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BREAST

Risk stratification of ductal carcinoma in situ using whole-lesion histogram analysis of the apparent diffusion coefficient

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Abstract

Objectives To investigate the value of the whole-lesion histogram apparent diffusion coefficient (ADC) metrics for differentiating low-risk from non-low-risk ductal carcinoma in situ (DCIS).

Methods The authors identified 93 women with pure DCIS who had undergone preoperative MR imaging and diffusion-weighted imaging from 2013 to 2016. Histogram analysis of pixel-based ADC data of the whole tumour volume was performed by two radiologists using a software tool. The results were compared between low-risk and non-low-risk DCIS. Associations between quantitative ADC metrics and low-risk DCIS were evaluated by receiver operating characteristics (ROC) curve and logistic regression analyses.

Results In whole-lesion histogram analysis, mean ADC and 5th, 50th and 95th percentiles of ADC were significantly different between low-risk and non-low-risk DCIS (1.522, 1.207, 1.536 and 1.854 × 10^{-3} mm^2/s versus 1.270, 0.917, 1.261 and 1.657 × 10^{-3} mm^2/s, respectively; $p = .004$, $p = .003$, $p = .004$ and $p = .024$, respectively). ROC curve analysis for differentiating low-risk DCIS revealed that 5th percentile ADC yielded the largest area under the curve (0.786) among the metrics of whole-lesion histogram, and the optimal cut-off point was 1.078 × 10^{-3} mm^2/s (sensitivity 80%, specificity 75.9%, $p = .001$). Multivariate regression analysis revealed that a high 5th percentile of ADC (> 1.078× 10^{-3} mm^2/s; odds ratio [OR] = 10.494, $p = .016$), small tumour size (≤ 2 cm; OR = 12.692, $p = .008$) and low Ki-67 status (< 14%; OR = 10.879, $p = .046$) were significantly associated with low-risk DCIS.

Conclusions Assessment with whole-lesion histogram analysis of the ADC could be helpful for identifying patients with low-risk DCIS.

Key Points

- *Whole-lesion histogram ADC metrics could be helpful for differentiating low-risk from non-low-risk DCIS.*
- *A high 5th percentile ADC was a significant factor associated with low-risk DCIS.*
- *Risk stratification of DCIS is important for their management.*

Keywords Breast neoplasm · Magnetic resonance imaging · Diffusion magnetic resonance imaging · Ductal carcinoma in situ · Risk

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Abbreviations

ADC	Apparent diffusion coefficient
AUC	Area under the curve
CI	Confidence interval
DCIS	Ductal carcinoma in situ
DWI	Diffusion-weighted imaging
ER	Oestrogen receptor
HER2	Human epidermal growth factor receptor 2
ICC	Intraclass correlation coefficient
OR	Odds ratio
PR	Progesterone receptor
ROC	Receiver operating characteristic
ROI	Regions of interest

Introduction

Although ductal carcinoma in situ (DCIS) is considered as a precursor lesion of invasive breast cancer, not all DCIS lesions progress to invasive breast cancer [1]. Approximately 25–50% of DCIS cases are shown to progress to invasive disease [2–4]. The natural history of low-grade DCIS differs from that of high-grade DCIS. Data from the long-term follow-up of 28 low-grade DCIS indicated progression to invasiveness even after more than 4 decades [2], raising concerns regarding potential overtreatment of indolent and low-risk DCIS. Furthermore, a recent study using the Surveillance, Epidemiology, and End Results database reported no significant difference in the weighted 10-year breast-cancer-specific survival between the surgery and nonsurgery groups for low-grade DCIS (98.6% vs. 98.8%, $p = .95$) [5]. An optimal treatment strategy for DCIS based on the individual tumour biology is warranted.

The utility of diffusion-weighted imaging (DWI) using apparent diffusion coefficient (ADC) values for differentiation of breast lesions has been well established [6, 7]. In recent years, increasing efforts have been made to better stratify DCIS biology using DWI [8–12]. Iima et al evaluated the potential role of ADC for DCIS grading and found that ADC could help identify low-grade DCIS lesions; the specificity and positive predictive value were 100% with a threshold ADC value of 1.30×10^{-3} mm^2/s [8]. However, the ADC measurement in the previous study was based on the manual regions-of-interest (ROI) placement from a single representative slice of the DCIS lesion, which might be limited in reflecting whole-tumour characteristics. Assessment with whole-lesion histogram analysis of the ADC might provide more reliable results to reflect biological characteristics of the heterogeneous DCIS lesions [13].

