

Role of Diffusion-Weighted Imaging in Differentiation Between Benign and Malignant Breast Lesions with Pathological Correlation

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Abstract

In diagnostic imaging, accurately differentiating benign from malignant breast lesions is still a significant issue. Measurements of the apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) have become essential noninvasive methods to improve breast MRI diagnostic accuracy. This aimed to detect the role of DWI in differentiation between benign and malignant breast lesions in correlation with pathological examination in comparison with full MRI protocol. This prospective study included 38 females with sono-mammographically detected breast lesions underwent MRI examination. Lesions were evaluated using DWI and ADC mapping. The imaging results were associated with histological diagnosis. The study was conducted between October 2021 and October 2022 at the Radiology Department of Mansoura University Hospitals in Egypt. The study group's mean age was 45.16 ± 11.65 years. DWI revealed restricted diffusion in all malignant lesions (100%) and only 7.1% of benign ones ($p < 0.001$). Malignant lesions had a mean ADC value of $0.809 \pm 0.120 \times 10^{-3} \text{ mm}^2/\text{s}$, which was significantly lower than that of benign lesions ($1.604 \pm 0.326 \times 10^{-3} \text{ mm}^2/\text{s}$, $p < 0.001$). Restricted DWI achieved 100% sensitivity, 92.9% specificity, and 94.7% accuracy for malignancy detection. ROC analysis of ADC values showed an AUC of 0.955, with an optimal cutoff point of $< 0.985 \times 10^{-3} \text{ mm}^2/\text{s}$. The DWI and ADC have a great diagnostic accuracy of measurements in distinguishing benign from malignant breast tumors. The quantitative ADC measurement can serve as a noninvasive, reliable biomarker complementing MRI-BIRADS assessment, boosting diagnostic confidence and perhaps minimizing needless biopsies.

Keywords: Benign; Breast Lesions; Diffusion-Weighted Imaging; Malignant.

Introduction

Breast cancer (BC), which exhibits significant disease heterogeneity, metastasis, and treatment resistance, continues to be a major cause of cancer-related death among women. Distinct cancer subtypes, important molecular drivers, clonal evolutionary trajectories, and prognostic indicators have been identified as a result of the unprecedented integration of genomic and transcriptome data over the past ten years [1]. Early management is the key factor that clarifies the reduction in the recorded mortality of BC [2].

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is worldwide approved as the test of choice for early detection of breast cancer, with sensitivities ranging from 81 to 100%. On the other hand, the established rate of MRI-induced biopsy in literatures ranged from 20 and 40%, which denotes that considerable number of patients are still undergoing invasive approaches for a benign breast lesion detected by MRI examination. DWI

has originated as a main radiological approach that supplements DCEMRI and improves the specificity of MRI breast examination. DWI enhances lesion depiction, consequently reducing the number of unnecessary biopsies [3].

A larger amplitude of the diffusion-sensitizing gradient is usually delivered during DW-MRI in order to raise the diffusion gradient strength, known as the b value [s/mm^2], which was dependent on duration, amplitude, and the interval between applications of the sensitizing gradient. Image sensitivity to the detection of restricted diffusion increased with rising b values; the degree of water molecule movement and the b value were proportional to the signal loss caused by the dephasing caused by the water molecules' migration between the several opposing gradients [4].

Even though DWI image at higher b values is highly sensitive to water diffusion and may give a higher contrast between benign and malignant tumors than a lower b value DWI, also using high b value results in overall reduced signal-to-noise ratio [5]. Micro perfusion, or blood flow, and Brownian motion both have an impact on the DWI. Therefore, to raise the net ADC value, a DWI signal can be combined with a perfusion signal. Since normal fibroglandular tissue is not a highly vascular organ, the contributing effect of microperfusion is reduced in ADC studies employing a high b value of at least 600s/mm^2 [6]. So, this study was done to detect DWI role in differentiation between benign and malignant breast lesions in correlation with pathological examination in comparison with full MRI protocol.

