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Original Article

Differentiation of malignant and benign breast lesions with diffusion-weighted imaging: What is the optimum apparent diffusion coefficient value?

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Abstract

Background and objective: To determine the optimum apparent diffusion coefficient (ADC) value in differentiating benign from malignant breast lesions.

Materials and Methods: The study is a retrospective review of the patients who underwent breast magnetic resonance imaging (MRI) at King Chulalongkorn Memorial Hospital between January 2017 and May 2020. ADC values were measured by placement of region of interest (ROI) within the breast lesions using Philips DynaCAD breast analysis system and comparing it with histopathological diagnosis. A receiver-operating-characteristics (ROC) analysis was plotted and the area under the curve (AUC) was evaluated to find the ideal ADC value in the differentiation of benign and malignant breast lesions.

Results: Two hundred and ten lesions in 163 female patients were included in the present study. One hundred twenty-six lesions (60%) were malignant and eighty-four lesions (40%) were benign. The mean ADC values of malignancy ($0.913x10^{-3}$ mm^2/s) were statistically lower than that of benign lesions ($1.080x10^{-3}$ mm^2/s) (mean difference $0.169x10^{-3}$ mm^2/s, $P < 0.001$). According to the ROC analysis, the optimum cut-off ADC value of $0.991x10^{-3}$ mm^2/s was an excellent predictor for differentiated benign and malignant breast lesions (AUC = 0.835, sensitivity 78.6%, specificity 82.5%, accuracy 81%, PPV 85.3% and NPV 75%).

Conclusion: Diffusion-weighted imaging (DWI) was an effective MRI sequence to assess breast cancer by using ADC value as a key parameter in addition to other important imaging findings from MRI. The present study showed the mean ADC value of malignancy was statistically significantly lower than that of benign lesions. The cut-off ADC value of $0.991x10^{-3}$ mm^2/s had good specificity, accuracy, and PPV to differentiate benign from malignant breast lesions.

Keywords: ADC, Benign breast lesion, DWI, Malignant breast lesion, MRI.

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Introduction

Breast cancer is the most common cancer in women worldwide and a major leading cause of cancer-related death in women in developing countries [1-2]. Therefore, women must be properly screened to detect breast cancer early to get effective treatment and better outcomes [3].

A mammogram is a common modality for breast cancer screening in average-risk women, but it has lower sensitivity in dense breast tissue [3, 4]. Ultrasound is an additional tool for mammograms in screening dense breasts [5]. However, it is an operator-dependent procedure and limited detection of breast calcifications [6]. Nevertheless, for high-risk women, magnetic resonance imaging (MRI) is highly recommended as a supplement modality [4].

Nowadays, MRI is an essential imaging modality for screening, diagnosis, staging, and follow-up for breast lesions, because of high sensitivity in the detection of breast cancer [7-8]. Diffusion-weighted imaging (DWI) is an advanced MRI technique that provides the apparent diffusion coefficient (ADC) value as a quantitative parameter, measuring the Brownian motion of water molecules within tissues and demonstrating the difference in cellular density, membrane integrity, and tissue microstructure [9-10]. In malignancy, a lower ADC value is commonly reflected due to increased cellular density while a benign lesion has a higher ADC value [8]. Therefore, DWI with ADC value is one of the effective tools to detect malignant breast lesions [11]. Nevertheless, there is no exact specific ADC value to differentiate malignant from benign breast lesions [11-12].

The purpose of this study was to find the optimum ADC value in DWI to accurately predict malignant breast lesions and to determine the ADC values among different types of breast cancers and benign breast lesions.

Materials and methods

Patients and lesions

This retrospective study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, with a waiver of informed consent. Demographic and clinical data were reviewed from the medical records in the hospital information system (HIS).

The study reviews all MRI data of female patients who underwent breast MRI at King Chulalongkorn Memorial Hospital between January 2017 and May 2020. The inclusion criteria were: 1) The size of the focal breast lesion was more than 5 mm, 2) MRI underwent DWI with a b-value of 800 s/mm^2, and 3) Pathologic or cytologic diagnosis was required in all breast lesions. When more than one pathological result was available for a patient, only the most clinically significant pathological result was recorded.