Therefore, the purpose of this study was to investigate the value of the whole-lesion histogram ADC metrics for differentiating low-risk from non-low risk DCIS.

Materials and methods

Subjects

The institutional review board of our hospital approved this retrospective study, and the requirement for informed consent was waived. A review of medical records between June 2013 and May 2016 at our institution identified 141 consecutive women who were diagnosed with DCIS by core needle biopsy and who had undergone preoperative breast MR imaging with DWI. Among them, 39 women who had invasive disease at final histologic reports from lumpectomy or mastectomy specimens (30 with invasive breast cancer and nine with DCIS with microinvasion), six women with inadequate DWI quality for analysis because of low signal-to-noise ratio, motion artefact or incomplete fat suppression, and three women with lesions too small to draw ROIs were excluded from the study. In four women with multicentric DCIS (tumours in different quadrants) in the ipsilateral breast and one woman with bilateral synchronous DCIS, only the largest tumours were included for analysis. Finally, 93 women (mean age, 51.9 years; range, 23–88 years) with 93 cases of pure DCIS were included in this analysis.

The time interval between core needle biopsy and MR imaging ranged from 9 to 45 days (mean, 18 days), and the time interval between MR imaging and surgery ranged from 3 to 25 days (mean, 15 days).

MR examinations

All breast MR examinations were performed using a 3-T system (MAGNETOM Trio Tim, Siemens Healthineers) with a dedicated 4-channel breast array coil (Siemens Healthineers) with patients in the prone position. The breast MR protocol included a localising sequence followed by axial fat-suppressed T2-weighted turbo spin-echo images (TR/TE, 7623/91 ms; matrix, 320 × 247; field-of-view, 220 × 220 mm^2; section thickness, 3.0 mm). Before contrast agent administration, DWI was obtained using a single-shot echo-planar imaging (EPI) technique with a spectral presaturation attenuated inversion-recovery fat-suppressed pulse sequence (TR/TE, 6600/91 ms; EPI factor, 84; bandwidth, 1488 Hz/pixel; matrix, 84 × 160; field-of-view, 200 × 380 mm^2; echo spacing, 0.76 ms; slice thickness, 5.0 mm; slice number, 30; NEX, 7.0; no gap). Diffusion gradients were applied in three orthogonal directions with b values of 0 and 1000 s/mm^2, and the scan time was 203 s. A T1-weighted, fat-suppressed, three-dimensional, fast low-angle shot sequence (TR/TE, 4.5/1.6 ms; matrix, 352 × 292; flip angle, 20°; field-of-view, 220 × 220 mm^2; section thickness, 2.0 mm; no gap) was performed before and five times after a rapid bolus injection of 0.1 mmol/kg gadobutrol (Gadovist; Bayer AG).

Imaging analysis

All DWI were retrospectively reviewed independently by two radiologists (an attending radiologist with 7 years of experience in breast MR imaging and a senior radiology resident) who were only informed of the pure DCIS diagnosis but were blinded to the clinical and pathological information. Whole-lesion histogram analysis of the ADC was performed using dedicated prototype software (Multi Parametric Analysis, Siemens Healthineers),

which allows for semiautomatic tumour segmentation based on a random walker technique. The reviewers manually drew foreground seed points to mark the tumour location and background seed points to define the outside of the tumour. Seed points were drawn on multiple different slices to improve the segmentation results. For discontinuous DCIS lesions, seed points for individual components were placed separately and summed. The early phase of contrast-enhanced T1-weighted images and T2-weighted images were used to help locate the lesions and verify the lesion boundaries. Then, three-dimensional tumour segmentation was conducted and volumes of interest (VOIs) were generated. Whole-lesion ADC histograms metrics (mean and 5th, 50th and 95th percentiles of ADC, skewness and kurtosis) were obtained (Fig. 1). A percentile represents the value below which a given percentage of observations are calculated. Skewness is a measure of histogram asymmetry and kurtosis is a measure of histogram peakedness.

In addition, tumour ADC values were estimated by using the conventional ROI method. An ADC map of the largest diameter of each tumour was selected, and an ROI was manually drawn within the tumour by using dynamic contrast-enhanced (DCE) MR imaging and DWI as a reference. The mean, minimum and maximum ADC pixel values of each ROI were measured and recorded as ADC_{mean}, ADC_{min} and ADC_{max}, respectively.