Patients and methods

This prospective study was conducted in MRI unit of radiology department at Mansoura University Hospital, from October 2021 to October 2022 on thirty-eight female patients with BIRADS IV and V breast lesions detected by ultrasound and mammogram and referred from the clinics of Oncology Centre, Mansoura University, and general surgery and radiotherapy departments in Mansoura University Hospitals. Patients who pathologically diagnosed with BC, patients with indeterminate mass lesion by sonomammographic examination, intraductal lesions and postoperative were included in this study. In addition, MRI contraindications (pregnancy, presence of pacemaker, coronary and peripheral artery stents, surgical clips, wire sutures or joint replacement or prosthesis) and patients who received neoadjuvant chemotherapy were excluded from this study.

Methods

Every participant in the research was exposed to thorough clinical evaluation and medical history. All earlier imaging data including US and mammogram were examined and reassessed. Each patient was examined initially by US for lesion detection and BIRADS classification, high frequency transducer 8:18 MHz was utilized. Low PRF color and spectral doppler was needed for evaluating the lesion vascularity. Patients were examined in supine position, with arms above the patient's head. US assessment of the axillary nodal status was also done. Conventional breast MRI examination was done on 1.5 T MRI device (Philips medical system, Netherlands) and dedicated double breast coil. The patient was examined in

prone position. Axial T1WI was our first step, followed by fat suppression, fast spin-echo T2WI, and high-spatial-resolution T2WI.

DW-MRI was performed using parallel imaging and the DW echo-planar imaging (EPI) procedure. Three orthogonal orientations were subjected to sensitizing diffusion gradients with b values of 0, 500, and 1000 s/mm². An axial fat-suppressed 3D volumetric spoiled gradient-echo sequence was used to get the DCE-MRI. As axial enhanced T1-W SE imaging, we employed an IV injection of 0.1 ml/kg of Gd DTPA-magnevist (IV injection) at a rate of 2 ml/s. The contrast-enhanced images were acquired at 20 s (arterial phase), 70 s (venous phase), and 3 min (delayed phase).

By manually positioning the ROI inside the solid area of each lesion, the mean ADC of each lesion was determined, and the DWI was assessed in relation to the signal intensity. The ADC maps were formed automatically and the ADC values were measured. Maximum intensity projection (MIP) views were acquired via each orthogonal plane, resulting in sagittal, coronal, and axial projections; image subtraction was achieved by subtracting each pre-contrast image from each post-contrast series image; and time to signal intensity curves for suspicious enhancing lesions were created.

Lesions were subjected to histopathological analysis following excisional or true cut biopsy. Lesion analysis correlated with histopathological results; biopsy was obtained using 14 Gauge core needle or after surgical excision.

Ethical Considerations

The study was conducted in agreement with the Declaration of Helsinki, following approval by the Institutional Research Board of the Faculty of Medicine, Mansoura University (Approval Code: MS.21.10.1723). An informed written consent was taken from each patient. All patients in this study were informed about the clinical research and were informed about how the operation is carried out. All data was collected by the researcher himself.

Statistical Analysis

IBM SPSS software package version 27 was used to assess the data fed into the computer. Numbers and percentages were used to define qualitative data. The Kolmogorov-Smirnov test was used to check for normality, and the median for non-parametric data and the mean $\pm$ SD for parametric data were used to summarize the quantitative data. The results' significance was assessed at the 0.05 level.

Results

Table (1) shows that the mean age of all studied cases was 45.16 ± 11.65 years. When classified by pathology, patients with benign lesions had a mean age of 43.25 ± 11.14 years, while those with malignant lesions were slightly older, with a mean age of 50.50 ± 11.91 years, indicating that malignancy tended to occur in relatively older individuals, with no statistically significant difference.

