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A Nomogram Using Imaging Features to Predict Ipsilateral Breast Tumor Recurrence After Breast-Conserving Surgery for Ductal Carcinoma In Situ

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Objective: To develop a nomogram that integrates clinical-pathologic and imaging variables to predict ipsilateral breast tumor recurrence (IBTR) in women with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery (BCS).
Materials and Methods: This retrospective study included consecutive women with DCIS who underwent BCS at two hospitals. Patients who underwent BCS between 2003 and 2016 in one hospital and between 2005 and 2013 in another were classified into development and validation cohorts, respectively. Twelve clinical-pathologic variables (age, family history, initial presentation, nuclear grade, necrosis, margin width, number of excisions, DCIS size, estrogen receptor, progesterone receptor, radiation therapy, and endocrine therapy) and six mammography and ultrasound variables (breast density, detection modality, mammography and ultrasound patterns, morphology and distribution of calcifications) were analyzed. A nomogram for predicting 10-year IBTR probabilities was constructed using the variables associated with IBTR identified from the Cox proportional hazard regression analysis in the development cohort. The performance of the developed nomogram was evaluated in the external validation cohort using a calibration plot and 10-year area under the receiver operating characteristic curve (AUROC) and compared with the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram.
Results: The development cohort included 702 women (median age [interquartile range], 50 [44–56] years), of whom 30 (4%) women experienced IBTR. The validation cohort included 182 women (48 [43–54] years), 18 (10%) of whom developed IBTR. A nomogram was constructed using three clinical-pathologic variables (age, margin, and use of adjuvant radiation therapy) and two mammographic variables (breast density and calcification morphology). The nomogram was appropriately calibrated and demonstrated a comparable 10-year AUROC to the MSKCC nomogram (0.73 vs. 0.66, $P = 0.534$) in the validation cohort.
Conclusion: Our nomogram provided individualized risk estimates for women with DCIS treated with BCS, demonstrating a discriminative ability comparable to that of the MSKCC nomogram.
Keywords: Ductal carcinoma in situ; Ipsilateral breast tumor recurrence; Nomogram; Mammography; Breast density

INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast is a non-invasive clonal proliferation of malignant epithelial cells, being increasingly diagnosed owing to organized mammography screening [1,2]. Mortality due to DCIS is rare [3]; however, ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) is relatively

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common, with 10-year incidence rates of 10%–15% [4,5]. DCIS with IBTR may indicate a more aggressive subtype than nonrecurrent DCIS. Understanding this information could be valuable in guiding the management of DCIS, in the context of surveillance trials for low-risk DCIS [6].

Multiple risk prediction models using clinical-pathologic information have been developed to evaluate the risk of IBTR after BCS [4,7,8]. The Van Nuys Prognostic Index (VNPI) [7], Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram [4], and Oncotype DX DCIS score [8] are the main models used in this field. The VNPI uses five clinical-pathologic variables: age, tumor size, margin width, nuclear grade, and necrosis [7]. The MSKCC nomogram uses ten clinical-pathologic variables: age, family history, initial presentation, adjuvant radiation therapy, adjuvant endocrine therapy, nuclear grade, necrosis, margin, number of excisions, and year of surgery [4]. The Oncotype DX score evaluates the risk of IBTR using 12 genes (seven cancer-related genes and five reference genes) and stratifies patients into three-risk groups [8]. These risk prediction models have been revised using updated data [9,10] and validated using external datasets [5,11-13]. However, pathological information may be limited owing to the heterogeneity of DCIS, varying reporting strategies between centers, and substantial interobserver variability [14,15]. Neither the VNPI nor the MSKCC nomogram has gained widespread acceptance [16].

Most DCIS lesions are detected through screening mammography, with some detected via supplemental ultrasound (US) or magnetic resonance imaging (MRI), or due to breast symptoms such as a lump or nipple discharge. While contrast-enhanced MRI can provide detailed information on the extent and characteristics of DCIS lesions, these lesions are typically already visible on mammography or US [17]. Basic mammography and US characteristics, such as morphological and distribution patterns of calcifications, presence or absence of masses, and breast density, may provide prognostic information. However, research on risk prediction models combining imaging features with clinical-pathologic information is limited [18].

Therefore, this study aimed to develop a nomogram that integrates clinical-pathologic and imaging variables to predict IBTR in women with DCIS treated with BCS.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Boards of Seoul National University Hospital (IRB No. 2206-093-1332) and the National Cancer Center (IRB No. NCC2023-0291). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Patient Selection

Consecutive women with a final diagnosis of DCIS who underwent BCS were identified from the breast cancer registries of the two hospitals. Women who underwent BCS between 2003 and 2016 at Seoul National University Hospital were classified into the development cohort, while those who underwent BCS between 2005 and 2013 at the National Cancer Center were classified into the validation cohort. The exclusion criteria were the unavailability of mammography and US at diagnosis (because patients were not brought in for their initial examinations after undergoing excision or biopsy at other hospitals), synchronous bilateral breast cancer, and an imaging follow-up period of less than 2 years after surgery.

Data Collection

The following clinical-pathologic data were obtained from the electronic medical records. The clinical data included age, family history, and initial presentation. Pathological data obtained from the surgical specimens included nuclear grade, comedo necrosis, number of excisions, margin, size of DCIS, and estrogen receptor (ER) and progesterone receptor (PR) statuses. All included patients had complete clinical-pathologic information required for this study. Detailed classification of the clinical-pathologic data is provided in the Supplementary Methods–data collection.