The first measurement by the attending radiologist was used for analysis. To evaluate intraobserver reproducibility, a second measurement was performed by the attending radiologist at 1-month interval without knowledge of the previous measurement. To access interobserver reproducibility, the first measurement was compared with the measurement obtained by the other radiologist.

Histopathological analysis

All patients underwent mastectomy or lumpectomy, and histopathologic evaluation was performed with use of the surgically resected specimens. All DCIS lesions were classified according to the Van Nuys classification [14], based on nuclear grade and necrosis; grade 1 is non-high nuclear grade without comedo-type necrosis, grade 2 is non-high nuclear grade with comedo-type necrosis, and grade 3 is high nuclear grade with or without comedo-type necrosis. In this study, low-risk DCIS was defined as grade-1 DCIS lesions, and non-low-risk DCIS was defined as grade-2 or grade-3 DCIS lesions. The Allred score was used to evaluate the oestrogen receptor (ER) and progesterone receptor (PR) statuses [15]. Tumours with Allred scores of at least 3 were considered to be positive. Tumours with human epidermal growth factor receptor 2 (HER2) scores 3+ and/or HER2 gene amplification confirmed by fluorescence in situ hybridization were regarded as HER2 positive [16]. For Ki-67, nuclear staining of at least 14% was

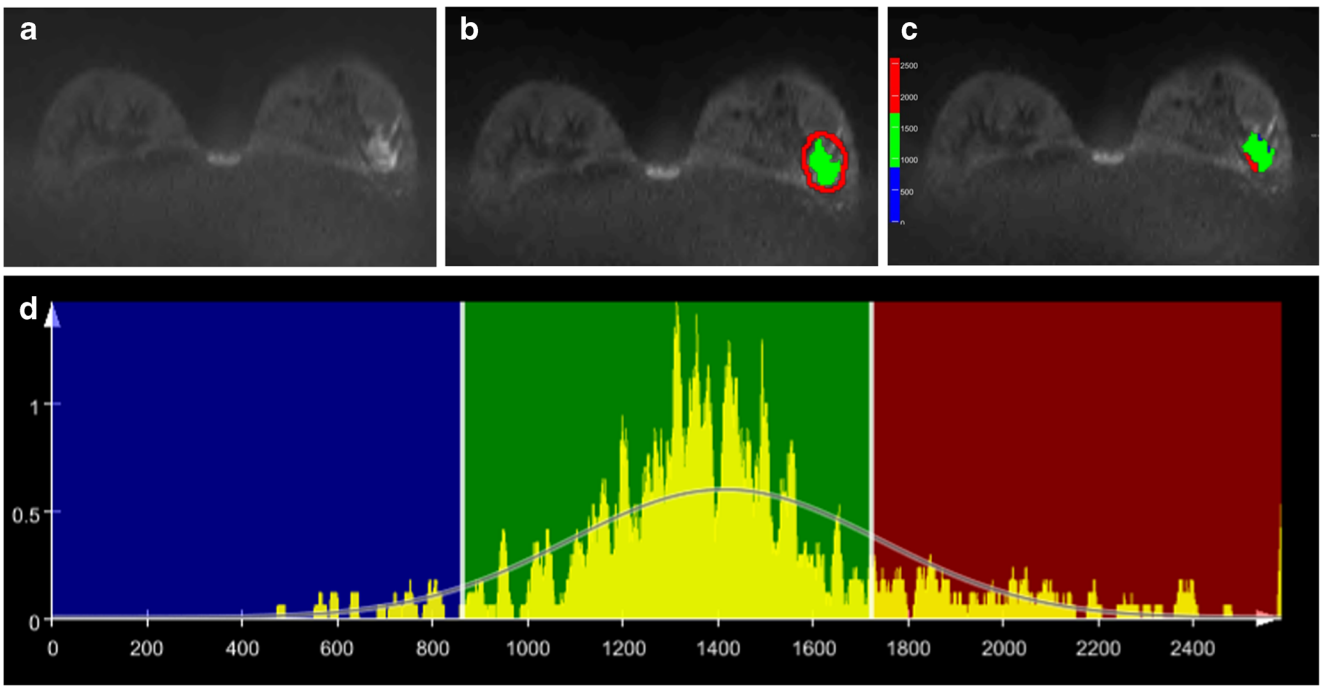

Fig. 1 Example of semiautomatic tumour segmentation using the random walker algorithm. The reviewers identified lesions with signal intensities higher than those in normal breast tissue on diffusion-weighted imaging (b = 1000 s/mm^2) (**a**) and manually tagged foreground seed points (**b**) (green area) to mark the tumour location and background seed points (**b**) (red outline) to define the outside of the tumour. Diffusion-weighted imaging with tumour volume reconstruction of apparent diffusion coefficient values (**c**) and the histogram of whole-lesion volume of interest (**d**) were generated

considered as high-level expression, and for p53, nuclear staining of at least 10% was considered as positive.