Patients with a history of chemotherapy, breast intervention, or radiotherapy on the lesion side, or insufficient imaging follow-up period (less than 2 years) were excluded from the study. Lesions with indeterminate pathological results or poor MRI quality such as significant artifacts or inadequate fat suppression were also excluded. A total of 210 lesions in 163 patients were enrolled in this study.

MRI technique

All MRIs were performed using a 1.5-Tesla system with a standard protocol. The pre-contrast sequences are as follows: axial T1-weighted with fat suppression, T2-weighted turbo spin echo (TSE), short-T1 inversion recovery (STIR), and coronal T1-weighted sequences.

Dynamic contrast-enhanced (DCE)-MRI was obtained, using a bolus injection of 0.1 mmol/kg gadobutrol (Gadovist; Bayer Healthcare Pharmaceuticals, Inc., Whippany, NJ, USA). Axial 3D T1-weighted high resolution, T1-weighted with fat suppression with and without subtraction, and sagittal T2-weighted with fat suppression were obtained. Maximum intensity projection (MIP) reconstruction images and DWI sequence were also acquired. ADC maps were created automatically by using b values of 800 s/mm^2.

THE ASEAN JOURNAL OF RADIOLOGY
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Imaging analysis

The authors reviewed the MRI images according to the American College of Radiology, Breast Imaging Reporting and Data System (ACR BI-RADS) MR Lexicon edition 2013. The MRI was reviewed to define patients with mass or non-mass enhancement. The kinetic curve type (1, 2, or 3), DWI, and ADC were assessed. ADC values were delineated by manual placement of region of interest (ROI) within the breast lesions using the Philips DynaCAD breast analysis system. Then, MRI findings were concluded into ACR-BIRADS categories. All clinical data and pathological diagnoses were blinded to the authors.

Histopathological acquisition

Pathological diagnosis was obtained subsequent to fine needle biopsy (FNA), core needle biopsy (CNB), excisional biopsy, lumpectomy, or mastectomy, based on pathological reports in HIS and considered as the reference standard. All of the breast lesions were classified as benign or malignant groups and subdivided into benign and malignant diseases.

Statistical analysis

Descriptive statistical data were reported as mean, standard deviation (SD), frequency, and percentage. Receiver Operating Characteristic (ROC) curve was plotted and Youden's index was used to identify the optimal cut-off of ADC value. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of this ADC value were reported.

The mean ADC values were compared within subgroups of benign and malignant lesions, using one-way analysis of variance and Tukey Post-Hoc Test as a multiple comparison method.

P value < 0.05 was considered to indicate the statistical significance.

All statistical analyses were performed using Jamovi version 2.3.21.0 [13].

Results

Patient demographics

A total of 163 patients with 210 lesions were evaluated. Demographic data of the patients were summarized in Table 1, the mean age of the patients was 51.1 years (range 20-84 years). About 37 (22.7%) patients had a family history of breast cancer.

The clinical indications for breast MRI were abnormal mammography or ultrasound in 53 (32.5%) cases, palpable mass in 86 (52.8%) cases, mastalgia or breast discomfort in 10 (6.1%) cases, nipple discharge in 10 (6.1%) cases, nipple retraction 1 (0.6%) case, and for screening 3 (1.8%) cases.

Table 1. *Demographic data of the patients.*

Patients, n = 163	Total
Age, years	
Mean (SD)	51.1 (12.1)
Range	20-84
Clinical indications, n (%)	
Abnormal mammography or ultrasound	53 (32.5)
Palpable mass	86 (52.8)
Mastalgia or breast discomfort	10 (6.1)
Nipple discharge	10 (6.1)
Nipple retraction	1 (0.6)
Screening	3 (1.8)
Family history, n (%)	
Breast cancer	37 (22.7)
None	105 (64.4)
Not mentioned	21 (12.9)

THE ASEAN JOURNAL OF RADIOLOGY
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Lesions characteristics

Characteristics of a total of 210 lesions were demonstrated in Table 2, which included benign and malignant lesions of 84 and 126 lesions, respectively. One hundred sixty-seven lesions (79.5%) were mass lesions, including 99 (59.3%) malignant lesions and 68 (40.7%) benign lesions. The other 43 lesions (20.5%) were non-mass lesions, including 27 (62.8%) malignant lesions and 16 (37.2%) benign lesions.

