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An improved nomogram including elastography to predict the histological upgrade of ductal carcinoma in situ of the breast

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Abstract. – OBJECTIVE: About 30% of the breast's ductal carcinoma in situ (DCIS) will be histological upstate according to the postoperative pathology. Sentinel lymph node biopsy (SLNB) is currently recommended on most DCIS excision in order to potentially avoid secondary surgery, which is apparently over-treated for most patients with DCIS. Hence, the decision to perform SLNB before DCIS excision remains controversial. The aim of this study is to establish an improved nomogram including elastography for predicting the risk of the histological upgrade of DCIS preoperatively.

PATIENTS AND METHODS: The medical records of 147 patients who were preoperatively diagnosed with DCIS and underwent breast surgery were retrospectively reviewed. They were divided into DCIS group (n=99) and DCIS with invasive components (DCIS-IC) group (n=48) according to the postoperative pathology results. The clinicopathologic and multimode ultrasonic records were analyzed and used to develop the nomogram. The difference in performance between the nomogram with and without acoustic radiation force impulse (ARFI) elastography was compared in this study.

RESULTS: Patients with high-grade lesions (OR = 4.762, $p = 0.032$), positive human epidemal growth factor receptor 2 (HER-2) expression (OR = 3.560, $p = 0.007$), comedo type of DCIS (OR: 3.163, $p = 0.041$), larger lesion size (OR = 3.253, $p = 0.002$), and higher mean SWV value (SWVmean) (OR: 5.083, $p < 0.001$) were found to be independent factors associated with the histologic upgrade. The discrimination of the nomogram (0.896), including the 5 independent predictors (ARFI elastography included), was higher than that without ARFI elastography (0.788). It could be utilized to predict the probability of the histologic upgrade of DCIS.

CONCLUSIONS: The developed nomogram incorporating ARFI elastography is expected to predict the risk of the histologic upgrade of DCIS preoperatively and to provide a reference for the decision making for SLNB. It showed improved performance owing to the elastography.

Key Words:
Ductal carcinoma in situ, Histological upstate, Sentinel lymph node biopsy, Nomogram, Elastography.

Introduction

With the widespread mammography and ultrasound screening, the incidence of ductal carcinoma *in situ* (DCIS) of the breast is increasing in recent years, accounting for 20% of screen-detected breast cancers[1]. Sentinel lymph node biopsy (SLNB) is typically not advised in DCIS since it is a noninvasive lesion with malignant ductal cells that no basement membrane is infiltrated[2]. However, about 30% of DCIS found invasive components based on the final postoperative pathology report[3-5]. In the clinical setting, SLNB is recommended on most DCIS excision in order to potentially avoid secondary surgery, which will result in an increased risk of surgical complications. Of note, many patients with DCIS are likely over-treated since the positive rate of SLNB is about 10%[6,7]. Moreover, even if invasive components are identified, the degree of lymph node metastasis is very limited[8]. Therefore, it is important to accurately predict the invasive components of DCIS before surgery to better identify patients who need SLNB.

Multiple studies[9,10] have reported the risk factors for the underestimation of invasion in preoperatively diagnosed DCIS. These researches suggested that the palpability and size of the lesion, characteristics on mammography or ultrasound,

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and histopathologic biopsy findings were associated with a risk of underestimation. However, none of these factors have been accepted as a definitive predictor to guide SLNB in DCIS. The decision to omit SLNB before DCIS excision remains controversial. Ultrasound elastography is capable of providing qualitative and quantitative measurements of lesion stiffness, which has been reported to be valuable in differentiating benign or malignant breast masses[11,12]. Krouskop et al[13] reported in their *in-vitro* study that the stiffness of DCIS with invasive components was higher than true DCIS, breast fat tissue, and normal glandular tissue but lower than invasive ductal carcinoma. It indicates that elastography may provide useful information for the prediction of the histological underestimation of DCIS before surgery.

In an attempt to develop a more precise prediction model, the purpose of this study was to establish a nomogram, including elastography for predicting the risk of the histological upgrade of DCIS in the preoperative setting.