Table 1. Age distribution in the cases of the study

Variables	Study cases (N = 38) Mean $\pm$ SD	Test of significance
Age (years)	45.16 $\pm$ 11.65	
Age in benign group (n= 28)	43.25 $\pm$ 11.14	t = - 1.735 p= 0.091
Age in malignant (n= 10)	50.50 $\pm$ 11.91	

Data are presented as mean $\pm$ SD; t= independent samples t-test

Table (2) shows that diagnostic performance clearly improves with higher MRI-BIRADS categories. Due to their benign or low-risk characteristics, BIRADS 2 and 3 demonstrated extremely poor sensitivity. The moderate accuracy of BIRADS 4 supports its function in initiating biopsy for suspected lesions. The higher sensitivity, specificity, and accuracy were attained by BIRADS 5, demonstrating its significant predictive value for cancer.

Table 2. Predictive ability of MRI-BIRADS to detect the occurrence of malignancy.

MRI-BIRADS	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
BIRADS 2	0	96.4	71.1	0	73
BIRADS 3	10	25	21.1	16.7	43.75
BIRADS 4	10	82.1	63.2	16.7	71.9
BIRADS 5	80	96.4	92.1	88.9	93.1

PPV= positive predictive value; NPV= negative predictive value; *: significant value < 0.05

Table (3) shows that DWI revealed restricted diffusion in all malignant lesions (100%) while, it was observed only in 7.1% of the benign lesions. In contrast, free diffusion existed in 92.9% of the benign lesions but not in any of the malignant ones. The highly significant difference between the two categories ($P < 0.001$) indicates that restricted diffusion strongly related with malignancy. Furthermore, compared to benign lesions ($0.809 \pm 0.120 \times 10^{-3} \text{ mm}^2/\text{s}$), the mean ADC value was statistically significantly decreased in instances with malignant tumors ($1.604 \pm 0.326 \times 10^{-3} \text{ mm}^2/\text{s}$).

Table 3. Relation between nature of the histopathological results and DWI& ADC.

	Nature		Test of significance
	Benign (n= 28)	Malignant (n= 10)	
DWI			FET = 29.405 P < 0.001*
Restricted	2 (7.1%)	10 (100%)	
Free	26 (92.9%)	0 (0%)	
ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)			t = 7.497 p < 0.001*
Mean $\pm$ SD	1.604 $\pm$ 0.326	0.809 $\pm$ 0.120	

Categorical data expressed as Number (%); P: probability; FET: Fischer's exact test; t= Independent samples t-test; *: significant value < 0.05

Table (4) shows that the restricted DWI pattern proved high diagnostic prediction in malignancy occurrence, showing 100% sensitivity and 92.9% specificity. Accuracy was 94.7%, with PPV of 83.3% and NPV of 100%, suggesting that malignancy is reliably excluded when restrictions are absent

Table 4. Predictive ability of restricted DWI to detect the occurrence of malignancy.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Restricted DWI	100	92.9	94.7	83.3	100

PPV= positive predictive value, NPV= negative predictive value, *: significant value < 0.05

Table (5) shows that the ADC value showed high predictive ability at AUC of 0.955 for discriminating malignant tumors from benign ones. The best cutoff point of ADC to identify the malignant tumors was $<0.985 \times 10^{-3} \text{ mm}^2/\text{s}$ with 100% sensitivity and 92.9% specificity. With a highly significant result ($p<0.001$), the accuracy was 96.3%, the PPV was 100%, and the NPV was 94.4%.

Table 5. Predictive ability of ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$) in prediction of malignancy.

	ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)
AUC	0.955
Cut off point	< 0.985
Sensitivity	100 %
Specificity	92.9 %
Accuracy	96.3 %
PPV	100 %
NPV	94.4 %
P	< 0.001*

AUC: Area under curve; CI: confidence interval; PPV: positive predictive value; NPV: Negative predictive value; P: Probability value.

Case (1) was a 48-year-old female patient complaining of right bloody nipple discharge with no family history. ADC value equals 1.990. Pathological evaluation revealed intra ductal papilloma (Fig. 1). Case (2) was a 53-year-old female patient with history of MRM of left breast, positive family history and the patient underwent routine follow up MRI examination. Pathological evaluation revealed recurrent grade II infiltrating duct carcinoma (Fig. 2).