In DCE-MRI, the dynamic curve features were categorized into 3 types of enhancement (type 1: persistent enhancement, type 2: plateau, type 3: rapid enhancement with washout) and no enhancement. The malignant group was more likely to present as type 3 (82.9%) compared with benign lesions (17.1%), while the benign lesions had type 1 (69.5%) ($P < 0.001$), predominantly. All the non-enhancing lesions were pathologically confirmed as benign.

According to BI-RADS, the majority of BI-RADS 4b, 4c, and 5 categories were pathologically diagnosed as malignancy ($P = 0.003$), about 19 lesions (61.3%), 13 lesions (61.9%) and 66 lesions (72.5%), respectively.

Table 2. *Lesions characteristics.*

Total lesions, n	210	Pathological diagnosis		P-value
		Benign, n (%)	Malignant, n (%)	
		84 (40)	126 (60)	
Types				
Mass lesions, n (%)	167	68 (40.7)	99 (59.3)	0.675
Non-mass lesions, n (%)	43	16 (37.2)	27 (62.8)	
Contrast uptake phase				
Type 1: Persistent enhancement, n (%)	82	57 (69.5)	25 (30.5)	
Type 2: Plateau, n (%)	49	11 (22.4)	38 (77.6)	< 0.001
Type 3: Rapid enhancement with washout, n (%)	76	13 (17.1)	63 (82.9)	
No enhancement, n (%)	3	3 (100)	0 (0)	
BIRADS				
2, n (%)	11	8 (72.7)	3 (27.3)	
3, n (%)	5	2 (40.0)	3 (60.0)	
4a, n (%)	51	29 (56.9)	22 (43.1)	0.003
4b, n (%)	31	12 (38.7)	19 (61.3)	
4c, n (%)	21	8 (38.1)	13 (61.9)	
5, n (%)	91	25 (27.5)	66 (72.5)	

ADC analysis

The mean ADC value of malignant lesions ($0.913x10^{-3}mm^2/s$) was significantly lower than that of benign lesions ($1.08x10^{-3}mm^2/s$), showing a mean difference of about $0.169x10^{-3}mm^2/s$, $P < 0.001$ (Table 3). Representative images of benign and malignant breast lesions were exhibited in Figure 1 and Figure 2, respectively.

Table 3. *Comparison of the mean ADC values between benign and malignant breast lesions.*

Mean ADC values ($1.08x10^{-3}mm^2/s$)		Means difference (95% CI)	P-value
Benign	Malignant		
1.080	0.913	0.169 (0.27-0.71)	< 0.001

