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Comparison of apparent diffusion coefficient and relative apparent diffusion coefficient values for differential diagnosis of breast lesions

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ABSTRACT

Objectives: The purpose the study was to evaluate the role of diffusion weighted magnetic resonance imaging (DW-MRI) in diagnosis of benign and malignant breast lesions, to calculate a cut-off apparent diffusion coefficient (ADC) value and to explore use of relative ADC (r ADC) for improving sensitivity and specificity of MRI in diagnosis of breast cancer.

Methods: This retrospective study based on a cohort of patients who underwent dynamic contrast enhanced (DCE)-MRI having suspicious breast mass by ultrasonography and mammography to whom DWI sequence was added to the routine diagnostic MRI. ADC and r ADC (lesion/normal breast tissue) values of breast masses were calculated. The threshold ADC values used to differentiate benign and malignant lesions were determined using receiver operating characteristic analysis, sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Results: Malignant masses had significantly lower ADC (mean: $1.03 \pm 0.36 \times 10^{-3}$ mm^2/s) and r ADC (mean: $0.66 \pm 0.22 \times 10^{-3}$ mm^2/s) values than those of benign masses with ADC (mean: $1.50 \pm 0.56 \times 10{-}3$ mm^2/s) and r ADC (mean: $0.97 \pm 0.31 \times 10^{-3}$ mm^2/s) values, respectively ($p = 0.001$ for both). The best cut-off value for the lesion ADC was 1.09×10^{-3} mm^2/s with a sensitivity of 72.73%, and specificity of 79.17%. The best cut-off value for r ADC was 0.83 with sensitivity of 78.79% and specificity of 70.83%.

Conclusions: DWI has high diagnostic value with high sensitivity and specificity differentiating benign and malignant breast lesions. ADC and r ADC values can improve the diagnostic accuracy of differentiating benign and malignant breast lesions.

Keywords: Diffusion weighted imaging, MRI, apparent diffusion coefficient, relative ADC, breast mass

Breast cancer is still a common malignancy and cause of cancer death. Despite improvements in detection of breast cancer with the widespread application of mammography and ultrasonography (US), other screening methods may contribute to early diagnosis for women at increased risk of breast cancer. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) plays a significant role in breast lesion characterization in those with high risk factors including family history or genetic predisposition and young women with dense breast tissue and it has higher sensitivity over both mammography and US [1]. DCE-MRI can also support breast cancer staging, solving the question of the actual size of the lesion, multicen-

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tricity, residual tumor distinction better than mammography and US [2-4]. Nonetheless, several studies have shown that conventional breast MRI, including T2-weighted imaging and contrast-enhanced T1-weighted imaging, is constrained in terms of breast tumor specificity [5-7]. Consequently, significant interest has been expressed in the development of adjunct MRI methods to improve the specificity of DCE-MRI and diffusion weighted breast imaging has been investigating for its potential to boost breast disease diagnosis at the expense of a slight increase in examination time. Diffusion weighted magnetic resonance imaging (DW-MRI) is based on the random Brownian motion of water molecules which has potential to alter the signal intensity [8, 9]. This motion of water molecules is more restricted in highly cellular tissues (e.g., high grade tumors) or in case with intact cellular membrane whereas water molecules can easily diffuse in low cellular environment or where there is cell membrane destruction. A low cellular environment enables a greater extracellular space for water molecules to disperse, which can also freely move through destructed cellular membranes from the extracellular to the intracellular compartment. Hence the degree of tissue water diffusion is inversely associated with the cellularity of the tissue and the cell membrane integrity. Based on this phenomenon, DW-MRI can be used to evaluate many pathologic conditions in the body and can help differentiate cellularity of the histologic structure [8-12].

Diffusion is quantified by calculating what is known as the apparent diffusion coefficient (ADC) value in square millimeter per second, which describes the average area covered by a molecule per unit time. The ADC value can be calculated by assessing the signal attenuation that occurs at diffusion-weighted imaging performed at different b values [10-12].

Recent studies have shown that ADC values were significantly lower in malignant breast lesions compared to benign breast lesions because of the higher cellular density (due to the intensity of the tumor tissue) in malignant lesions [13-15].

Unfortunately, menstrual cycle and hormone-replacement therapy influence the ADC values obtained from diffusion weighted imaging (DWI) [16, 17]. Relative ADC (r ADC) value is defined to optimize ADC value, which is calculated by dividing ADC value of the breast lesion by adjacent breast parenchyma therefore minimizing the individual differences as well as the potential therapy effects. Furthermore, the r ADC value has been supposed to be unaffected by the menstrual cycle [18, 19].