Patients and Methods

Patient Selection

This study was approved by the Ethical Review Committee of Shanghai Shidong Hospital (2020-029-01). A retrospective review of medical records identified 158 consecutive patients who were preoperatively diagnosed with DCIS and underwent definitive surgery between 2016 and 2020 at Shanghai Shidong hospital. Patients with prior invasive breast cancer or missing variables for significant predictors were excluded. A total of 147 patients were included in this study, and they were divided into true DCIS group (n=99) (namely DCIS group) and DCIS with invasive components group (n=48) (namely DCIS-IC group) according to the postoperative pathological results. The clinical, ultrasonic, and histological records between the two groups were analyzed and used to develop the nomogram.

Acquisition of Multimode Ultrasound Data

B-mode ultrasound and acoustic radiation force impulse (ARFI) elastography for the DCIS were obtained using an Acuson S3000 ultrasound system (Siemens Healthcare, Erlangen, Bavaria, Germany) with a 9L4 linear array probe (frequency, 4-9 MHz). Two sonographers with more than 10 years of experience in breast ultrasound and more than 3 years of experience in ARFI who were blinded to the clinicopathologic findings performed the sonographic examinations. The characteristics of DCIS in B-mode ultrasound (Figures 1A and 1a), including the presence of a mass lesion, multicentric lesion, lesion size, shape, margin, echo pattern, posterior acoustic feature, calcification, color Doppler flow imaging (CDFI, grade 0,1,2,3)[14], and breast image report-

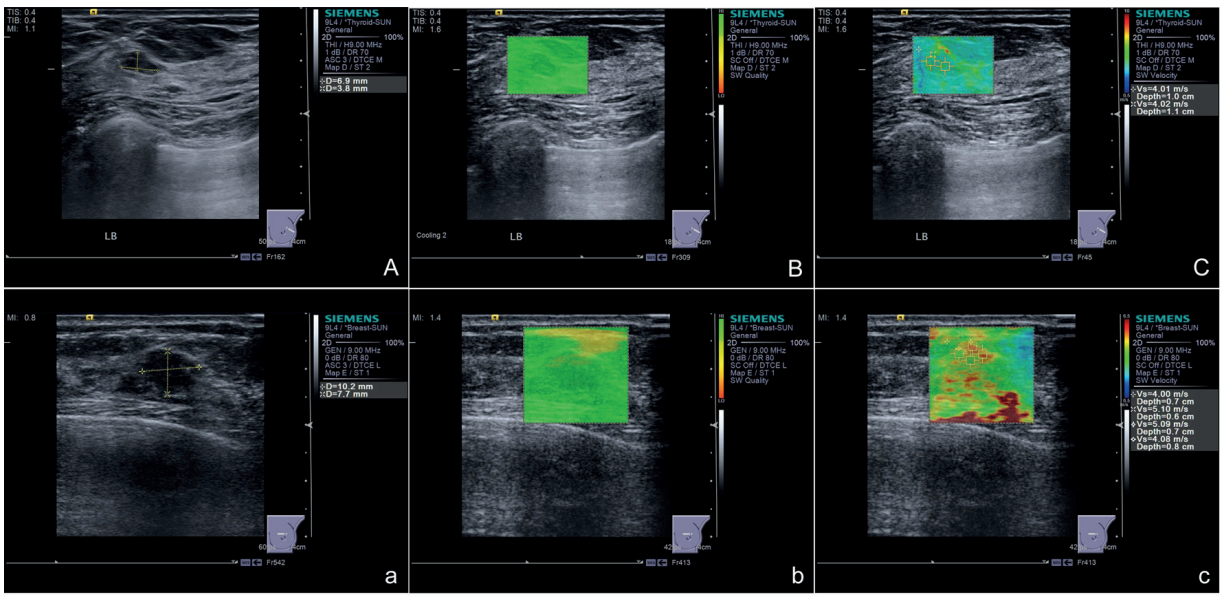

Figure 1. Multimode ultrasound examination for DCIS of the breast with **(a, b, c)** or without invasive components **(A, B, C)**. **(A** and **a)** for B-mode ultrasound, **(B** and **b)** for shear wave quality of VTIQ, and **(C** and **c)** for SWV assessment in VTIQ. DCIS: ductal carcinoma *in situ*, VTIQ: virtual touch tissue quantification, SWV: shear wave velocity.