Imaging Protocol and Analysis

Preoperative mammography and US were routinely performed at both hospitals, whereas MRI was not. Information regarding the imaging machines is provided in the Supplementary Methods–imaging protocol and analysis.

In the development cohort, mammography and US images were retrospectively reviewed by a breast radiologist (S.Y.K.) with 10 years of experience who was blinded to the clinical information, based on the fifth edition of the Breast Imaging Reporting and Data System (BI-RADS) lexicon [19]. BI-RADS density was graded as a (almost entirely fatty), b (scattered areas of fibroglandular density), c (heterogeneously dense), and d (extremely dense) and then dichotomized into non-extremely dense (a-c) and extremely dense (d). The detection modality was dichotomized into mammography or

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US detection. DCIS lesions visible on both mammography and US were categorized as detected on mammography, whereas DCIS lesions visible only on US were categorized as detected on US. Mammography patterns were classified as negative (non-visualization), mass (with or without calcifications), calcification, or other (e.g., asymmetry or architectural distortion without calcifications). Calcification morphology was defined as amorphous, coarse heterogeneous, fine pleomorphic, or fine linear branching. Calcification distribution was defined as diffuse/regional, grouped, or linear/segmental. US patterns were classified as negative (non-visualization), mass (with or without calcifications), or non-mass (hypoechoic area or ductal abnormality without a definite mass, with or without calcifications) [20,21].

Quantitative mammographic breast density was evaluated using an open-access software in the development cohort [22]. Detailed information regarding this evaluation is provided in the Supplementary Methods–imaging protocol and analysis.

Interobserver variability was assessed for the two imaging variables (breast density and calcification morphology) included in the nomogram. To achieve this, a breast radiologist (N.C.) with 21 years of experience independently reviewed the imaging findings for all patients in the development cohort.

In the validation cohort, breast density and calcification morphology were independently reviewed by a breast radiologist (B.H.C.) with 9 years of experience who was blinded to the clinical information.

Adjuvant Treatment

Adjuvant treatment strategies were consistent across hospitals. Adjuvant radiation therapy was recommended for patients with DCIS treated with BCS. However, some patients with a small DCIS size, low nuclear grade, wide margin width, old age, and comorbidities chose to omit radiation therapy after consultation with radiation oncologists. Adjuvant endocrine therapy (tamoxifen or an aromatase inhibitor for 5 years) was recommended for patients with ER-positive DCIS.

Imaging Surveillance After Surgery

Details regarding routine imaging surveillance methods are provided in the Supplementary Methods–imaging surveillance after surgery. Briefly, Seoul National University Hospital conducted mammography, US, and MRI, whereas the National Cancer Center conducted mammography and US.

Statistical Analysis

IBTR was defined as the occurrence of invasive cancer or DCIS in the treated breast tissue. Time to IBTR was defined as the interval between the final surgery and IBTR diagnosis. Patients who did not develop IBTR were censored on their last follow-up imaging date. The distribution of quantitative breast density according to the BI-RADS lexicon was compared using the Kruskal–Wallis test. Univariable and multivariable Cox proportional hazard regression analyses were performed to identify the variables associated with IBTR in the development cohort. Univariable analysis was performed first, and variables with *P*-values of less than 0.1 were selected for inclusion in the multivariable analysis. This threshold was selected to ensure that potentially important variables were not excluded at an early stage. Subsequently, these selected variables were included in the multivariable analysis using the "Enter" method. Variables with *P*-values of less than 0.05 in the multivariable analysis were considered statistically significant and were included in the final model used to construct the nomogram. Inter-observer agreement was evaluated using kappa as follows: <0, poor; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect [23].

A nomogram for predicting the 10-year probability of IBTR was constructed using variables independently associated with IBTR in the multivariable Cox proportional hazard regression analysis. Nomogram performance was evaluated using a calibration plot and the time-dependent area under the receiver operating characteristic curve (AUROC) for 10-year. To avoid overfitting, internal validation was performed using the bootstrapping method with 1000 re-samples, yielding an optimism-corrected 10-year AUROC and optimism-corrected calibration plot. The optimal cutoff value for stratifying the low- and high-risk groups was determined using the minimum *P*-value approach in the development cohort and then applied unchanged to the validation cohort [24].

In the validation cohort, the nomogram was evaluated using the 10-year AUROC and calibration curve. To evaluate the MSKCC nomogram, all variables included in it were collected, and the total points of the nomogram were calculated for each patient [4]. To compare the 10-year AUROC of the two nomograms, standard errors were calculated using the Inverse Probability of Censoring Weighting method, and the *P*-value was determined using the Z-test. Finally, to evaluate whether the performance of the nomogram differed according to the use of preoperative MRI, the 10-year AUROC was compared between the two

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Table 1. Characteristics of the development and validation cohorts