Statistical analysis

Categorical variables were analysed using the chi-square test or Fisher's exact test when the expected value in any cell was less than 5. Continuous variables were checked for normality and equal variance, using the Shapiro–Wilk test and Levene's F test, respectively, and were expressed as the mean ± standard deviation. Variables that did not show normality and equal variance were analysed using Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) were used to evaluate the ability of each ADC parameter to discriminate low-risk DCIS from non-low-risk DCIS lesions. On the basis of ROC analysis, the optimal cut-off value was determined by using the maximum Youden index (i.e. sensitivity + specificity − 1). Multivariate logistic regression analysis was performed to identify independent variables that were associated with low-risk DCIS by including all significant variables ($p < 0.05$) from univariate analysis. A forward stepwise selection procedure was used for analysis. The intra- and interobserver variabilities of the ADC measurements were evaluated using the intraclass correlation coefficient (ICC). ICCs were interpreted according to the criteria of Landis and Koch [17]: ICC ≤ 0.20, slight agreement; 0.2 < ICC ≤ 0.4, fair agreement; 0.4 < ICC ≤ 0.6, moderate agreement; 0.6 < ICC ≤ 0.8, substantial agreement; 0.8 < ICC, almost perfect agreement.

Data were analysed using the software packages SPSS (version 18.0; SPSS) and MedCalc (ver. 10.3.0.0, MedCalc software). A p value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

Of 93 pure DICS lesions, 37 (39.8%) presented as masses and 56 (60.2%) as non-mass enhancement on MR imaging. Among them, 10 (10.8%) were classified as low-risk DCIS and 83 (89.2%) were classified as non-low-risk DCIS (43 grade 2 and 40 grade 3). Nine (90.0%) lesions of low-risk DCIS and 51 (61.4%) lesions of non-low-risk DCIS were asymptomatic. The mean tumour size on final pathologic examination is significantly different between low-risk DCIS lesions and non-low-risk DCIS lesions (mean ± standard deviation, 1.15 cm ± 0.72 cm vs. 4.37 cm ± 2.22 cm, respectively; $p < .001$). The low-risk DCIS group had more cases of smaller tumour size (< 2 cm) and low Ki-67 expression compared with non-low-risk DCIS group (80.0% vs. 14.5%, $p < .001$; 90.0% vs. 38.6%, $p = .002$; respectively). There were no significant differences in the mean age, lesion type on MR imaging, type of surgery, breast symptoms and the expression statuses of ER, PR, HER2 and P53 between the two groups (Table 1).

Comparison of ADC parameters between low-grade DCIS and non-low-grade DCIS

The mean and 5th, 50th and 95th percentiles of ADC from whole-lesion histogram analysis all showed significant differences between low-risk DCIS and non-low-risk DCIS (1.522, 1.207, 1.536 and 1.854 × 10^{-3} mm^2/s vs. 1.270, 0.917, 1.261 and 1.657 × 10^{-3} mm^2/s, respectively; $p = .004$, $p = .003$, $p = .004$ and $p = .024$, respectively). Skewness also showed a significant difference between low-risk DCIS and non-low-risk DCIS (− 0.205 ± 0.603 vs. 0.253 ± 0.636, $p = .047$). Kurtosis, however, did not demonstrate a significant difference ($p = .077$) (Table 2).

When the ROI-based measurements were used, ADC_{mean}, ADC_{min} and ADC_{max} were not significantly different between low-risk DCIS and non-low-risk DCIS (1.354, 1.109 and 1.576 × 10^{-3} mm^2/s vs. 1.265, 0.987 and 1.578 × 10^{-3} mm^2/s; $p = .132$, $p = .090$ and $p = .980$, respectively) (Table 2).