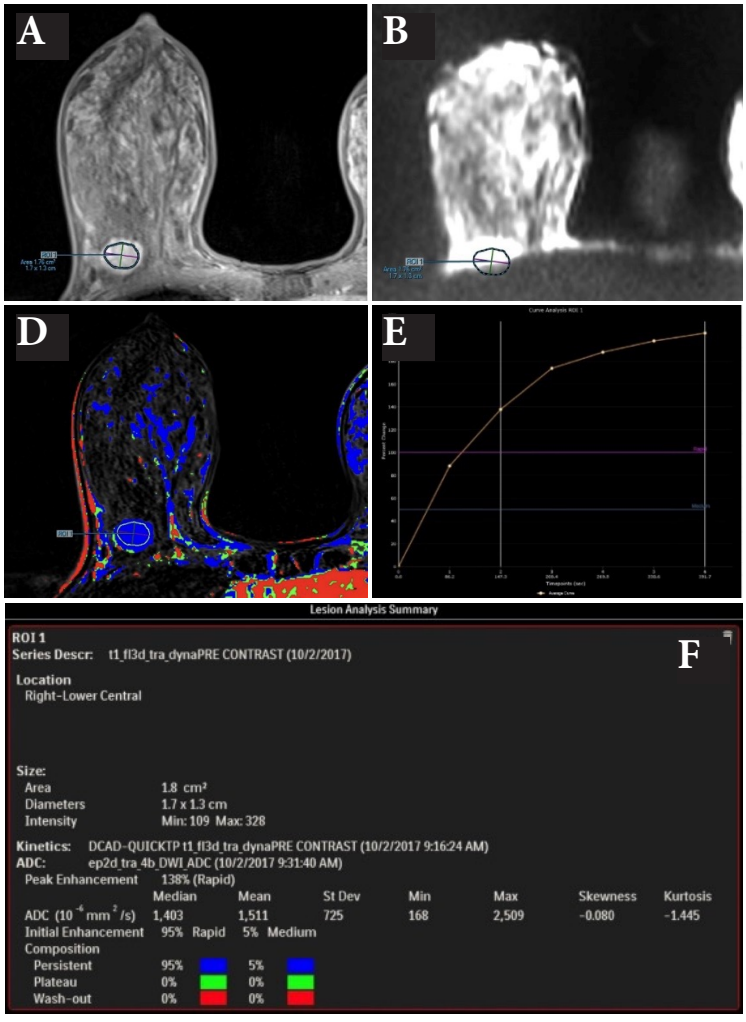

Figure 1. *A 41-year-old woman presented with palpable right breast mass. (A) DCE imaging showed circumscribed homogeneous enhancing mass in the posterior central part of the right breast. (B) DWI and (C) ADC showed no restricted diffusion. (D) The ADC value was calculated by placement of the region of interest (ROI) within the breast lesions. (E) Type 1 kinetic curve enhancement pattern was noted. (F) The mean ADC value of the ROI placed within the lesion was $1.511x10^{-3}$ mm^2/s. The patient underwent lumpectomy and pathology revealed benign dense fibrotic breast tissue.*

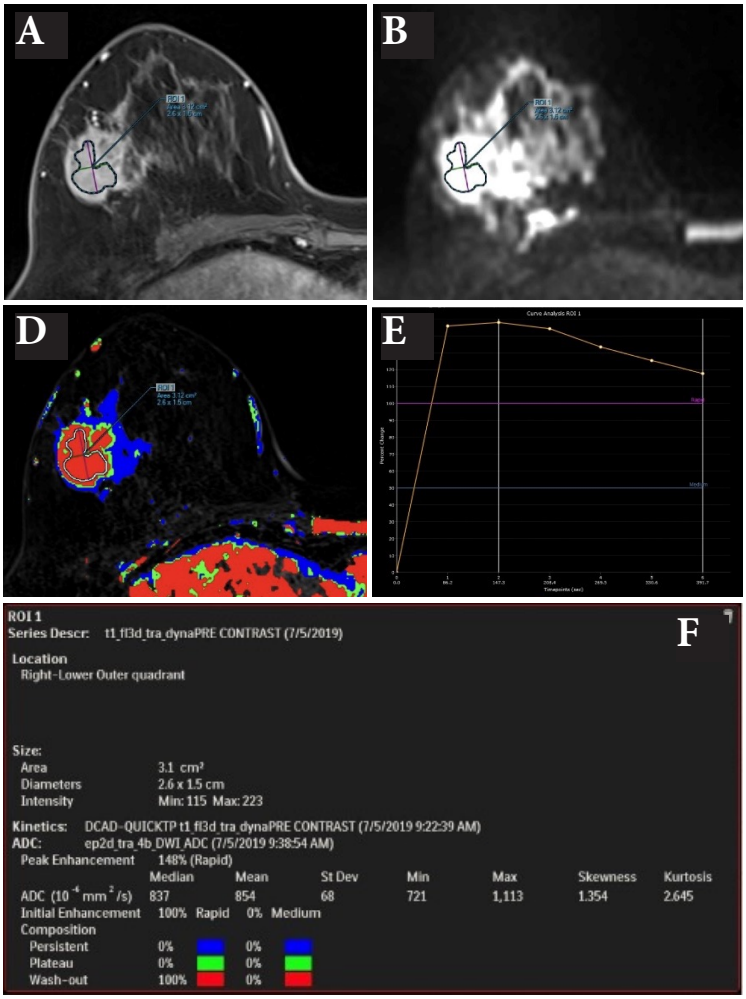

Figure 2. *A 42-year-old woman had invasive ductal carcinoma in her right breast. (A) DCE imaging showed an irregular heterogeneous enhancing mass in the lower outer quadrant of the right breast. (B) DWI and (C) ADC showed restricted diffusion, seen as low signal intensity in ADC image. (D) The ADC value was calculated by placement of the ROI within the breast lesions. (E) Type 3 kinetic curve enhancement pattern was seen. (F) The mean ADC value of the ROI placed within the lesion was 0.854x10^{-3} mm^2/s.*