Characteristics	Development cohort (n = 702)	Validation cohort (n = 182)	*P*
Age, yr	50 (44, 56)	48 (43, 54)	0.052
Age, yrs			0.504
<40	80 (11)	24 (13)	
≥40	622 (89)	158 (87)	
Menopausal status			0.003
Pre	414 (59)	129 (71)	
Post	288 (41)	53 (29)	
Family history			0.221
Absent	622 (89)	167 (92)	
Present	80 (11)	15 (8)	
Initial presentation			<0.001
Screening	604 (86)	59 (32)	
Clinical	98 (14)	123 (68)	
Nuclear grade			<0.001
Low or intermediate	375 (53)	126 (69)	
High	327 (47)	56 (31)	
Comedo necrosis			0.360
No	359 (51)	100 (55)	
Yes	343 (49)	82 (45)	
Number of excisions			<0.001
One	532 (76)	166 (91)	
Multiple	170 (24)	16 (9)	
Margin			<0.001
Negative	637 (91)	125 (69)	
Close or positive	65 (9)	57 (31)	
DCIS size, cm	2.0 (1.0, 3.2)	2.2 (1.0, 3.0)	0.202
ER status			0.077
Negative	158 (22)	30 (17)	
Positive	544 (78)	152 (83)	
PR status			0.065
Negative	219 (31)	44 (24)	
Positive	483 (69)	138 (76)	
Adjuvant endocrine therapy*			0.878
No	56 (10)	15 (10)	
Yes	488 (90)	137 (90)	
Adjuvant radiation therapy			<0.001
No	63 (9)	51 (28)	
Yes	639 (91)	131 (72)	
BI-RADS density			<0.001
a	5 (1)	0 (0)	
b	71 (10)	24 (13)	
c	281 (40)	102 (56)	
d	345 (49)	56 (31)	
Breast density by LIBRA, %	32.2 (18.0, 45.2)	NA	NA
Detection mode		NA	NA
Mammography	506 (72)		
US	196 (28)		
Mammography pattern		NA	NA
Negative	196 (28)		
Others	39 (5)		
Calcifications	322 (46)		
Mass	145 (21)		
Morphology of calcifications			0.008
Absent	288 (41)	74 (41)	
Amorphous	193 (27)	37 (20)	
Coarse heterogeneous	28 (4)	4 (2)	
Fine pleomorphic	152 (22)	44 (24)	
Fine linear branching	41 (6)	23 (13)	
Distribution of calcifications		NA	NA
Absent	288 (41)		
Regional	1 (1)		
Grouped	285 (40)		
Linear or segmental	128 (18)		
Ultrasound pattern		NA	NA
Negative	127 (18)		
Mass	437 (62)		
Non-mass lesion	138 (20)		

For continuous variables, data are medians with interquartile ranges in parentheses. For categorical variables, data are number of women with percentages in parentheses.
*Proportion among estrogen receptor-positive DCIS.
DCIS = ductal carcinoma in situ, ER = estrogen receptor, PR = progesterone receptor, BI-RADS = Breast Imaging Reporting and Data System, LIBRA = laboratory for individualized breast radiodensity assessment, NA = not analyzed, US = ultrasound

groups with and without MRI in each cohort. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and SPSS (version 29.0; IBM, Armonk, NY, USA), aided by a statistician (S.K.) with 14 years of experience. A *P*-value of less than 0.05 indicated statistical significance.

RESULTS

Patients

Patient characteristics in the development and validation cohorts are presented in Table 1. There were no recorded cases of death or ipsilateral completion mastectomy according to the electronic medical records of either cohort.

Development Cohort

At the Seoul National University Hospital, 986 women

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were diagnosed with DCIS after undergoing BCS between 2003 and 2016. Of these, 284 women were excluded because of the unavailability of mammography or US (n = 201), bilateral breast cancer (n = 53), or a follow-up period of less than 2 years after surgery (n = 30) (Fig. 1A). Accordingly, 702 women (median [interquartile range (IQR)] age, 50 [44–56] years) were included in the development cohort. During a median follow-up of 7.8 [5.6–10.5] years, 30 (4%) women experienced IBTR; among them, 15 women had DCIS recurrence and the other 15 women had invasive recurrence. In total, 27% (8/30) of the recurrences were detected based on symptoms, and 73% (22/30) were detected on surveillance imaging.

Validation Cohort

In the National Cancer Center, 234 women were diagnosed with DCIS after undergoing BCS between 2005 and 2013. Of these, 52 women were excluded because of unavailable mammography (n = 26), bilateral breast cancer (n = 10), or a follow-up period of less than 2 years after surgery (n = 16) (Fig. 1B). Accordingly, 182 women (median [IQR] age, 48 [43–54] years) were included in the validation cohort. During a median follow-up of 8.2 [IQR, 5.9–10.2] years, 18 (10%) women experienced IBTR; among them, 5 and 13 women had DCIS and invasive recurrences, respectively. Overall, 22% (4/18) of the recurrences were detected based on symptoms and 78% (14/18) on surveillance imaging.

Nomogram Development

Variables with *P*-values less than 0.1 in the univariable Cox proportional regression analysis were age <40 years, close or positive margins, size of DCIS on surgical specimen,

Table 2. Multivariable analysis for predictors of ipsilateral breast tumor recurrence in the development cohort

Characteristics	Hazard ratio	95% CI	*P*
Age, yrs			
<40	2.8	1.2–6.6	0.011*
≥40	Ref		
Margin			
Negative	Ref		
Close or positive	4.1	1.8–9.6	0.001*
DCIS size, cm	1.1	0.9–1.3	0.427
Adjuvant endocrine therapy			
No	1.8	0.8–3.9	0.126
Yes	Ref		
Adjuvant radiation therapy			
No	2.9	1.1–7.6	0.038*
Yes	Ref		
BI-RADS density			
a-c	Ref		
d	2.7	1.1–6.4	0.037*
Morphology of calcifications			
Absent	Ref		
Amorphous	0.1	0.02–0.9	0.047*
Coarse heterogeneous	0.9	0.1–7.3	0.948
Fine pleomorphic	1.1	0.4–2.8	0.846
Fine linear branching	3.5	1.02–12.3	0.046*
Ultrasound pattern			
Negative	Ref		
Mass	3.3	0.4–26.9	0.263
Non-mass lesion	2.4	0.3–21.3	0.437