ROC curve analysis

The results of ROC analysis for the various ADC parameters are shown in Table 3 and Fig. 2. In the differentiation of low-risk DCIS from non-low-risk DCIS, 5th percentile ADC yielded the largest AUC (0.786; 95% confidence interval [CI], 0.688, 0.864) among the histogram ADC metrics, followed by 50th percentile ADC, mean ADC, 95th percentile ADC and skewness (0.782, 0.780, 0.720 and 0.693, respectively) (Table 3); however, the differences of AUCs were not statistically significant ($p > .05$ for all comparisons). Among the ROI-based ADC parameters, ADC_{min} yielded the largest AUC (0.664; 95% CI, 0.559, 0.759), which was significantly lower than that of 5th percentile ADC ($p = .045$).

On the basis of ROC curve analysis, the optimal cut-off value for the 5th percentile ADC to discriminate low-risk DCIS from non-low-risk DCIS was 1.078 × 10^{-3} mm^2/s, yielding sensitivity and specificity values of 80% and 75.9%, respectively (Fig. 2). With use of this cut-off value, 5th percentile ADC was stratified into two groups and entered as a categorical variable in the logistic regression model.

Univariate and multivariate analysis

In the univariate analysis, a high 5th percentile ADC (> 1.078 × 10^{-3} mm^2/s) ($p = .002$), small tumour size (≤ 2 cm) ($p < .001$) and low expression of Ki-67 (< 14%) ($p = .013$) were

Table 1 Comparison of clinicopathological characteristics between low-risk and non-low-risk ductal carcinoma in situ

Variable	Total (n = 93)	Low-risk DCIS (n = 10)	Non-low-risk DCIS (n = 83)	p value
Mean age, years[a]	51.90 ± 9.51	52.22 ± 8.57	49.30 ± 10.54	.401
Lesion type on MR imaging				0.167
Mass	37 (39.8)	6 (60.0)	31 (37.3)	
Non-mass enhancement	56 (60.2)	4 (40.0)	52 (62.7)	
Type of surgery				.184
Breast-conserving surgery	54 (58.1)	8 (80.0)	46 (54.4)	
Mastectomy	39 (41.9)	2 (20.0)	37 (44.6)	
Breast symptoms				.091
No	60 (64.5)	9 (90.0)	51 (61.4)	
Yes	33 (35.5)	1 (10.0)	32 (39.6)	
Mean tumour size (cm)[a]	4.02 ± 2.33 (0.4, 10.5)	1.15 ± 0.72 (0.5, 2.5)	4.37 ± 2.22 (0.4, 10.5)	< .001
Tumour size				< .001
≤ 2 cm	20 (21.5)	8 (80.0)	8 (80.0)	
> 2 cm	73 (78.5)	2 (20.0)	71 (85.5)	
ER status				.098
Negative	31 (33.3)	1 (10.0)	30 (36.1)	
Positive	62 (66.7)	9 (90.0)	53 (63.9)	
PR status				.120
Negative	40 (43.0)	2 (20.0)	38 (45.8)	
Positive	53 (57.0)	8 (80.0)	45 (54.2)	
HER2 status				.111
Negative	43 (46.2)	7 (70.0)	36 (43.4)	
Positive	50 (53.8)	3 (30.0)	47 (56.6)	
Ki-67 status				.002
< 14%	41 (44.1)	9 (90.0)	32 (38.6)	
≥ 14%	52 (55.9)	1 (10.0)	51 (61.4)	
P53 status				.111
Negative	63 (67.7)	9 (90.0)	54 (65.1)	
Positive	30 (32.3)	1 (10.0)	29 (34.9)	

[a] Data are mean values ± standard deviations, and numbers in parentheses are the ranges. Unless otherwise noted, numbers in parentheses are percentages

DCIS ductal carcinoma in situ, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

associated with a higher probability of low-risk DICS. Variables that showed statistical significance ($p < .05$) at univariate analysis were entered into the multivariate analysis. Finally, multivariate regression analysis showed that a high 5th percentile ADC (> 1.078×10^{-3} mm^2/s) (adjusted odds ratio (OR), 10.494; 95% CI, 1.550, 71.053; $p = .016$), small tumour size (≤ 2 cm) (adjusted OR, 12.692; 95% CI, 1.929, 83.498; $p = .008$) and low expression of Ki-67 (< 14%) (adjusted OR, 10.879; 95% CI, 1.040, 113.863; $p = .046$) were significantly associated with low-risk DCIS (Table 4).