The box plot of the ADC values of benign and malignant lesions was demonstrated in Figure 3. According to ROC analysis (Figure 4), the AUC was 0.837 and the optimum cut-off ADC value of 0.991x10^{-3} mm^2/s was an excellent predictor for differentiated benign and malignant breast lesions, showing sensitivity (78.6%), specificity (82.5%), accuracy (81%), PPV (85.3%) and NPV (75%) as shown in Table 4.

Table 4. *The optimal ADC value.*

ADC value (mm^2/s)	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)
$0.991x10^{-3}$	78.6% (74.8-88.7)	82.5% (68.3-86.8)	81% (75.0-86.0)	85.3% (79.2-89.8)	75.0% (66.9-81.7)

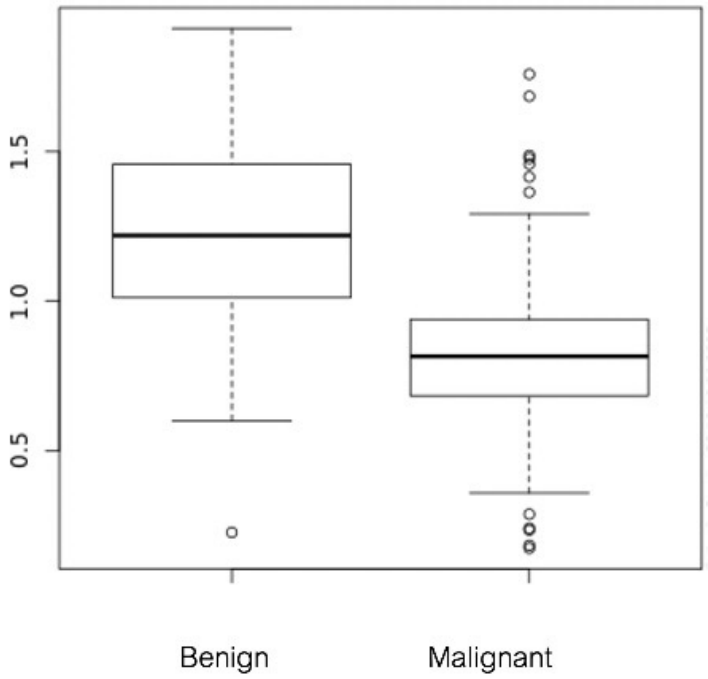

Figure 3. *Box plot of ADC values of benign and malignant breast lesions.*

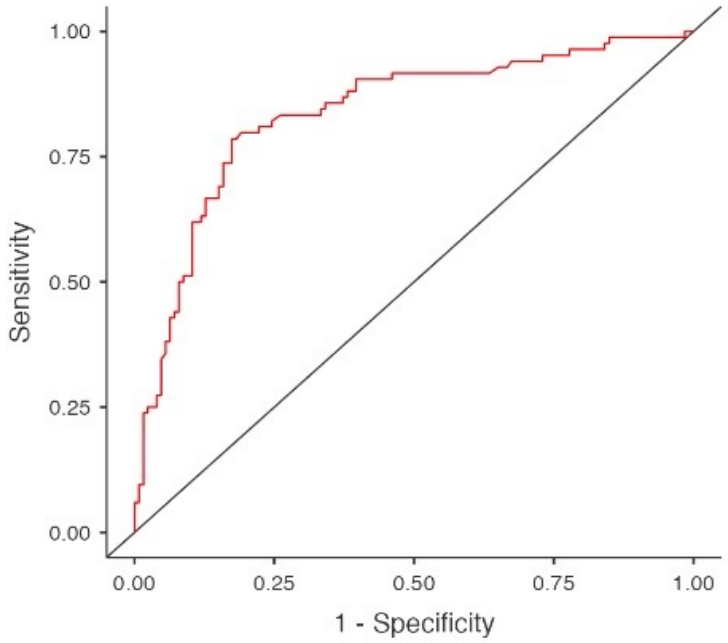

Figure 4. *Graph of ROC Curve demonstrates the diagnostic performance of ADC value of all breast lesions.*