ing and data system (BI-RADS) category were recorded. ARFI was performed after positioning the lesion at the center of the image. Quantitative measurement of elasticity was achieved on each virtual touch tissue quantification (VTIQ) image with a rectangular region of interest (ROI) located over the stiffest part of the lesion to obtain a high shear wave quality (Figures 1B and 1b). The shear wave velocity (SWV, m/s) in the ROI was calculated automatically (Figures 1C and 1c). The mean SWV value (SWV_{mean}) was obtained after averaging each SWV values in the ROI.

Histopathologic Evaluation

Surgical specimens were fixed in 10% neutral buffered formalin, dehydrated with graded ethanol, infiltrated with paraffin wax, and embedded in wax blocks. The tumor specimens were divided into two sections. One was stained with hematoxylin and eosin to evaluate histological grade (low, intermediate, and high), histological type (comedo, cribriform, solid, micropapillary, and papillary), surgical margin involvement, and lymph node status. The other was subjected to immunohistochemical analysis to detect the expression of estrogen receptor (ER), progesterone receptor (PR), and human epithelial growth factor receptor 2 (HER-2). An invasive component was defined in tissues with basement membrane invasion. The pathology results of surgical specimens were reviewed by two pathologists with more than 10 years of experience in breast pathology.

Data Collection

The clinicopathologic factors (age, menstrual status, symptom, histological grade, histological type and status of ER, PR, and HER-2) and ultrasound features (presence of a mass lesion, multicentric lesion, lesion size, shape, margin, echo pattern, posterior acoustic feature, calcification, CDFI, and BI-RADS category) were collected and compared between the two groups to better understand the variables that might be predictive for the histological upstage of DCIS.

Statistical Analysis

The statistical analyses in this study were performed with SPSS (version 22.0; IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY, USA), Medcalc software (version 11.0, Ostend, West Flanders, Belgium), and R package version 3.6.2. The comparison between the DCIS group and the DCIS-IC group was performed for univariate analysis (Mann-Whitney U test for nonnormally distributed continuous data and chi-square test for categorical data). Multivariable logistic regression was used to link the predictors that were significant at $p < 0.05$ in the univariate analysis and the histological upstage of DCIS, which was served as the basis of the nomogram. The performance of the nomogram was assessed by Harrell's concordance index (C-index)[15]. Bootstrap resampling (1,000 times) was used for internal validation[16]. Hosmer-Lemeshow test was used for calibration.

Results

Of the 147 patients with a preoperative diagnosis of DCIS, 88 patients underwent breast-conserving surgery and 59 underwent mastectomy. SLNB was performed for all patients. A total of 48 patients (32.7%) were upstaged to DCIS with invasive components after surgery. Of these, 6 patients (12.5%) had positive SLNB and received axillary lymph node dissection.

Factors Associated with the Histological Upstage of DCIS

On univariable analysis, upstaging to DCIS with invasive components was associated with histological grade, comedo, and cribriform subtype, HER-2 expression, lesion size, calcification, and SWV_{mean} (Tables I and II).

Multivariable analysis further revealed that patients with high-grade lesions (OR = 4.762, p =0.032), positive HER-2 expression (OR = 3.560, p = 0.007), comedo type of DCIS (OR = 3.163, p = 0.041), larger lesion size (OR = 3.253, p = 0.002), and higher SWV_{mean} (OR = 5.083, $p < 0.001$) were found to be independent factors associated with the histologic upgrade (Figure 2).