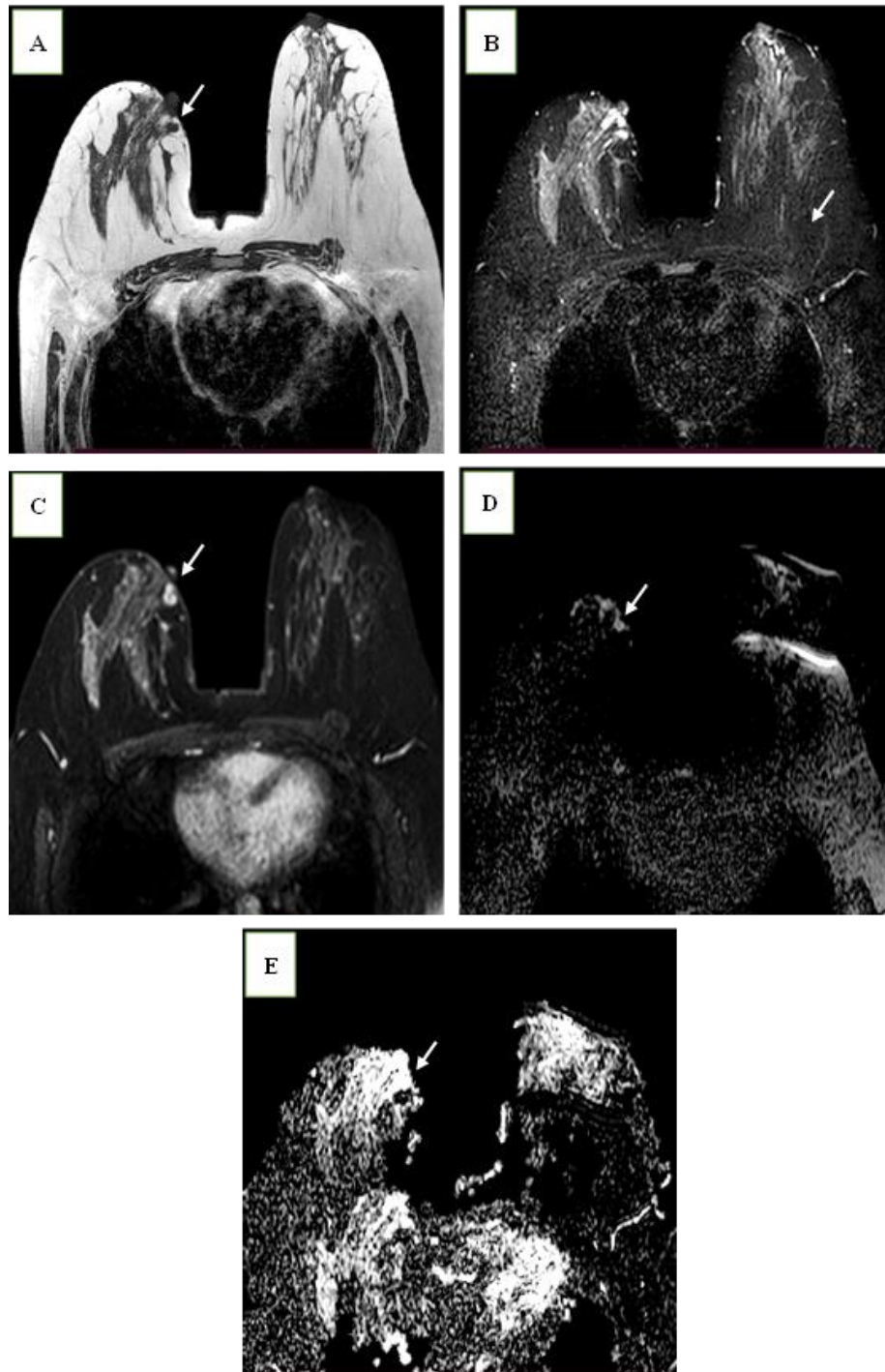


Figure 1. A 48-year-old female patient. On T_1W_1 (A) there is intraductal lesion shows dark signal. Seen at right (UIQ) at 3 o'clock. (B) STIR image, the lesion displays high signal. (C) Post Contrast T_1W_1 with subtraction revealed heterogeneous enhancement of the lesion. (D) DWI, the lesion shows high signal. (E) ADC, the lesion shows high signal (free diffusion) and ADC value equals 1.990. Pathological evaluation revealed intra ductal papilloma.