The variables selected in the univariable analysis (Supplementary Table 1) were all included in the multivariable analysis. Statistically significant variables with *P*-values of less than 0.05 in the multivariable analysis (indicated by * markings for *P*-values) were used to construct the nomogram.
CI = confidence interval, Ref = reference, DCIS = ductal carcinoma in situ, BI-RADS = Breast Imaging Reporting and Data System

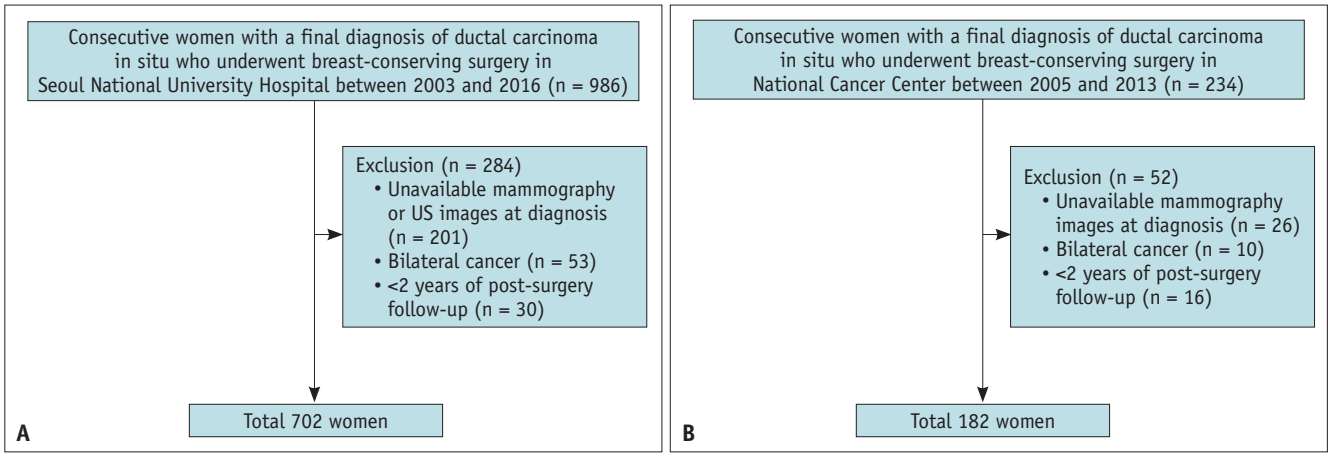

Fig. 1. Study flowchart. **A:** Development cohort. **B:** Validation cohort.

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omission of adjuvant endocrine or radiation therapy, extremely dense breast tissue on mammography, amorphous or fine linear branching calcifications on mammography, and mass on US (Supplementary Table 1). The quantitative breast density showed a significant difference across BI-RADS densities; the median quantitative densities were 1.6%, 10.7%, 23.5%, and 42.9% for BI-RADS density grades a, b, c, and d, respectively (P < 0.001, Supplementary Fig. 1). However, quantitative density was not significantly associated with IBTR (P = 0.172, Supplementary Table 1).

In the subsequent multivariable Cox proportional hazard regression analysis (Table 2), age <40 years (hazard ratio [HR], 2.8; 95% confidence interval [CI]: 1.2, 6.6; P = 0.011), close or positive margins (HR, 4.1; 95% CI: 1.8, 9.6; P = 0.001), omission of adjuvant radiation therapy (HR, 2.9; 95% CI: 1.1, 7.6; P = 0.038), and extremely dense breast tissue (HR, 2.7; 95% CI: 1.1, 6.4; P = 0.037) were independently associated with a higher risk of IBTR. Compared to the absence of calcifications, amorphous calcifications were associated with a lower risk of IBTR (HR, 0.1; 95% CI: 0.02, 0.9; P = 0.047). Meanwhile, fine linear branching calcifications were associated with a higher risk of IBTR (HR, 3.5; 95% CI: 1.02, 12.3; P = 0.046). The Kappa value was 0.70 (95% CI: 0.65, 0.75) for breast density and 0.67 (95% CI: 0.52, 0.82) for calcification morphology, indicating substantial inter-observer agreement.

The developed nomogram is shown in Figure 2. Details of the formula used to calculate the 10-year probability of IBTR are provided in the Supplementary Results–nomogram development. The nomogram was well-calibrated (Fig. 3A) and showed an optimism-corrected 10-year AUROC of 0.79 (95% CI: 0.72, 0.87). With the cutoff value set at 100 points, the low- and high-risk groups were stratified on the Kaplan–Meier curve (P < 0.001, Supplementary Fig. 2A).