According to the histopathological diagnosis (Table 5), the 126 malignant lesions were divided into 5 subtypes, including ductal carcinoma in situ (DCIS) (n = 21), invasive ductal carcinoma (IDC) (n = 94), invasive lobular carcinoma (ILC) (n = 3), papillary carcinoma (n = 6), and mixed IDC with ILC (n = 2). The 84 benign lesions were categorized into 7 subtypes, including fibroadenoma/fibrocystic change (n = 27), ductal hyperplasia (n = 2), papilloma (n = 19), sclerosing lesion (n = 3), mastitis (n = 2), benign lesions with unspecified pathological diagnosis (n = 16), normal breast tissues (n = 6), and mixed subtypes (n = 9). Mixed subtypes included fibrocystic change with sclerosing adenosis, complex sclerosing with ductal hyperplasia, fibrocystic change with ductal hyperplasia, papilloma with ductal hyperplasia, and fibrocystic change with sclerosing adenosis with ductal hyperplasia. The mean ADC values of all subtypes of the benign and malignant lesions were reported in Table 5, showing the first and second lowest mean ADC values of all lesions were mixed IDC with ILC (0.638 $x10^{-3}$ mm^2/s) and IDC (0.784 $x10^{-3}$ mm^2/s), respectively. As compared with the cut-off ADC value of 0.991$x10^{-3}$ mm^2/s, the maximal ADC values of ILC (0.989 $x10^{-3}$ mm^2/s), and mixed IDC with

ILC (0.713 x10^{-3} mm^2/s) were lower than the cut-off ADC value, whereas mastitis was the only benign breast lesion presented as higher minimum ADC value than the cut-off ADC value.

Table 5. *The optimal ADC value.*

ADC value (mm^2/s)	n (%)	Mean ADC (x10^{-3} mm^2/s) (SD)	Minimum ADC (x10^{-3} mm^2/s)	Maximum ADC (x10^{-3} mm^2/s)
Subtypes				
Fibroadenoma/Fibrocystic change/Cyst	27 (32.1)	1.320 (0.26)	0.607	1.790
Ductal hyperplasia	2 (2.4)	1.123 (0.52)	0.754	1.490
Papilloma	19 (22.6)	1.176 (0.30)	0.879	1.710
Benign complex sclerosing/ Sclerosing adenoma	3 (3.6)	1.196 (0.45)	0.701	1.910
Mastitis	2 (2.4)	1.444 (0.07)	1.393	1.500
Benign lesion, unspecified	16 (19)	1.200 (0.37)	0.600	1.890
Normal breast tissue	6 (7.1)	1.367 (0.43)	0.636	1.870
Mixed subtypes	9 (10.7)	0.978 (0.35)	0.226	1.520
Malignant, n = 126	**n (%)**	**Mean ADC (x10^{-3} mm^2/s) (SD)**	**Minimum ADC (x10^{-3} mm^2/s)**	**Maximum ADC (x10^{-3} mm^2/s)**
Subtypes				
DCIS	21 (16.7)	1.004 (0.36)	0.240	1.685
IDC	94 (74.6)	0.784 (0.24)	0.173	1.759
ILC	3 (2.4)	0.840 (0.17)	0.654	0.989
Papillary carcinoma	6 (4.8)	0.879 (0.43)	0.287	1.415
Mixed IDC with ILC	2 (1.6)	0.638 (0.11)	0.563	0.713

Among the mean ADC values of subtypes of malignancy, the mean ADC values of IDC and DCIS showed significant differences (mean difference = 0.220, P Tukey = 0.009), as displayed in Table 6. On the other hand, there was no statistically significant difference between the mean ADC values of subtypes of the benign group.