Development and Validation of a Nomogram for Predicting the Histologic Upgrade of DCIS

A nomogram including the 5 independent predictors was constructed to predict the risk of histologic upstage of DCIS (Figure 3). The bia-corrected C-index of the nomogram was 0.896 (95% CI 0.835 to 0.940), demonstrating good discrimination (> 0.75) (Figure 4A). The calibration test indicated no significant lack of departure (χ^2 = 13.247, p = 0.104, Hosmer-Lemeshow test), which demonstrated a good calibration of the nomogram. If elastography was excluded, the C-index of the nomogram was 0.788 (95% CI 0.713 to

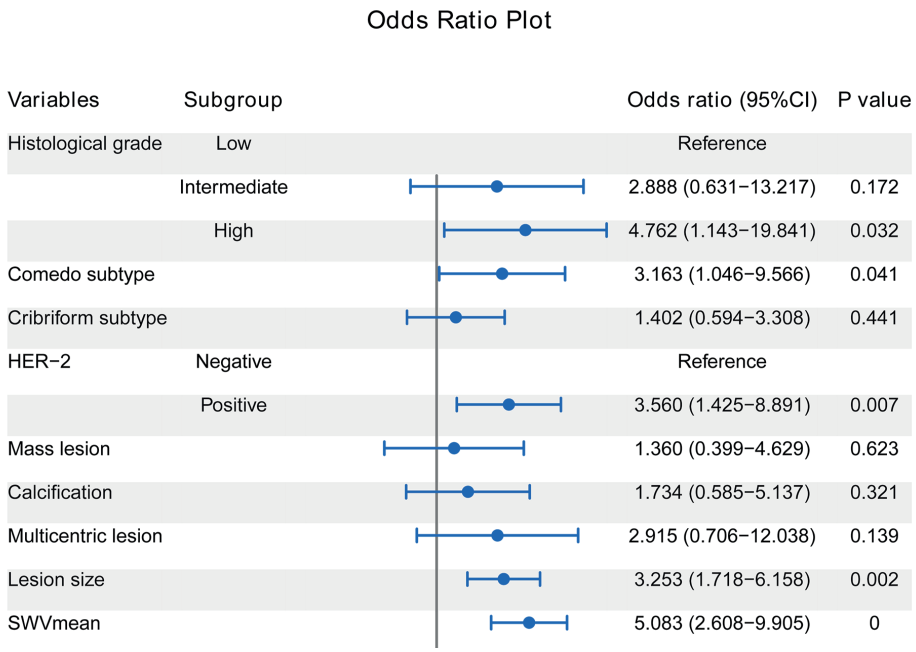

Figure 2. Forest plot of the multivariable analysis to explore the independent predictors of the histological upstage of DCIS. HER-2: human epidemal growth factor receptor 2, SWV_{mean}: mean SWV value.

Table I. Univariate analysis of the clinicopathologic factors associated with the histological upstage of DCIS.

Variables			DCIS group (n=48)	DCIS-IC group (n=99)	*p*-value
Age (years)			52.32±8.56	52.90±6.80	0.686#
Menstrual status	Premenopausal		32 (66.7%)	65 (65.7%)	0.904*
	Postmenopausal		16 (33.3%)	34 (34.3%)	
Symptom	Non-palpable		43 (89.6%)	89 (89.9%)	0.953*
	Palpable		5 (10.4%)	10 (10.1%)	
Histological grade	Low		4 (8.3%)	20 (20.2%)	0.008$
	Intermediate		13 (27.1%)	37 (37.4%)	
	High		31 (64.6%)	42 (42.4%)	
Histological type	Comedo	Yes	26 (54.2%)	34 (34.3%)	0.022*
		No	22 (45.8%)	65 (65.7%)	
	Solid	Yes	19 (39.6%)	39(39.4%)	0.982*
		No	29 (60.4%)	60 (60.6%)	
	Cribriform	Yes	30 (62.5%)	44 (44.4%)	0.040*
		No	18 (37.5%)	55 (55.6%)	
	Papillary	Yes	2 (4.2%)	6 (6.1%)	0.635*
		No	46 (95.8%)	93 (93.9%)	
	Micropapillary	Yes	5 (10.4%)	11 (11.1%)	0.899*
		No	43 (89.6%)	88 (88.9%)	
ER	Negative		9 (18.8%)	15 (15.2%)	0.581*
	Positive		39 (81.3%)	84 (84.8%)	
PR	Negative		9 (18.8%)	16 (16.2%)	0.696*
	Positive		39 (81.3%)	83 (83.8%)	
HER-2	Negative		20 (41.7%)	66 (66.7%)	0.004*
	Positive		28 (58.3%)	33 (33.3%)	

DCIS: ductal carcinoma *in situ*, DCIS-IC: DCIS with invasive components, HER-2: human epidemal growth factor receptor 2, PR: progesterone receptor, ER: estrogen receptor. *for chi-square test; #for independent sample t-test; $for Mann-Whitney U test.