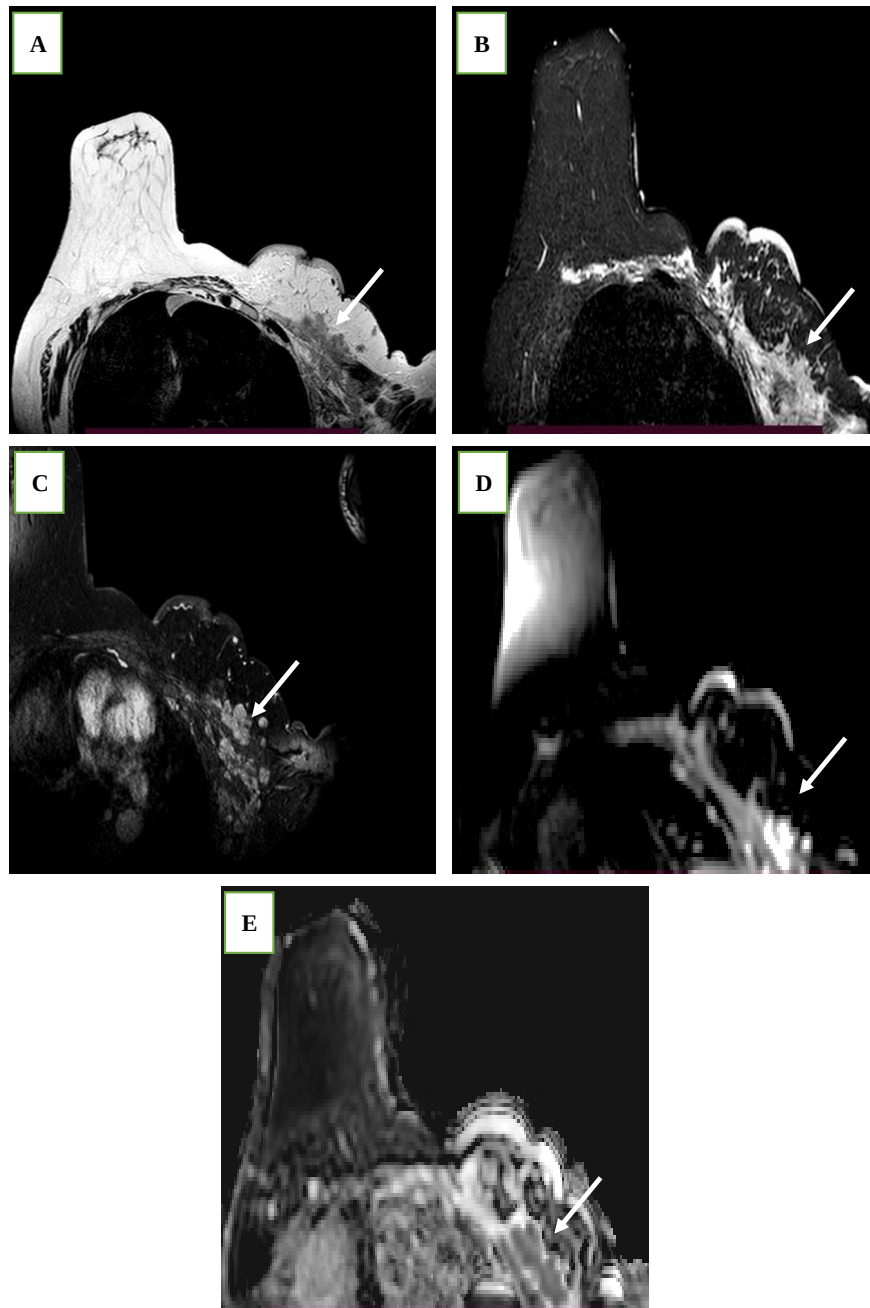


Figure 2. A 53-year-old female patient. On T_1W_1 (A) there is irregular shaped mass with speculated margins displays low signal seen at left operative bed with multiple adjacent smaller masses in infiltrating left anterior chest wall muscles. (B) STIR image, the masses show high signal. (C) Post Contrast T_1W_1 with subtraction revealed heterogeneous enhanced mass seen at left operative bed & multiple adjacent enhanced smaller masses. (D) DWI, the masses show high signal. (E) ADC, the masses show low signal, (Restricted diffusion) and ADC value equals 0.630. Pathological evaluation revealed recurrent grade II infiltrating duct carcinoma.

Discussion

Breast cancer is a common malignant tumor in women globally. To enhance the prognosis, breast cancer must be detected, diagnosed, and treated early. The gold standard for diagnosing breast lesions at the moment is pathological results. Due to risk of invading testing, non-invasive and economical methods like imaging examination are becoming more popular [7].

The diagnosis of BC can be made with good sensitivity and specificity using magnetic resonance imaging [8]. DWI has demonstrated considerable clinical promise for assessing breast cancer in particular because it can characterize the diffusion of water molecules and yield valuable biological information. ADC has been utilized extensively in clinical practice as a traditional quantitative diffusion function parameter [9].

In our study, the mean age of participants was 45.16 years, and despite the malignant group was slightly older on average (50.5 years) than the benign group (43.25 years), this difference wasn't significant. Similarly, **Mohamed et al., [10]** demonstrated a mean age of 47.4 years with no significant variation among benign and malignant cases. In contrast, **He et al. [11]** demonstrated a statistically significant difference, where patients with malignant lesions were older (mean= 52.1 years) than those with benign lesions (mean =43.8 years).