The purpose of this study was to evaluate the role of DW-MRI in the diagnosis of benign and malignant breast lesions, to calculate a cut off ADC value and to explore use of r ADC for improving sensitivity and specificity of MRI in diagnosis of breast cancer.

METHODS

Study Population

This retrospective study was based on a cohort of patients who underwent DCE-MRI having suspicious breast mass by ultrasonography and mammography to whom a specific DWI sequence was added to the routine diagnostic focused MRI. The lesions categorized as Breast Imaging Reporting and Data System (BI-RADS) 3, 4 or 5 were included in the study. Part of the BIRADS 3 lesions which were followed for 2 years and decided as stable thus re-categorized as BI-RADS 2 were excluded from the study.

A 110 breast masses of 107 adult female patients with histopathological proven diagnosis were retrieved from the database over a 3-year-old period and retrospectively reviewed for the breast masses on the DWI images. Over the 110 breast masses, 22 were excluded due to the inability to reach the raw data of the images, 18 excluded due to poor image quality, 8 excluded because of uncertainty in identifying the match lesion with the pathology and 5 excluded as the lesions were smaller than 10 mm in size and diffusion weighted images were not identifiable. Eventually, 24 benign breast masses of 24 patients and 33 malignant breast masses of 32 patients were included in our study.

Magnetic Resonance Imaging

All individuals underwent a diagnostic focused MRI performed with a 1.5-Tesla (T) superconducting 8 channel MRI system (Phillips, Achieva) equipped with high-speed gradients. The MR images of breast in the sagittal and axial planes were obtained in the supine positions with a high-resolution breast-array coil. Turbo spin-echo T1-weighted (TR/TE, 514/10), turbo spin-echo T2-weighted (TR/TE, 4044/70), T1-weighted SPIR (600/minimum) with and without

gadolinium Gd-based contrast agents (0.1 mmol/kg of body weight) were acquired. DWI using single-shot spin-echo echo-planar imaging (EPI) was performed in axial plane with diffusion gradient b values of 0 and 800 mm²/s. The following DWI parameters were used: field of view (FOV) 175 (R-L) × 278 (AP) mm; number of excitations (NEX) 2; matrix size, 116 × 185; slice thickness, 3 mm intersection gap, none.

Image Interpretation

Before evaluating MR images, identifying information was removed from images. A radiologist (seven years of experience in breast imaging) evaluated the images for the quality, and to locate and mark the matched histopathological masses from the pathology records as well as evaluation of masses. After all images were reviewed, the diffusion-weighted images were transferred to a separate workstation (Phillips, Extended MR workspace, 2.6.3.4, Netherlands). Apparent diffusion coefficient (ADC) maps were generated. After four-week period, the same radiologist without looking at any patient data, measured the ADC values on the previously marked images. A circular region of interest (ROI) with a value of 50-70 mm² was placed on the center of the mass. We placed a single ROI smaller than lesion in the solid tumor and care was taken to avoid calcified, hemorrhagic or necrotic areas of the masses or the breast parenchyma while placing the ROI. Another ROI was placed on the mass free breast parenchyma. Measurements were repeated three times for both masses and the breast parenchyma. The average values were calculated. ADC values were expressed as square millimeters per second. Relative ADC (r ADC) values were calculated by dividing the mean ADC values of each patient's mass by the mean ADC values of each patient's parenchyma.

Ethics Statement

This study was approved by the Institutional Ethics Committee (2014- 41/ 8) written informed consent was obtained from all subjects prior to MRI examination. Patient records and information were anonymized and de-identified prior to analysis.

Statistical Analysis

Data were analyzed using the Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA). Descriptive statistics included frequency, percentage, mean, median, standard deviation (SD) minimum, maximum. Kolmogorov-Smirnov and Shapiro Wilks test was used for the normality of the dependent and independent measures. Independent samples t-test and Mann–Whitney U test were used to compare the measurements of benign and the malignant group. Pearson Chi-Square test was used to compare categorical variables. The threshold ADC values used to differentiate between benign and malignant lesions were determined using receiver operating characteristic (ROC) analysis, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

RESULTS

Fifty-seven breast lesions of 56 patients with a mean age of 45.54 ± 11.03 years were included in this study. Four-two percent of 24/57 breast masses of 24 female patients were benign (mean age: 39.96 ± 9.81 years) and 33/57 (58%) breast masses of 32 female patients were malignant (mean age: 49.72 ± 10.12 years) were included.