Table II. Univariate analysis of the ultrasound characteristics associated with the histological upstage of DCIS.

Variables		DCIS group (n=48)	DCIS-IC group (n=99)	*p*-value
Mass lesion	No	37 (77.1%)	89 (89.9%)	0.037*
	Yes	11 (22.9%)	10 (10.1%)	
Multicentric lesion	No	40 (83.3%)	93 (93.9%)	0.040*
	Yes	8 (16.7%)	6 (6.1%)	
Lesion size	2.2 (1.6, 2.9)	1.7 (1.1, 2.3)	0.000$	
Shape	Oval	4 (8.3%)	10 (10.1%)	0.770*
	Round	1 (2.1%)	4 (4.0%)	
	Irregular	43 (89.6%)	85 (85.9%)	
Margin	distinct	5 (10.4%)	13 (13.1%)	0.755*
	Indistinct	31 (64.6%)	57 (57.6%)	
	Angular	10 (20.8%)	21 (21.2%)	
	Microlobulated	2 (4.2%)	8 (8.1%)	
Echo pattern	Anechoic	1 (2.1%)	2 (2%)	0.384*
	Hyperechoic	0 (0%)	1 (1%)	
	Cystic and solid	2 (4.2%)	0 (0%)	
	Hypoechoic	32 (66.7%)	73 (73.7%)	
	Isoechoic	3 (6.3%)	7 (7.1%)	
	Heterogeneous	10 (20.8%)	16 (16.2%)	
Posterior acoustic feature	No posterior features	16 (33.3%)	46 (46.5%)	0.286*
	Enhancement	9 (18.8%)	13 (13.1%)	
	Shadowing	11 (22.9%)	25 (25.3%)	
	Combined pattern	12 (25.0%)	15 (15.2%)	
Calcification	No	23 (47.9%)	65 (65.7%)	0.040*
	Yes	25 (52.1%)	34 (34.3%)	
CDFI	0	0 (0%)	0 (0%)	0.763$
	1	9 (18.8%)	17 (17.2%)	
	2	37 (77.1%)	77 (77.8%)	
	3	2 (4.2%)	5 (5.1%)	
BI-RADS category	3	0 (0%)	2 (2.0%)	0.357$
	4A	19(39.6%)	40 (40.5%)	
	4B	23 (47.9%)	53 (53.5%)	
	4C	5 (10.4%)	4 (4.0%)	
	5	1 (2.1%)	0 (0%)	
$SWVm_{ean}$	5.51 (4.26, 6.58)	4.00 (3.52, 4.47)	<0.001$	

SWV_{mean}: mean SWV value, BI-RADS: breast imaging-reporting and data system, CDFI: color doppler flow imaging; DCIS: ductal carcinoma *in situ*, DCIS-IC: DCIS with invasive components. *for chi-square test; $for Mann-Whitney U test.

0.851), which was lower than the nomogram including elastography (Figure 4B).

Utility of the Nomogram

The nomogram could be utilized to calculate the scores corresponding to each independent predictor of the histologic upgrade, and the predicted probability corresponding to the sum of the scores was the risk of the histologic upgrade of DCIS. It could help select the patients with a high risk of histologic upgrade and develop preventive treatment strategies. For example, when a DCIS patient with high-grade lesion, positive HER-2 expression, comedo subtype of DCIS, 2cm in lesion size, and 5m/s in SWV_{mean}, the total score was about 110. It indicated that the probability of a patient with histologic upgrade of DCIS was about 72%.

Discussion

In this study, 5 clinicopathological factors (histological grade, HER-2 expression, comedo type of DCIS, lesion size, and SWV_{mean}) associated with the histological grade of DCIS were obtained. A nomogram was developed using these variables to predict the risk of the histologic upgrade of DCIS preoperatively. This nomogram showed improved discrimination and satisfied calibration owing to the elastography. By identifying high-risk patients who may be upgraded to DCIS with invasive components, SLNB may be performed concurrently with breast surgery; thus, some unnecessary SLNB may be avoided.