External Validation of the Nomogram

In the external validation cohort, our nomogram was appropriately calibrated (Fig. 3B) and showed a comparable 10-year AUROC to the MSKCC nomogram (0.73 [95% CI: 0.57, 0.90] for our nomogram vs. 0.66 [95% CI: 0.44, 0.89] for

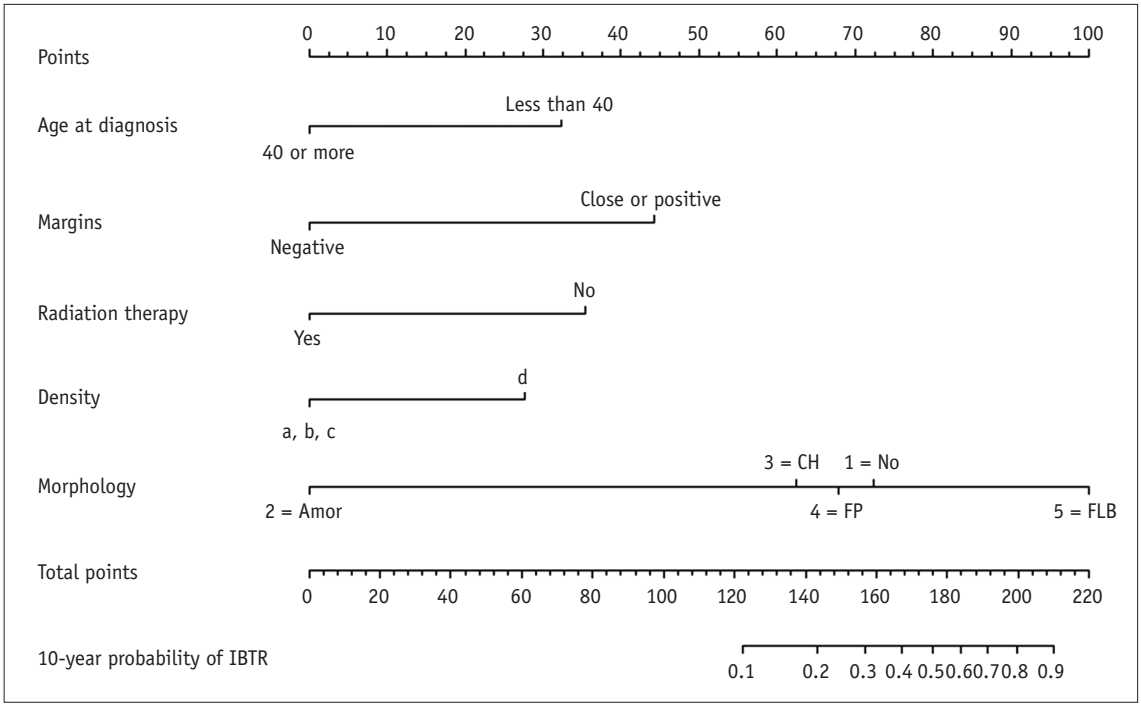

Fig. 2. Nomogram for predicting the 10-year probability of IBTR-free survival after breast-conserving surgery for ductal carcinoma in situ. To estimate risk, a straight line is drawn from each variable to the axis labeled "Points." Age <40 years = 32 points; age ≥40 years = 0 points. Close or positive resection margins = 44 points; clear margins = 0 points. Omission of radiation therapy = 35 points; performance of radiation therapy = 0 points. Extremely dense breast tissue (d) = 28 points; other breast density categories (a-c) = 0 points. Amor, CH, FP, and FLB calcifications = 0, 63, 68, and 100 points, respectively; absence of calcifications (No) = 72 points. The total points are summed, and a straight line from the "Total Points" axis to the "10-year probability of IBTR" axis is drawn. The low-risk group was defined as having 100 points or less, whereas the high-risk group was defined as having more than 100 points. IBTR = ipsilateral breast tumor recurrence, Amor = amorphous, CH = coarse heterogeneous, FP = fine pleomorphic, FLB = fine linear branching

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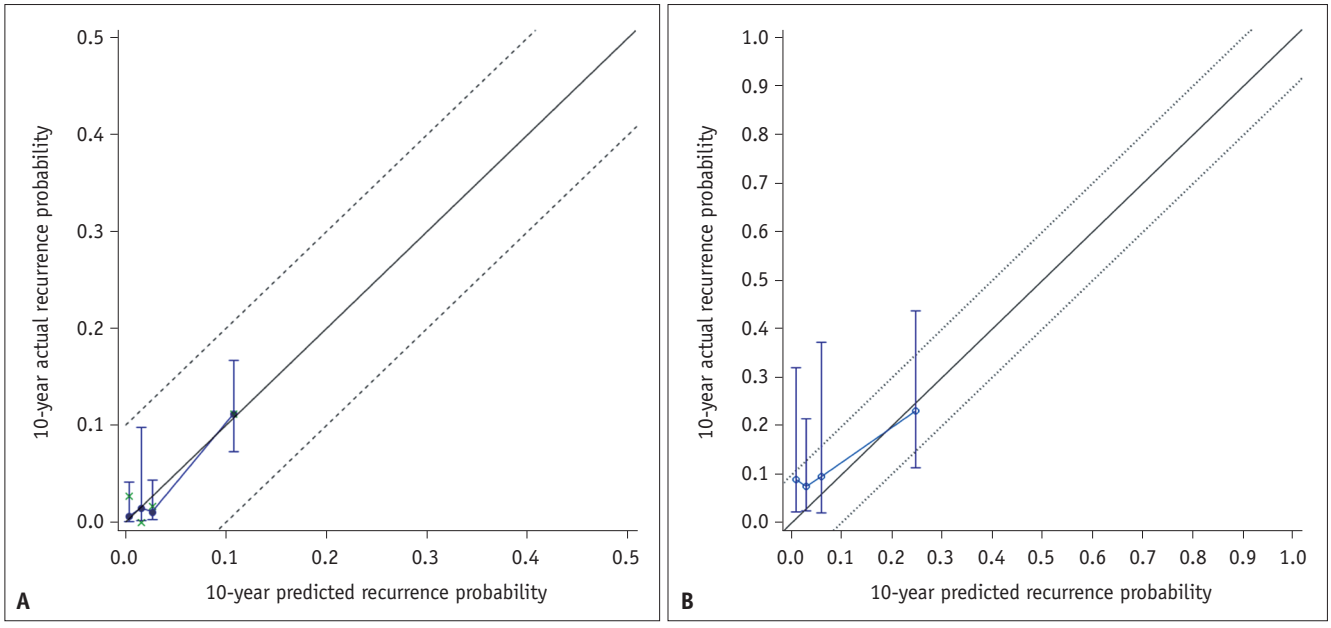