The benign lesions included 11 fibroadenomas, 2 sclerosing adenosis, 1 adenoid ductal hyperplasia, 5 granulomatous mastitis, 2 mastitis, 2 papilloma, 1 radial sclerosing lesion. The malignant lesions included 23 invasive ductal carcinomas (IDC), 5 ductal carcinoma in-situ (DCIS), 4 invasive lobular carcinomas and 1 invasive mucinous carcinoma (Table 1) (Fig. 1).

The ADC of breast masses ranged between 0.5 × 10^{-3} mm²/s and 2.6 × 10^{-3} mm²/s (mean: 1.23 ± 0.51 × 10^{-3} mm²/s). The r ADC values of breast masses ranged between 0.3 × 10^{-3} mm²/s and 1.6 × 10^{-3} mm²/s (mean: 0.79 ± 0.31 × 10^{-3} mm²/s).

As for the ADC measurements of the lesions, the lowest ADC lesion value was 0.49 × 10^{-3} mm²/s with IDC, and the highest ADC lesion value was 2.62 × 10^{-3} mm²/s with granulomatous mastitis. The lowest (lesion/normal breast tissue) r ADC rate was (0.30) in an IDC case, whereas the highest was (1.61) in a case of granulomatous mastitis.

The mean ADC value was found to be 1.50 ± 0.56 × 10^{-3} mm²/s for all the benign lesions. Among the be-

Table 1. Histopathologic distribution, age, apparent diffusion coefficient (ADC) and relative ADC values of benign and malignant lesions

	Malignant lesions (n = 33)	Benign lesions (n = 24)	*p value*
Breast Lesions (n = 57)	Invasive ductal carcinoma (n = 23), Invasive lobular carcinoma (n = 4), Ductal carcinoma in-situ (n = 5), Invasive mucinous carcinoma (n = 1)	Fibroadenoma (n = 11), Granulomatous mastitis (n = 5), Mastitis (n = 2), Papilloma (n = 2), Adenoid ductal hyperplasia (n = 1) Radial sclerosing lesion (n = 1) Sclerosing adenosis (n = 1), Adenosis (n = 1)	
Age (year) (mean ± SD)	39.96 ± 9.81	49.72 ± 10.12	[a]**0.001****
Lesion ADC (mean ± SD) × 10^{-3} mm^2/sec	1.03 ± 0.36	1.50 ± 0.56	[b] **0.001****
Parenchyma ADC (mean ± SD) × 10^{-3} mm^2/sec	1.57 ± 0.22	1.54 ± 0.28	[a] 0.551
Relative ADC (mean ± SD)	0.66 ± 0.22	0.97 ± 0.31	[b] **0.001****

[a]Student t Test, [b]Mann Whitney U Test, ** $p < 0.01$

n = Number of cases, ADC = Apparent diffusion coefficient, SD = Standard deviation,

$p < 0.05$ was considered as statistically significant.

nign lesions, the lowest ADC value was belonged to a mastitis with 0.57 × 10^{-3} mm^2/s and the highest ADC value was 2.62 × 10^{-3} mm^2/s in a granulomatous mastitis. The mean (lesion/normal breast tissue) r ADC rate was 0.97 ± 0.31 in these lesions. The lowest rate among all the benign lesions was 0.41 in an intraductal papilloma and the highest rate was 1.61 in a granulomatous mastitis.

The mean ADC value was 1.03 ± 0.36 × 10^{-3} mm^2/s for all the malignant lesions. Among the malignant lesions, the lowest ADC value was 0.49 × 10^{-3} mm^2/s in an IDC, and the highest ADC value was 2.13 × 10^{-3} mm^2/s in an invasive mucinous carcinoma. The mean (lesion/normal breast tissue) r ADC rate was 0.66 ± 0.22 in these lesions. The lowest rate was 0.30 in an IDC and the highest rate was 1.34 in an invasive mucinous carcinoma among all the malignant lesions (Figs. 2 and 3).