Reliability of ADC measurements

All measurements of whole-lesion histogram analysis showed almost perfect intraobserver and interobserver reliability (ICC = 0.902–0.946 and ICC = 0.871–0.920, respectively). All measurements of ROI-based analysis showed substantial intraobserver and interobserver reliability (ICC = 0.702–0.756 and ICC = 0.674–0.749, respectively).

Discussion

Our results showed that histogram-based ADC metrics derived from whole-lesion assessment could be helpful for differentiating between low-risk DCIS and non-low-risk DCIS lesions. Furthermore, multivariate analysis showed that a high 5th percentile ADC (> 1.078×10^{-3} mm^2/s) was a significant factor associated with low-risk DCIS, in addition to small tumour size (≤ 2 cm) and low expression of Ki-67 status (< 14%). Our findings suggest that assessment with whole-lesion histogram analysis of the ADC could play a role in risk stratification of patients with DCIS, thereby preventing the potential overtreatment of patients with low-risk tumours.

Table 2 Apparent diffusion coefficient parameters between low-risk and non-low-risk ductal carcinoma in situ

Variable	Total (n = 93)	Low-risk DCIS (n = 10)	Non-low-risk DCIS (n = 83)	p value
Whole-lesion histogram analysis				
Mean ADC ($\times 10^{-3}$ mm^2/s)	1.297 ± 0.218	1.522 ± 0.227	1.270 ± 0.201	.004
5th percentile ADC ($\times 10^{-3}$ mm^2/s)	0.948 ± 0.279	1.207 ± 0.258	0.917 ± 0.266	.003
50th percentile ADC ($\times 10^{-3}$ mm^2/s)	1.291 ± 0.227	1.536 ± 0.249	1.261 ± 0.207	.004
95th percentile ADC ($\times 10^{-3}$ mm^2/s)	1.678 ± 0.270	1.854 ± 0.266	1.657 ± 0.264	.024
Skewness	0.204 ± 0.645	– 0.205 ± 0.603	0.253 ± 0.636	.047
Kurtosis	0.191 ± 1.579	– 0.518 ± 0.447	0.277 ± 1.645	.077
ROI-based measurement				
ADC_{mean} ($\times 10^{-3}$ mm^2/s)	1.272 ± 0.210	1.354 ± 0.118	1.265 ± 0.217	.132
ADC_{min} ($\times 10^{-3}$ mm^2/s)	1.000 ± 0.248	1.109 ± 0.182	0.987 ± 0.252	.090
ADC_{max} ($\times 10^{-3}$ mm^2/s)	1.578.16 ± 0.265	1.576 ± 0.162	1.578 ± 0.275	.980

DCIS ductal carcinoma in situ, *ADC* apparent diffusion coefficient

With the widespread use of screening mammography, the incidence of DCIS has increased over the past three decades [18], and currently accounts for 20–25% of screening-detected cancers [19]. Recently, many researchers have been made efforts to better stratify the risk of DCIS using DWI [8–11]. Iima et al reported a negative correlation between DCIS grade and ADC obtained with DWI, and suggested that ADC could play a role as a biomarker for low-grade DCIS [8]. However, in the other DWI studies, no significant differences were observed in the ADC values based on the DCIS grade [9–12]. This discrepancy may be attributed to the ROI-based ADC measurements used in the previous DWI studies. ROI-based analysis is based on the selected ROI placed on a representative image of the tumour, and the ROI size and positioning have been shown to influence tumour ADC values [20]. In addition, in cases of non-mass lesions, this assessment may involve more partial volume averaging with normal tissue compared to ADC measurement of focal mass lesions [21]. The lower diagnostic accuracy of DWI in lesions with non-mass enhancement has also been reported [22].

Recently, histogram-based assessment has been used for improving the performance of ADC in a quantitative manner. This assessment can be used to evaluate the distribution of ADC values within the lesion by using metrics that reflect the frequency of intralesional voxels. It generally uses a volumetric approach, incorporating all voxels within the lesions on all slices and thus provides a more comprehensive evaluation of the entirety of the heterogeneous tumours [23]. The value of whole-lesion histogram analysis of the ADC for estimating tumour aggressiveness has been observed in invasive breast cancer [24–26]. However, to our knowledge, the utility of this approach for differentiating DCIS grade has not been fully evaluated. In our study, tumour ADC values were analysed using both whole-lesion histogram-based assessment and conventional ROI-based method. In addition, volumetric histogram analysis was performed semiautomatically using dedicated software. Our results showed that histogram-based ADC metrics (mean and 5th, 50th and 95th percentiles of ADC) for low-risk DCIS were significantly higher than those for non-low-risk DCIS lesions. Although ROI-based