Fig. 3. A calibration plot of the nomogram. **A:** Development cohort. **B:** Validation cohort. The X-axis indicates the 10-year probability of IBTR predicted by the nomogram, and the Y-axis indicates the actual 10-year probability of IBTR observed in our study. The four blue dots represent the fourths of the cohort divided based on the predicted probability. Each blue dot shows the average predicted probability and average actual probability within the group. The upper and lower bars indicate 95% confidence intervals. The solid black line at 45° indicates the perfect calibration line. The two dashed black lines indicate ±10% intervals from the perfect calibration line. The blue line connecting the four blue dots is close to the perfect calibration line, suggesting that the calculated probability by the nomogram corresponds well with the actual probability. Green x markings in the development cohort **(A)** indicate the optimism-corrected values through the internal validation and are located slightly farther from the perfect calibration line than the uncorrected values (blue dots). IBTR = ipsilateral breast tumor recurrence

the MSKCC nomogram, $P = 0.534$). The Kaplan–Meier curve did not reveal significant stratification between the low-risk (≤100 points) and high-risk (>100 points) groups ($P = 0.213$, Supplementary Fig. 2B). In both cohorts, the 10-year AUROC of our nomogram did not differ significantly with or without preoperative MRI (Supplementary Results–the impact of preoperative MRI on the nomogram performance). Figures 4-6 illustrate the practical application of the nomogram.

DISCUSSION

A reliable prediction model for patients with DCIS treated with BCS is crucial in individualizing treatment and reducing overtreatment. We developed a nomogram that combines clinical-pathologic and mammographic variables to predict the 10-year probability of IBTR. In the external validation cohort, our nomogram, which used three clinical-pathologic (age, margin, and use of adjuvant radiation therapy) and two mammography (density and calcification morphology) variables, showed a discrimination performance comparable to that of the MSKCC nomogram, which uses ten clinical-pathologic variables. Thus, our simpler nomogram may be more practical.

Extremely dense breast tissue on mammography was significantly associated with IBTR. This correlation may be attributed to the incomplete resection of multifocal or multicentric DCIS, possibly due to the masking effect of dense breasts [25]. Furthermore, extremely dense breast tissue is an independent risk factor for breast cancer [26]. Similarly, previous studies have highlighted the association between extremely dense breast tissue and IBTR among patients with DCIS [25,27]. For example, in a study of 504 women with DCIS from the National Surgical Adjuvant Breast and Bowel Project B-17 trial, Habel et al. [25] found that women with extremely dense breast tissue had a 3.0 times higher risk of IBTR than those with fatty breasts. In a single-institution retrospective study of 1657 women with DCIS, Rauch et al. [27] found that extremely dense breast tissue was associated with positive margins, multicentricity, and an increased risk of IBTR.

In our development cohort, amorphous calcifications were associated with a lower risk of IBTR, whereas fine linear branching calcifications were associated with a higher risk, which is consistent with previous studies [27-29]. For

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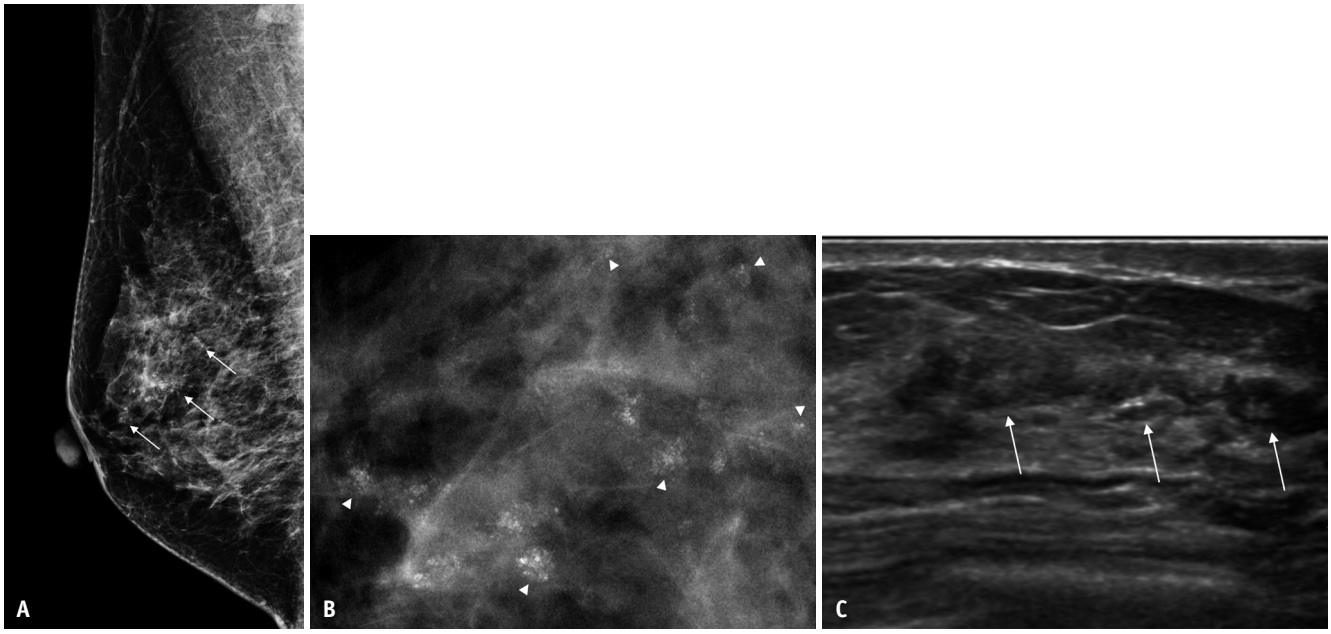