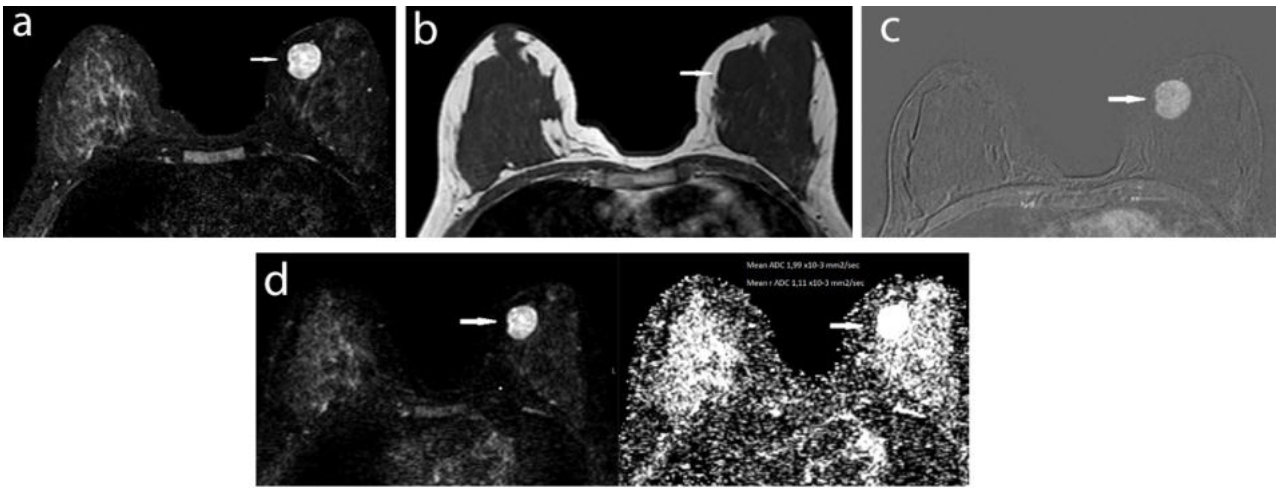

Fig. 1. (a) A well circumscribed 20 × 15 mm mass in the left upper-inner-quadrant of left breast, hyperintense in T2 weighted images; (b) hypointense in T1 weighted images; (c) homogeneously diffuse enhancing (arrow) in T1 weighted post contrast images; and (d) Non-restricted in DWI with ADC 1.99 × 10^{-3} mm^2/s and r ADC 1.11 × 10^{-3} mm^2/s . The pathology report showed fibroadenoma.

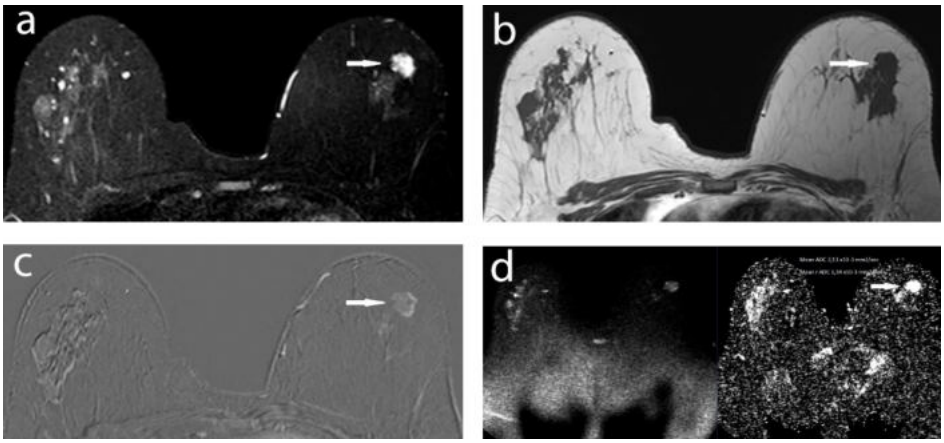

Fig. 2. (a) A 18 × 15 mm mass in the left upper-outer quadrant of the left breast, very high signal in T2 weighted images; (b) Low signal in T1 weighted images and has lobulated not well circumscribed contour; (c) rim-like enhancing pattern in post contrasted T1 weighted images; and (d) In DWI shows non-restricted diffusion (arrow). The ADC was 2.13 × 10^{-3} mm^2/s and r-ADC was 1.34 × 10^{-3} mm2/s. It was an invasive mucinous carcinoma, according to histopathology.

The difference between the mean ADC values of the malignant lesions and those of benign lesions was statistically significant (p = 0.001). Also, the difference between the (lesion/normal breast tissue) r ADC values of the malignant lesions and those of benign lesions was statistically significant (p = 0.001) (Table 1).