Table 3 Area under the receiver operating characteristic curve in the differentiation of low-risk ductal carcinoma in situ for non-low-risk ductal carcinoma in situ

Variable	Area under the curve	Standard error	95% confidence interval	p value
Whole-lesion histogram analysis				
Mean ADC	0.780	0.082	0.682, 0.859	.001
5th percentile ADC	0.786	0.087	0.688, 0.864	.001
50th percentile ADC	0.782	0.081	0.684, 0.861	.001
95th percentile ADC	0.720	0.094	0.617, 0.808	.020
Skewness	0.693	0.091	0.589, 0.785	.035
ROI-based measurement				
ADC_{mean}	0.605	0.077	0.499, 0.705	.174
ADC_{min}	0.664	0.086	0.559, 0.759	.058
ADC_{max}	0.502	0.077	0.397, 0.608	.975

ADC apparent diffusion coefficient

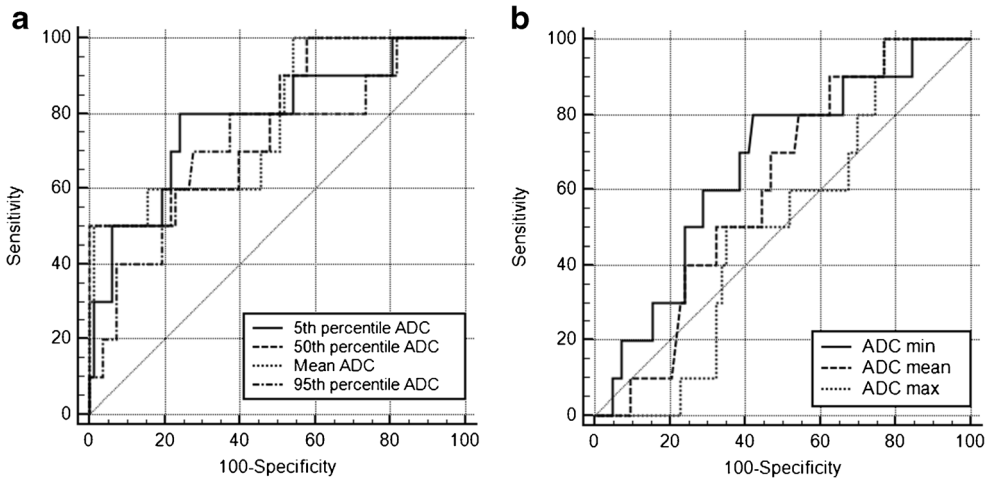

Fig. 2 Receiver operating characteristic curves of **a** whole-lesion histogram apparent diffusion coefficient (ADC) metrics and **b** ROI-based ADC parameters for differentiating low-risk ductal carcinoma in situ (DCIS) from non-low-risk DCIS

ADC metrics (ADC_{min}, ADC_{mean} and ADC_{max}) demonstrate a similar trend, they did not show a significant difference. Furthermore, AUC for 5th percentile ADC was significantly larger than that of ROI-based ADC parameters. Because DCIS is heterogeneous and frequently presents as non-mass enhancement or multifocal tumours on MR imaging [27], manual ROI-based assessment may be prone to sampling bias and might not fully reflect the actual biology of DCIS. In contrast to our findings, in the study by Mori et al [25], all ADC parameters of the conventional method and histogram analysis showed significant negative correlations with Ki-67 index. Thus, the authors suggested the conventional method would be practical to use for estimating the Ki-67 index. However, in that study, luminal-type invasive breast cancers were evaluated and the segmentation method was different from our study. Semiautomated volumetric ADC measurements have been reported to have better interobserver agreement than manual ROI-based axial measurements [28]. Reproducible measurement methods are required to develop quantitative biomarkers of DCIS. We believe that assessment with whole-lesion histogram analysis of the ADC may be more appropriate for evaluation and characterisation of DCIS, and such ADC metrics could have the potential to further improve the role of ADC in risk stratification of DCIS.