Fig. 4. A 66-year-old woman with DCIS was classified into the low-risk group and experienced no recurrence. **A:** Mediolateral oblique mammogram showing a heterogeneously dense breast, with biopsy-proven DCIS presenting as calcifications (arrows) in the right upper center breast. **B:** Magnified view showing amorphous calcifications (arrowheads). **C:** Ultrasound image showing an ill-defined hypoechoic non-mass lesion (arrows) with calcifications. The patient underwent breast-conserving surgery, adjuvant radiation therapy, and endocrine therapy. The DCIS measured 2.5 cm, was estrogen receptor positive, and had a negative resection margin on the surgical specimen. The total points on the nomogram were 0, indicating the low-risk group. No recurrence developed during follow-up for more than 10 years after the surgery. DCIS = ductal carcinoma in situ

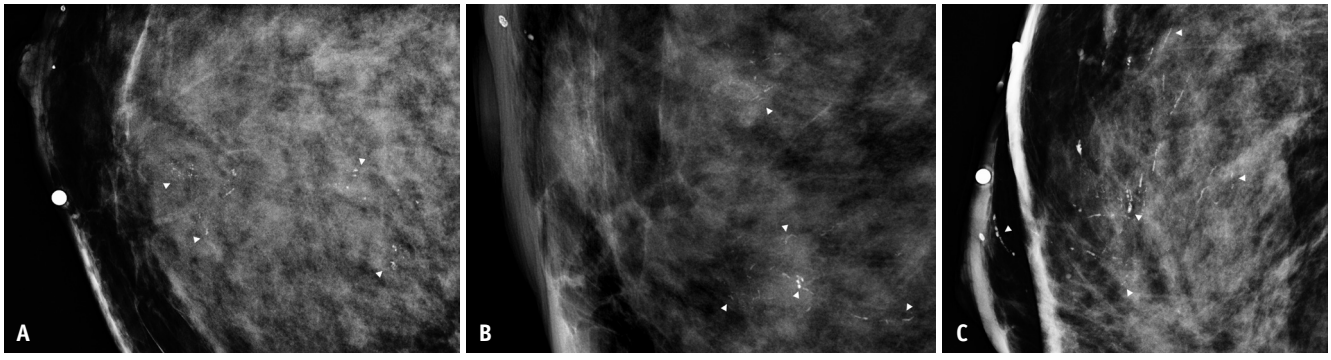

Fig. 5. A 42-year-old woman with DCIS was classified into the high-risk group and experienced IBTR twice. **A:** Initial magnified view showing an extremely dense breast with segmental fine pleomorphic calcifications (arrowheads) in the right upper inner breast with biopsy-confirmed DCIS. The patient underwent breast-conserving surgery and adjuvant radiation therapy. The DCIS measured 8.5 cm, was estrogen receptor negative, and had a close nipple margin on the surgical specimen. The total points on the nomogram were 140, with 44 points for the margin, 28 points for density, and 68 points for fine pleomorphic calcifications, indicating the high-risk group. **B:** Magnified view 2 years after surgery showing new fine linear branching calcifications (arrowheads) in the right upper inner and subareolar breast. Stereotactic biopsy confirmed DCIS recurrence, and wide excision was performed. The surgical specimen revealed an estrogen receptor-negative DCIS measuring 2.5 cm with clear margins. **C:** Magnified view 4 years after the second surgery showing new fine linear branching calcifications (arrowheads) in the right central breast. Ultrasound-guided vacuum-assisted biopsy confirmed DCIS recurrence, and mastectomy was performed. DCIS = ductal carcinoma in situ, IBTR = ipsilateral breast tumor recurrence

instance, in a study involving 58 women with DCIS, amorphous calcifications exhibited the lowest Oncotype DX scores, whereas fine linear branching calcifications showed the highest scores [28]. Other studies have also correlated fine linear branching calcifications with high nuclear grade, comedo necrosis, and increased risk of IBTR [27,29].