Malignant masses had a significantly lower ADC (mean: 1.03 ± 0.36 × 10^{-3} mm^2/s) and r ADC (mean: 0.66 ± 0.22 × 10^{-3} mm^2/s) values than those of benign masses (ADC, mean: 1.50 ± 0.56 × 10^{-3} mm^2/s and r ADC, mean: 0.97 ± 0.31 × 10^{-3} mm^2/s; respectively, p = 0.001) (Table 1).

Benign lesions showed a similar or slightly lower signal intensity than parenchyma in ADC maps, while the vast majority of malignant lesions showed a significantly lower signal intensity than those of parenchyma. No significant differences were observed between the normal breast tissue of the malignant and the benign group (Table 1).

Of the benign lesions, 5 (20.8%) had lower ADC values than the determined threshold value of 1.09 × 10^{-3} mm^2/sec. Of these 5, 2 were intraductal papilloma, 2 were mastitis, and 1 was granulomatous mastitis. Of the malignant lesions, 9 (27.3%) had higher ADC values than the determined threshold value of 1.09 × 10^{-3} mm^2/s. Of these 9, 3 were DCIS, 3 were IDC, 2 were invasive lobular carcinoma and 1 was invasive mucinous carcinoma.

Of the benign lesions, 7 (29.2%) had lower r ADC

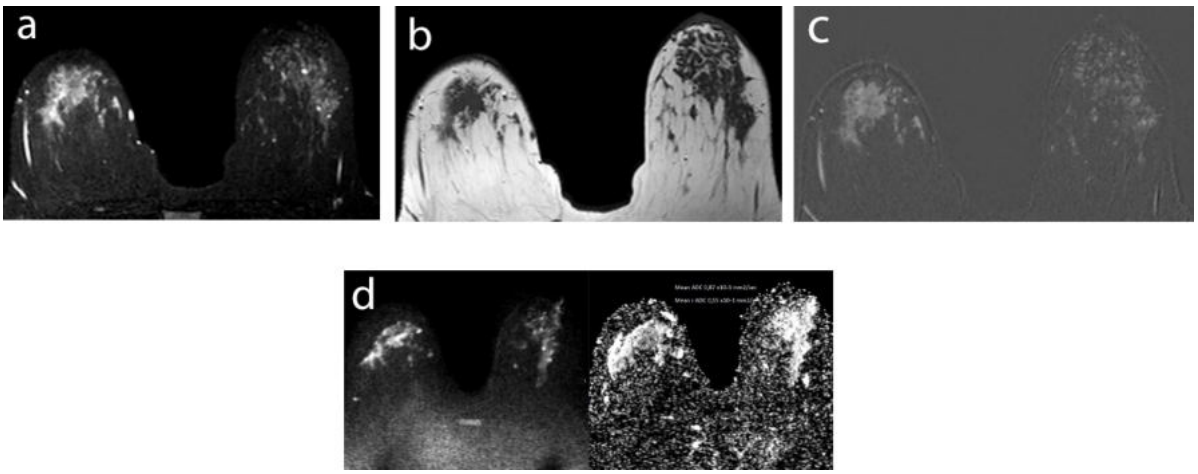

Fig. 3. (a, b) A non-mass like lesion in the upper-outer-quadrant of the right breast in T1 and T2 weighted images; (c) Clumped pattern enhancement in post-contrast images; and (d) it is mildly restricted in DWI with ADC 0.87 × 10^{-3} mm^2/s and r-ADC 0.55×10^{-3} mm^2/s. . The histopathology result was invasive ductal carcinoma.

Table 2. Receiver operating characteristic analysis for apparent diffusion coefficient (ADC) and relative ADC values for benign and malignant lesions by pathology

	Diagnostic Scan					ROC Curve		*p value*
	Cut-off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
Lesion ADC	≤ 1.09	72.73	79.17	82.76	67.86	0.758	0.622-0.894	**0.001****
Relative ADC	≤ 0.83	78.79	70.83	78.79	70.83	0.804	0.685-0.924	**0.001****

***p* < 0.05 was considered as statistically significant.

values than the determined threshold value 0.83 × 10^{-3} mm^2/s. Of these 7, 2 were intraductal papilloma, 2 were mastitis, 2 were granulomatous mastitis and 1 was fibroadenoma. Of the malignant lesions, 7 (21.2%) had higher ADC values than the determined threshold value 0.83 × 10^{-3} mm^2/s. Of these 7, 3 were DCIS, 2 were IDC, 1 were invasive lobular carcinoma and 1 was invasive mucinous carcinoma (Figs. 2 and 3).