Currently, SLNB is advised for most patients who underwent mastectomy or breast-conserving

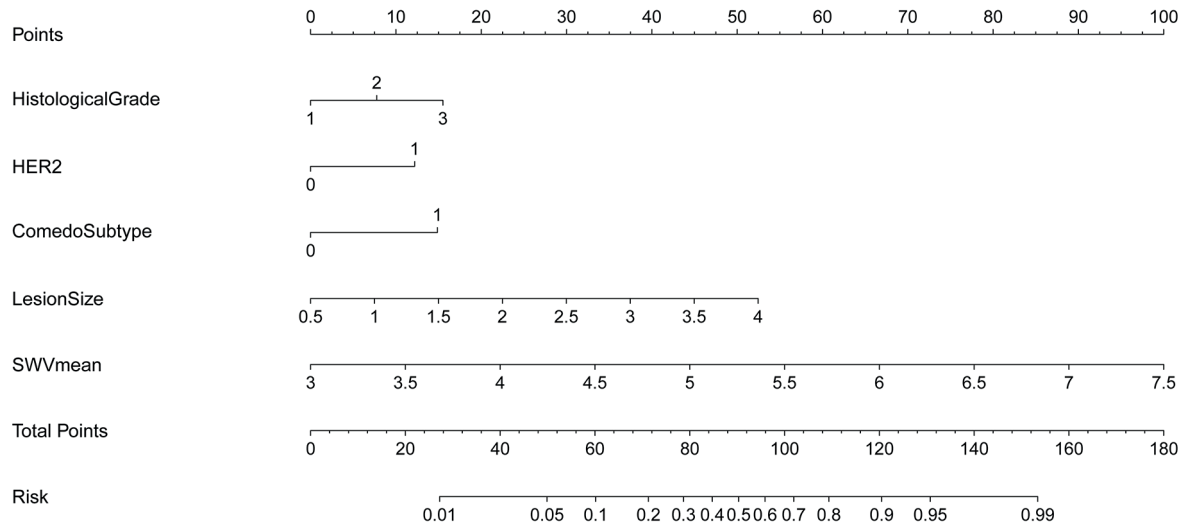

Figure 3. The nomogram predicting the histologic upgrade of DCIS of the breast. The top row shows the point assignment for each variable. Rows 2-6 indicate the variables included in the nomogram. The bottom row shows the probability of the patient with histologic upgrade of DCIS. HER-2: human epidemal growth factor receptor 2, SWVmean: mean SWV value.

surgery in clinical settings although axillary lymph node dissection in the DCIS setting is controversial. In our study, all of the patients underwent SLNB, and only 12.5% had positive SLNB, although 32.7% were upstaged to DCIS with invasive components. It demonstrated that indiscriminate axillary staging may be excessive for patients with DCIS.

Except elastography, the C-index of the constructed nomogram was 0.788, which was in accordance with the studies of Jakub et al (c-index 0.71)[17], Coufal et al (c-index 0.76)[18], Lee et al (c-index 0.82)[19], Park et al (c-index 0.71)[20] and Kondo et al (c-index 0.69)[21]. We also found that histological grade, HER-2 expression, comedo type of DCIS, and lesion size were closely associated with the histological upgrade of DCIS compared with the previously reported studies[4,22-24]. In comparing these previous predictors with ours, our