Table 6. *Post Hoc test shows mean difference of mean ADC values among different subtypes of breast cancers.*

	ILC	DCIS	Papillary carcinoma	Mixed IDC with ILC
IDC				
Mean difference	- 0.0555	- 0.220	- 0.0947	0.146
P-value	0.997	0.009	0.921	0.943
ILC				
Mean difference	-	- 0.165	- 0.0392	0.202
P-value	-	0.862	1.000	0.926
DCIS				
Mean difference	-	-	0.1256	0.366
P-value	-	-	0.855	0.363
Papillary carcinoma				
Mean difference	-	-	-	0.241
P-value	-	-	-	0.812

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Discussion

In the present study, BI-RADS 4b, 4c, and 5 categories show more likely to be malignant lesions than other BI-RADS categories. In the detail of lesion characteristics, the pathological diagnosis and kinetic curve features in DCE-MRI are significantly correlated, showing more likely to be malignancy in the type 3 kinetic curve, which has been reported in the previous literature [14]. However, our subgroup analyses of mass and non-mass lesions were found to be insignificant parameters in the differentiation of benign and malignant lesions.

Overall, the malignant group showed a significantly lower mean ADC value than that of the benign group, which agrees with the results of previous studies [15, 16, 17]. Nevertheless, there was still an overlapping of ADC values between these two groups. As shown in our study, the ideal cut-off ADC value of 0.991x $10^{-3}mm^2/s$ is an excellent predictor and improves the diagnostic performance of breast cancer with good specificity (82.5%), accuracy (81%), and PPV (85.3%). In several previous studies, ADC threshold values were still a broad spectrum to differentiate benign and malignant lesions due to several variable factors that could affect the ADC values such as different tesla strength [12]. One study also reported influencing factors, including MRI machine types and different b-values, with significant ADC diagnostic values in Asians [18]. Another study suggested that a b-value of 800 s/mm^2 be obtained as the best cut-off ADC value for the diagnosis of breast cancer [14] which is consistent with our study.

Furthermore, the comparison with our cut-off ADC value may imply that any breast lesion with a higher ADC value could be excluded from ILC, and mixed IDC with ILC. On the other hand, breast lesions with lower ADC values could be excluded from benign lesions such as mastitis. We observed that the ADC value among the malignant subtypes (DCIS, IDC, and papillary carcinoma) can present as high ADC values as compared to this cut-off ADC value which is consistent with the previous report by Gity et al. indicating that the highest ADC values of all benign and malignant lesions were papillary carcinoma and DCIS [19]. While the maximal ADC value of the IDC in their study was not predominantly high, our study investigated a larger number of IDC subtypes than the previous studies. Thus, these lesions should be carefully interpreted and correlated with other MRI sequences.

The current study also demonstrated that mean ADC values of IDC and DCIS were significantly different, consistent with the results reported by the previous study [12, 14]. Several studies have assessed the correlation between subgroups of benign and malignant breast lesions and ADC values, but there were still no previous studies that suggested the efficient ADC threshold for each subtype of benign and malignant lesions.

The limitations of our study include the fact that it has a retrospective design and it was conducted in a single institution with a relatively small sample size. Further prospective studies using the same MRI techniques with a larger number of malignant and benign lesions could increase statistical power.

Finally, the parameters adopted as predictors of breast cancer, including the cut-off ADC value, were unique in each institution due to several influencing factors such as tesla strength and b-value.

Conclusion

DWI was an effective MRI sequence to assess breast cancer by using ADC value as a key parameter. The present study showed that the mean ADC value of malignancy was statistically significantly lower than that of benign lesions. The cut-off ADC value of $0.991 \times 10^{-3} mm^2/s$ had good specificity, accuracy, and PPV to differentiate benign from malignant breast lesions. Moreover, using this cut-off ADC value can exclude some of the subgroups of benign and malignant breast lesions. However, some other breast lesions cannot be diagnosed using ADC alone due to variations in ADC values. To improve diagnostic performance, using ADC values with other important MRI findings is recommended.

Disclosure of Potential Conflicts of Interest
The authors declare that they have no conflict of interest.

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