Using ROC analysis, we compared the ability of DWI to differentiate malignant and benign lesions by pathology, and found that the best cut-off value for the lesion ADC measurement was 1.09 × 10^{-3} mm^2/s his resulted in sensitivity of 72.73 %, specificity of 79.17%, PPV of 82.76% and NPV of 67.86 % (Table 2). Area under curve (AUC) was 0.758 (95% CI 0.622-0.894, $p = 0.001$) which was statistically significant and indicated that using ADC value, DWI could discriminate benign and malignant lesions with high probability (Fig. 4). The odds of a lesion with an ADC value of ≤ 1.09 × 10^{-3} mm^2/s receiving a malignant diagnosis were 10.133 times (95% CI: 2.909-35.296)

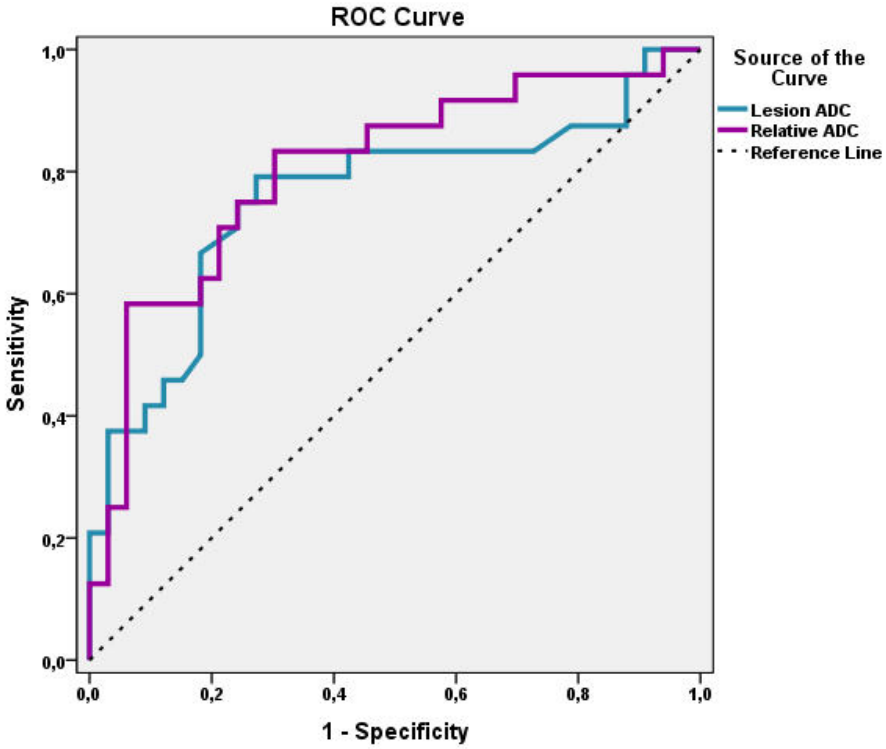

Fig. 4. ROC curve of DWI for discriminating benign and malignant breast lesions. Diagonal lines denote apparent diffusion coefficient (ADC) and r-ADC values.

Table 3. The best cut-off values for lesion apparent diffusion coefficient (ADC) and relative ADC values for benign and malignant lesions by pathology

		Pathological Results				*p value*
		Benign		Malignant		
	Cut-off	n	%	n	%	
Lesion ADC	**> 1.09**	19	79.2	9	27.3	**0.001****
	≤ 1.09	5	20.8	24	72.7	
Relative ADC	**> 0.83**	17	70.8	7	21.2	**0.001****
	≤ 0.83	7	29.2	26	78.8	

Pearson's Chi-square Test **$p < 0.01$

that of a benign lesion (Table 3).

We also determined best cut-off value for r ADC using ROC analysis and found that 0.83 was the best cut-off value for discriminating malignant and the benign lesions with sensitivity of 78.79 %, specificity of 70.83%, PPV of 78.79% and NPV of 70.83% (Table 2). AUC was 0.804 (95% CI, 685-0.924, $p = 0.001$) which was statistically significant and indicated that use of r ADC could discriminate benign and malignant lesions with high probability (Fig. 4). The odds of a lesion with a r ADC value of ≤ 0.83 receiving a malignant diagnosis were 9.020 times (95% CI: 2.682-30.340) that of a benign lesion (Table 3).

DISCUSSION

Diffusion weighted imaging (DWI) based on the random and thermal (Brownian) motion of water which can be quantified by calculating apparent diffusion coefficient (ADC) values in square millimeter per second depending on the degree of water molecule diffusion at in vivo MRI [8-12]. ADC values obtained from DWI can be affected by menstrual cycle and hormone replacement therapy [16, 17]. Relative ADC (r ADC) value has been defined to optimize ADC value, and supposed to be unaffected by the menstrual cycle [18-20].