In ongoing active surveillance trials for DCIS, patients who satisfy certain selection criteria do not undergo surgery

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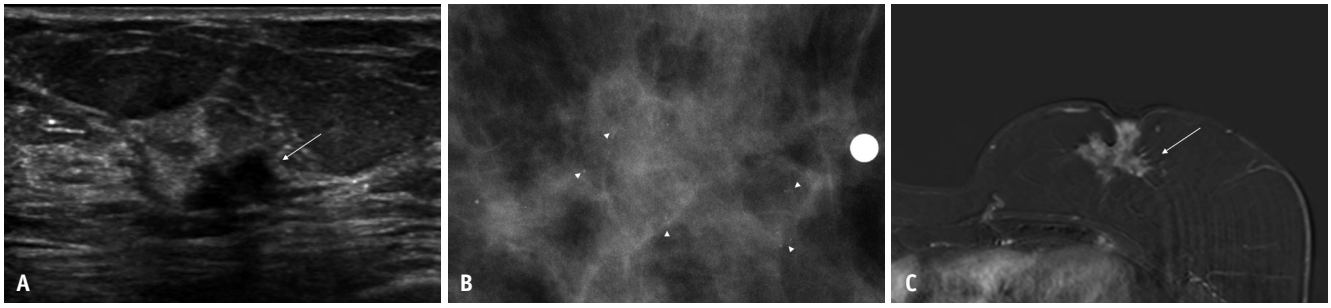

Fig. 6. A 57-year-old woman with DCIS was classified into the low-risk group but experienced IBTR. **A:** Ultrasound image showing an irregular hypoechoic mass (arrow) in the left upper outer breast with biopsy-confirmed DCIS. **B:** Magnified mammogram with a skin marker for the mass showing a heterogeneously dense breast and subtle asymmetry with a few amorphous calcifications (arrowheads). The patient underwent breast-conserving surgery and adjuvant radiation therapy. The DCIS measured 1.5 cm, was estrogen receptor negative, and had a close medial margin on the surgical specimen. The total score on the nomogram was 44 points because of the margins, indicating the low-risk group. **C:** Six years after surgery, IBTR was diagnosed using surveillance mammography and ultrasonography (images not shown). The first subtraction image of the dynamic contrast-enhanced MRI after recurrence diagnosis shows a heterogeneously enhancing mass (arrow) in the left central area with nipple involvement. Therefore, our nomogram was not accurate in predicting IBTR in this patient. DCIS = ductal carcinoma in situ, IBTR = ipsilateral breast tumor recurrence

and are monitored using mammography [6]. However, these trials do not account for mammographic density and calcification morphology when selecting participants or recommending follow-up imaging methods. Our findings suggest that individuals with extremely dense breast tissue or fine linear branching calcifications might not be suitable candidates for surveillance trials given their association with IBTR. Moreover, postoperative MRI as a supplement to mammography for patients at a higher risk of IBTR is advisable, as noncalcified recurrence might be missed with mammography alone [30].

Among the clinical-pathologic variables, young age, positive or close margins, and omission of adjuvant radiation therapy were independently associated with an increased risk of IBTR in the development cohort, consistent with the published literature [31-34]. Young age is associated with aggressive pathological characteristics such as high nuclear grade and comedo necrosis [31] and a higher risk of IBTR [34]. Moreover, positive or close margins are well-known risk factors of IBTR [32]. Multiple randomized controlled trials have demonstrated that adjuvant radiation therapy reduces IBTR by 50% [33,34].

Our study had several limitations. First, the validation cohort comprised patients from a single institution with a small sample size and few IBTR events, differing in many clinical, pathological, and imaging characteristics from the development cohort. The small sample size and composition of the validation cohort may have affected nomogram performance. To ensure generalizability, our nomogram should be validated in larger cohorts from multiple institutions. Second, patient selection and treatment biases may have been present in this retrospective study. Both hospitals in this study actively administered adjuvant treatment for DCIS; however, strategies for adjuvant treatment may differ across centers [35]. Third, our nomogram was developed based on the imaging interpretations by a radiologist. Breast density and calcification morphology are qualitative imaging features that are subject to interobserver variability. Fourth, we did not obtain survival information from the National Statistical Office. Therefore, we cannot rule out the possibility that some deaths occurred. Fifth, a longer follow-up period may be more appropriate for the accurate prediction of IBTR. Sixth, a subgroup analysis comparing in situ and invasive recurrences was not performed because of the small number of total IBTR events. Seventh, MRI features may predict the IBTR risk of DCIS [36] but were not analyzed because preoperative MRI for DCIS was not routinely performed. Eighth, we observed a comparable performance of the nomogram regardless of the use of preoperative MRI. However, this analysis may have been limited by the predominant use of MRI in both hospitals and the small sample size of each subgroup. Finally, risk stratification using a 100-point cutoff was not significant in the validation cohort. This may indicate the need to refine the variables within the nomogram and establish an optimal cutoff point. This could be accomplished with an extended follow-up period and a larger sample size.

In conclusion, our nomogram for predicting 10-year IBTR probabilities provided individualized risk estimates for women with DCIS treated with BCS, demonstrating a

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discriminative ability comparable to that of the MSKCC nomogram.

Supplement

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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Soo-Yeon Kim. Data curation: Bo Hwa Choi, Soo-Yeon Kim. Formal analysis: all authors. Investigation: all authors. Methodology: Soohee Kang, Soo-Yeon Kim. Project administration: Soo-Yeon Kim. Resources: Bo Hwa Choi, Soo-Yeon Kim. Software: Soo-Yeon Kim. Supervision: Bo Hwa Choi, Soo-Yeon Kim. Validation: Bo Hwa Choi. Visualization: Bo Hwa Choi, Soohee Kang, Soo-Yeon Kim. Writing—original draft: Soo-Yeon Kim. Writing—review & editing: all authors.

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