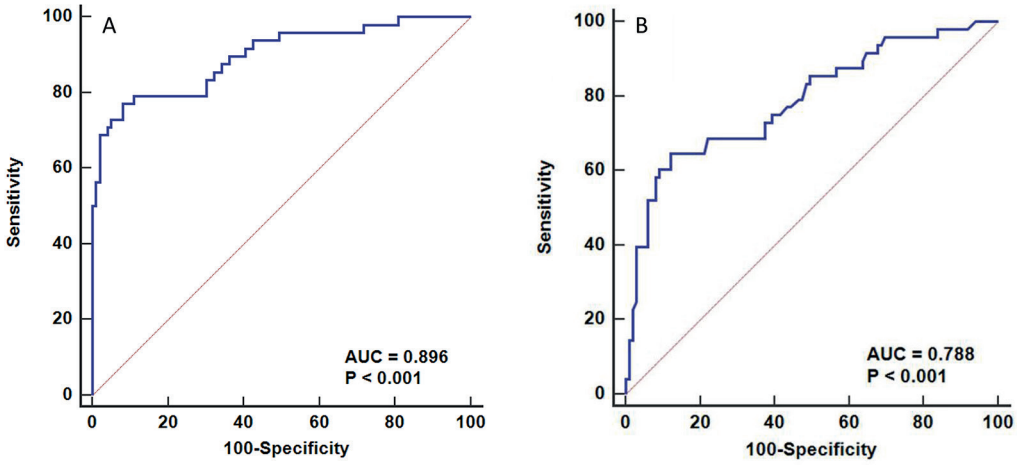

Figure 4. Receiver operating characteristic (ROC) curve for discrimination of the nomogram. **(A)** for the nomogram including elastography. The area under the curve (AUC) (C-index) of the nomogram was 0.896 (95% CI 0.835 to 0.940), demonstrating very good discrimination. **(B)** for the nomogram without elastography. The C-index was 0.788 (95% CI 0.713 to 0.851). 95% CI: 95% confidence interval.

nomogram showed improved performance when the elastography was included (a greater C-index and satisfied calibration). Therefore, making the decision for the existence of invasive components preoperatively would be difficult only to rely on B-mode ultrasound findings[25], and ARFI elastography may be a useful complementary tool in identifying the histological upstage of DCIS.

ARFI elastography allows a quantitative assessment of lesion stiffness *in vivo* and can be performed during routine breast ultrasound examinations. In our study, the SWV in ARFI elastography was the independent predictor for the histological upstage in DCIS, which was in line with the study by Berg et al[26], who reported that the stiffness of invasive cancer was higher than DCIS. The possible reason could be explained by the histopathologic composition of a lesion. The mechanism is already clear that a tumor tends to be stiffer as it grows due to an increasing proportion of fibrosis and a decreasing proportion of necrosis[27]. Invasive breast lesions tend to exert a stronger desmoplastic effect on peritumoral tissues. The numbers of mitoses increased, reflecting enhanced cellularity and an excessive desmoplastic reaction, which explains why DCIS with invasive components may show a higher stiffness value[28].

There are several limitations to this study. First, this is a retrospective study conducted in a single institution. It reduced the analyzable sample since the complete data was limited. Besides, the comparison between ARFI elastography and other elastographies (shear wave elastography, transient elastography, or magnetic resonance elastography) was not performed due to hospital equipment limitation. Second, repeated measurements in the same tumors were not performed, which may cause some unavoidable errors. Third, the nomogram to predict the histological upstage of DICS was not validated in other populations. Hence, a further prospective investigation with a larger study population is planned to improve and validate the performance of the constructed nomogram.

Conclusions

To our knowledge, this is the first nomogram incorporating ARFI elastography to predict the histological upstage of DCIS. Owing to the elastography, improved discrimination and satisfied calibration was demonstrated in this study. The established nomogram is expected to be used to identify DCIS patients at risk of histological upstage and to provide a reference for the decision making of SLNB preoperatively.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Xiao-lan Sun and Yu-ping Dai contributed equally to this study and are co-first authors. Zhen Chen and Jun Zhang are co-corresponding authors. Study design: Xiao-lan Sun, Yu-ping Dai, Zhen Chen, and Jun Zhang. Data collection and analysis: Xiao-lan Sun and Yu-ping Dai. Supervision: Zhen Chen and Jun Zhang. Statistics: Xiao-lan Sun and Yu-ping Dai. Manuscript writing: Xiao-lan Sun and Yu-ping Dai. Manuscript revision: Zhen Chen and Jun Zhang. Approval of the manuscript: all authors.

Ethical Approval

Ethical approval for the study was obtained from the Ethics Committee of Shanghai Shidong hospital (2020-029-01).

Informed Consent

Written informed consent was obtained from all patients

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