Recent studies have shown that ADC values in malignant breast lesions were substantially lower than in benign breast lesions due to the higher cellular density in malignant lesions [21-23]. Our study results revealed that ADC values and r ADC values were significantly lower in malignant breast lesions compared to benign breast lesions. Our findings were consistent with those of past studies in literature [24-26].

Akin *et al*. [26] published a research, the threshold value for the mean ADC value of the lesions was considered 1.08×10^{-3} mm^2/s, in the ROC analysis the AUC was 0.95 and the sensitivity and specificity of detecting malignant lesions were 92.1% and 92.4%, respectively. The difference between the mean ADC values of the malignant lesions and benign lesions was statistically significant ($p = 0.001$). Also, the difference between the r ADC values of the malignant lesions and benign lesions was statistically significant ($p = 0.001$).

According to the ROC curve in our study, the best threshold value was 1.09×10^{-3} mm^2/s for lesion ADC. Akin *et al*. [26] revealed the similar results with high sensitivity and specificity provided that threshold ADC 1.08×10^{-3} mm^2/s. There was a statistically significant difference between the ADC values of the malignant breast lesions and those of the benign breast lesions ($p < 0.01$), and the diagnostic value of the ROC analysis for ADC values yielded AUC value of 0.758 with a sensitivity of 72.73% and specificity of 79.17% in our study. These results are within the range of previously reported values in literature and is closer to lower values [27, 28]. Our results are much more similar with Yilmaz *et al*. [28].

Şahin and Arıbal [29] revealed significant differences in ADC and r ADC ratios of benign and malignant lesions in their study. They found threshold ADC value of mass/ normal fibro glandular tissue was 0.8 with 91.4% sensitivity and 100% specificity for differentiating between benign and malign lesions. Although our results were consistent with their study in

terms of statistically significant differences of ADC and r ADC values for malignant and benign lesions, sensitivity and specificity values of the current study are not as high as Cennet S *et al*. study. However, the results of this study were also higher than those of many literature studies results probably as they used the minimum ADC and r ADC values while the others and we used mean ADC and r ADC values [25, 26]. Nadrljanski and Milosevic [30] published a research, the matched female premenopausal patients with confirmed histological diagnosis of either BIRADS 3 or BIRADS 5 lesions. They reported the selected parameters: r ADC and ADC for N1 and N2 and the differences between B3 and B5 lesions were considered highly statistically significant, with p-values ($p <$ 0.00001 for both). The data was regarding the selected parameters for the group of patients with B3 lesions (N1 = 52, ADC = 1.45 ± 0.13 × 10^{-3} mm2/s; r ADC = 0.81 ± 0.08 × 10^{-3} mm^2/s) and for the group of patients with B5 lesions (N2 = 52, ADC = 1.00 ± 0.11 × 10^{-3} mm^2/s; r ADC = 0.58 ± 0.07 × 10^{-3} mm^2/s). In our study the mean r ADC values for the benign lesions were 0.97 and 0.66 for the malignant lesion which were consistent with their study.

DW-MRI provides information on microstructure such as tissue cellularity, which has been shown to be an important index of tumor grade and local tissue architecture, which is a sensitive early indicator of abnormality [15, 21-24]. The lowest cellular zone has the maximum ADC value, while the highest cellular zone has the minimum ADC value. In addition, the ADC value may be affected by the components of fibrosis and necrosis in tumors [25]. Yoshikawa *et al*. [31] study's results support these findings. ADC values of IDC were significantly lower than those of non-IDC. Also, ADC values of both types were significantly lower than those of normal breast parenchyma.

Yoshikawa *et al*. [31] reported that the mean ADC values of the histological types were calculated as follows: The mean ADC values for IDC, NIDC, and normal breasts were 1.07 ± 0.19 × 10^{-3} mm^2/s, 1.42 ± 0.17 × 10^{-3} mm^2/s, and 1.96 ± 0.21 × 10^{-3} mm^2/s, respectively. The ADC values for IDC and NIDC were significantly different from those of normal breasts ($p <$ 0.001 each). Mean ADC values were also significantly different between IDC and NIDC ($p < 0.001$). In our study mean ADC values for NIDC and IDC were 1.22 ± 0.47 × 10^{-3} mm^2/s and 0.99 ± 0.33 × 10^{-3} mm^2/s, respectively and mean r ADC values for NIDC and IDC were 0.73 ± 0.27 and 0.64 ± 0.22, respectively. In our study the results were lower for non-IDC similar to Yoshikawa *et al*. [31] results however we could not find a statistically significance. Infect the number of cases in their study was also low similar to our study. However, in the current study ADC and r ADC values for one of the non-IDC lesions were much smaller than those of all the IDC since the non-IDC lesions especially frequently in DCIS it is hard to evaluate the lesion with DWI.

