future studies are needed to externally validate the nomogram.

Acknowledgment

Author contributions

Conceptualization: Rong Fu, Jun Lyu.
Data Curation: Jin Yang, ShengPeng Wang, Jun Lyu.
Methodology: Hui Wang, Yuzhi Kang, Li Lin, ShengPeng Wang, Jun Lyu.
Software: Jin Yang, Rahel Elishilia Kaaya, Jun Lyu.
Writing – original draft: Rong Fu.
Writing – review & editing: ShengPeng Wang, Jun Lyu.

References

[1] Chen Z, Yang J, Li S, et al. Invasive lobular carcinoma of the breast: a special histological type compared with invasive ductal carcinoma. PloS One 2017;12:e0182397.

[2] McCart Reed AE, Kutasovic JR, Lakhani SR, et al. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. Breast Cancer Res 2015;17:12.

[3] Thomas M, Kelly ED, Abraham J, et al. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. Semin Oncol 2019;46:121–32.

[4] Sikora MJ, Jankowitz RC, Dabbs DJ, et al. Invasive lobular carcinoma of the breast: patient response to systemic endocrine therapy and hormone response in model systems. Steroids 2013;78:568–75.

[5] Vo TN, Meric-Bernstam F, Yi M, et al. Outcomes of breast-conservation therapy for invasive lobular carcinoma are equivalent to those for invasive ductal carcinoma. Am J Surg 2006;192:552–5.

[6] Zhu MZ, Yu XF, He XM, et al. Clinicopathological features of invasive lobular carcinoma of the breast: a nationwide multicenter study in China. J Cancer Res Ther 2015;11 Suppl 1:C89–94.

[7] Weiss SA, Hanniford D, Hernando E, et al. Revisiting determinants of prognosis in cutaneous melanoma. Cancer 2015;121:4108–23.

[8] Zhang G, Wu Y, Zhang J, et al. Nomograms for predicting long-term overall survival and disease-specific survival of patients with clear cell renal cell carcinoma. Onco Targets Ther 2018;11:5535–44.

[9] Zheng W, Huang Y, Chen H, et al. Nomogram application to predict overall and cancer-specific survival in osteosarcoma. Cancer Manag Res 2018;10:5439–50.

[10] Wen J, Yang Y, Liu P, et al. Development and validation of a nomogram for predicting survival on the base of modified lymph node ratio in breast cancer patients. Breast (Edinburgh, Scotland) 2017;33:14–22.

[11] Huang Z, Sun B, Wu S, et al. A nomogram for predicting survival in patients with breast cancer brain metastasis. Oncol Lett 2018;15:7090–6.

[12] Liu RZ, Zhao ZR, Ng CS. Statistical modelling for thoracic surgery using a nomogram based on logistic regression. J Thorac Dis 2016;8:E731–736.

[13] Lim ST, Yu JH, Park HK, et al. A comparison of the clinical outcomes of patients with invasive lobular carcinoma and invasive ductal carcinoma of the breast according to molecular subtype in a Korean population. World J Surg Oncol 2014;12:56.

[14] Wasif N, Maggard MA, Ko CY, et al. Invasive lobular vs. ductal breast cancer: a stage-matched comparison of outcomes. Ann Surg Oncol 2010;17:1862–9.

[15] Parvaiz MA, Yang P, Razia E, et al. Breast MRI in invasive lobular carcinoma: a useful investigation in surgical planning? Breast J 2016;22:143–50.

[16] Guiu S, Wolfer A, Jacot W, et al. Invasive lobular breast cancer and its variants: how special are they for systemic therapy decisions? Crit Rev Oncol Hematol 2014;92:235–57.

[17] Katz A, Saad ED, Porter P, et al. Primary systemic chemotherapy of invasive lobular carcinoma of the breast. Lancet Oncol 2007;8:55–62.

[18] Jacobs C, Clemons M, Addison C, et al. Issues affecting the loco-regional and systemic management of patients with invasive lobular carcinoma of the breast. Breast J 2016;22:45–53.

[19] Fu D, Zuo Q, Huang Q, et al. Molecular classification of lobular carcinoma of the breast. Scientific Rep 2017;7:43265.

[20] El-Hage A, Ruel C, Afif W, et al. Metastatic pattern of invasive lobular carcinoma of the breast-Emphasis on gastric metastases. J Surg Oncol 2016;114:543–7.

[21] Shen K, Yao L, Wei J, et al. Worse characteristics can predict survival effectively in bilateral primary breast cancer: A competing risk nomogram using the SEER database. Cancer Med 2019;8:7890–902.

[22] Wu J, Sun H, Li J, et al. Increased survival of patients aged 0-29 years with osteosarcoma: A period analysis, 1984-2013. Cancer Med 2018;7:3652–61.

[23] Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 2009;115:1531–43.

[24] Cristofanilli M, Gonzalez-Angulo A, Sneige N, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 2005;23:41–8.

[25] Pestalozzi BC, Zahrieh D, Mallon E, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol 2008;26:3006–14.

[26] Ishikawa MK, Pinsky RW, Smith LB, et al. Morphologic mimics of invasive lobular carcinoma. Arch Pathol Lab Med 2015;139:1253–7.

[27] Inoue M, Nakagomi H, Nakada H, et al. Specific sites of metastases in invasive lobular carcinoma: a retrospective cohort study of metastatic breast cancer. Breast cancer (Tokyo, Japan) 2017;24:667–72.

[28] Sharma SD, Barry M, O'Reilly EA, et al. Surgical management of lobular carcinoma from a national screening program: a retrospective analysis. Eur J Surg Oncol 2015;41:79–85.

[29] Anwar IF, Down SK, Rizvi S, et al. Invasive lobular carcinoma of the breast: should this be regarded as a chronic disease? Int J Surg 2010;8:346–52.

[30] Riba LA, Russell T, Alapati A, et al. Characterizing response to neoadjuvant chemotherapy in invasive lobular breast carcinoma. J Surg Res 2019;233:436–43.

[31] de Nonneville A, Jauffret C, Goncalves A, et al. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit. Breast Cancer Res Treat 2019;175:379–87.

[32] Wagner J, Boughey JC, Garrett B, et al. Margin assessment after neoadjuvant chemotherapy in invasive lobular cancer. Am J Surg 2009;198:387–91.

[33] Tsai M, Finkelstein M, Lillemoe T, et al. Pathologic predictors of treatment response to neo-adjuvant chemotherapy for invasive lobular breast carcinoma. Breast J 2017;23:607–9.

[34] Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. Thromb Haemost 2017;117:1848–58.

[35] Garcia-Fernandez A, Roldan V, Rivera-Caravaca JM, et al. Does von Willebrand factor improve the predictive ability of current risk stratification scores in patients with atrial fibrillation? Sci Rep 2017; 7:41565.

[36] Rodrigues G, Gonzalez-Maldonado S, Bauman G, et al. A statistical comparison of prognostic index systems for brain metastases after stereotactic radiosurgery or fractionated stereotactic radiation therapy. Clin Oncol 2013;25:227–35.