In our study, among the whole-lesion histogram ADC metrics, the best discriminative power to differentiate low-risk from non-low-risk DCIS was achieved by 5th percentile ADC, which represents the lowest percentile provided in the current study. Likewise, Suo et al reported that the minimum and 25th percentile ADCs derived from histogram analysis outperformed the mean or median ADC in differentiating malignant from benign breast lesions [29]. In an ROI-based study, minimum ADC also had the largest AUC among the various studied ADC parameters [30]. It is well known that the ADC is inversely correlated with tissue cellularity [31]. The region showing minimum ADC may reflect the highest cellular area within the tumour, which is more representative of tumour grade or aggressiveness. We assume that low percentile ADC based on whole-lesion histogram analysis may facilitate accurate grading of DCIS.

Table 4. Univariate and multivariate logistic regression analysis for low-risk ductal carcinoma in situ

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	*p* value	Odds ratio (95% confidence interval)	*p* value
5th percentile ADC (> 1.078×10^{-3} mm^2/s)	12.60 (2.471, 64.251)	.002	10.494 (1.550, 71.053)	.016
Age	0.971 (0.908, 1.039)	.398		
Size (≤ 2 cm versus > 2 cm)	23.667 (4.474, 125.204)	< .001	12.692 (1.929, 83.498)	.008
ER status (positive versus negative)	5.094 (0.615, 42.186)	.131		
PR negativity (positive versus negative)	3.378 (0.676, 16.874)	.138		
HER2 positivity (negative versus positive)	3.046 (0.736, 12.609)	.124		
Ki-67 status (< 14% versus ≥ 14%)	14.344 (1.734, 118.635)	.013	10.879 (1.040, 113.863)	.046
P53 status (negative versus positive)	4.833 (0.583, 40.054)	.144		

ADC apparent diffusion coefficient, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

DCIS is a heterogeneous disease entity with variable malignant potential, meaning that the treatment should be personalised according to its characteristics. Although the mortality of pure DCIS is less than 1–2% [32], most women with DCIS are undergoing the same treatment as for invasive cancer. Moreover, a steady increase in the percentage of women undergoing mastectomy for DCIS between 2004 and 2011 in the USA has been reported [33]. Better characterisation of DCIS biology with non-invasive imaging methods in conjunction with an established knowledge of the histopathologic, molecular and genomic profiles of tumours could help to allow individualised treatment strategies. Some previous studies attempted to differentiate the grade of DCIS with DCE MR imaging. Although variable results have been noted, recent studies did not show a significant difference in the kinetic and morphological characteristics of pure DCIS lesion based on DCIS grade [20, 34, 35]. DWI is a functional MR technique that assesses distinct tissue properties quantitatively compared with DCE MR imaging. Our study yielded promising results, which might provide valuable preoperative information regarding the grade of DCIS if verified in future prospective studies. To establish the ADC as a more clinically relevant imaging biomarker, further standardisation of DWI acquisition protocol is required.

Our study had limitations. First, this is a retrospective study from a single tertiary academic institution with a limited number of patients. Selection bias may exist because all patients were diagnosed with DCIS by core needle biopsy and had undergone breast MR imaging and DWI; thus, the results may not be generalizable to other populations. Second, DWI was performed in patients with DCIS confirmed through core needle biopsy, which may affect the results of ADC measurement. Third, quantitative analysis of ADC metrics was performed using a software package, which was developed by the manufacturer of the MR system and not currently available. Fourth, as a result of the small sample size, we did not perform a subgroup analysis of small DCIS lesions. Only 20 (21.5%) were less than 2 cm in diameter in this study. Furthermore, partial-volume averaging may lead to inaccurate ADC measurements in these small lesions, especially if they demonstrate non-mass enhancement on breast MR imaging. Further improvements in DWI techniques may provide thinner slice thickness to reduce the partial-volume averaging.

In conclusion, whole-lesion histogram ADC metrics could be helpful for differentiating low-risk DCIS from non-low-risk DCIS. In addition, a high 5th percentile ADC (> 1.078 $\times 10^{-3}$ mm^2/s) was a significant factor for predicting low-risk DCIS on multivariate analyses. Our results suggest that histogram ADC metrics obtained from whole-lesion assessment of DWI might serve as imaging biomarkers for risk stratification of patients with DCIS, thereby allowing better tailoring of treatment strategies and potentially reducing overtreatment in patients with low-risk DCIS. Prospective studies with large cohorts of patients with DCIS are warranted to further validate this technique.

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Compliance with ethical standards

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Ethical approval Institutional review board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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