In a study of Tao *et al*. [32] made with only DCIS lesions, they found that most middle and high-grade DCIS lesions showed non mass like enhancement so it is hard to be recognized by DWI. They used DCE-MRI and intravoxel incoherent motion DWI (IVIM-DWI) and reduce the misdiagnosis of DCIS. We thought maybe we could hardly find DCIS lesions and ADC and r ADC values were not truly evaluated. Maybe a study using IVIM, DWI must be done and evaluate ADC and r ADC value with this technique [32].

There was histological diversity in malignant breast masses. The number of cases for IDC, invasive lobular carcinoma, DCIS and invasive mucinous carcinoma was 23, 4, 5, and 1, respectively which leads to influence on statistical analysis. For instance, ADC and r ADC values for invasive mucinous carcinoma were 2.13 × 10^{-3} mm^2/s and 1.34 respectively which was significantly higher than other types of malignant diagnosis. If the number of invasive mucinous carcinoma was higher, cut-off value would be significantly increased. The same condition applies for benign lesions as well. Two lesions with histological diagnosis of papilloma had ADC values of 0.99 × 10^{-3} mm^2/s and 0.83 × 10^{-3} mm^2/s and r ADC values of 0.69 and 0.53 which were quite low value compared to remaining benign cases.

Hatakenaka *et al*. [33] reported a study about tumor cellularity and tumor ADC for the differential diagnosis of breast tumors and they found that ADC values correlate inversely with tumor cellularity. Mucinous carcinoma demonstrates lower cellular density and higher extracellular water content. They also have very high signal intensity on T2- weighted images. The increase in extracellular water in stroma may have contributed to higher ADC values [33]. Similar to this past study, ADC values of mucinous carcinoma and

granulomatous mastitis resulted in increase of mean ADC values in our study. Further studies with more homogenously distributed group of histological diagnosis with larger sample size would be beneficial.
Another limitation was that the diagnostic accuracy of DWI may decrease due to diameter of lesions, Kinoshita *et al* [34] have reported that the lesions < 10 mm in diameter cannot be demonstrated by DWI .
Another concern was that, non-IDCs, including lobular carcinoma in situ, atypical ductal hyperplasia, as well as mastitis and granulomatous mastitis may enhance similar to the parenchyma due to the lower cellular density, and these lesions may show less restricted diffusion. In our study we have the similar results because of the patients with mastitis and granulomatous mastitis. In these lesions we had less restricted diffusion but in Yilmaz *et al*. [28] study, the granulomatous mastitis showed restricted diffusion and r ADC values were calculated as 0.927. We had 2 mastitis and 2 granulomatous mastitis with r ADC values ranged 0.63 to 1.61. The number of cases in the current study was not enough for further analysis and a study with only mastitis patients would better clarify the condition .

Limitations

Our study presents a number of limitations. Firstly, it was a retrospective study which to some extent, facilitates the evaluation, since the histological findings were readily available. However, this resulted in exclusion of number of patients due to the lack of patients' data. Another limitation was that IDC was dominant in the histopathologic subgroup distribution of malignant lesions, and the number of other lesions was small compared to IDC which leads to inevitable election bias.

CONCLUSION

There is rapidly growing evidence of the potential value of DWI to improve breast cancer detection and characterization. The technique is relatively easy for incorporation into clinical breast MRI protocols and provides complementary information to conventional breast MRI examinations. Furthermore, diffusion characteristics of malignant and benign lesions can be quantified by ADC measurements and using both ADC and r ADC techniques together can increase the diagnostic performance of breast MRI in the diagnosis of breast lesions.

Authors' Contribution

Study Conception: AEP; Study Design: AEP, BY; Supervision: AEP, BY; Funding: N/A; Materials: AEP; Data Collection and/or Processing: AEP; Statistical Analysis and/or Data Interpretation: AEP, BY; Literature Review: AEP, BY; Manuscript Preparation: AEP, BY and Critical Review: BY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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