In this study, BIRADS 5 displayed the highest sensitivity (80%), specificity (96.4%), accuracy (92.1%), PPV (88.9%) and NPV (93.1%) in prediction of malignancy occurrence. These findings are consistent with **Bello et al., [12]** who found that the BIRADS 5 diagnostic accuracy rates for breast lesions were 89%, 94%, 89%, 94%, and 92%, respectively, for sensitivity, specificity, PPV, NPV, and diagnostic accuracy.

In another study, BI-RADS 3 was assigned to 13.2% of masses, BI-RADS 4 to 56.8%, and BI-RADS 5 to 30%. Out of all the BI-RADS categories, BI-RADS 4 demonstrated the highest sensitivity (70.1%). Among the BI-RADS categories, BI-RADS 3 and 5 had the highest specificity (100%) of all. Additionally, BI-RADS 5 had the highest accuracy (80.3%). Additionally, according to BI-RADS 5, a biopsy is necessary since the lesions have a high risk of malignancy [13].

Regarding DWI, all malignant lesions exhibited restricted diffusion (100%) in the current study, while only 7.1% of benign lesions showed this pattern, with high statistically significant difference between the two categories. Likewise, **Ali And Mounir [14]** displayed that all of the breast cancerous tumors were restricted with the exception of five that displayed free diffusion and turned out to be benign. Similarly, **Fareed et al., [15]** and **Johnson et al., [16]** demonstrated that malignant lesions showed restriction with DWI imaging. This may be due to higher cellular density, reduced extracellular space and limiting water molecule mobility in malignant tumors as described by **Ma et al., [17]**.

In our study, the restricted DWI pattern proved high diagnostic prediction in malignancy occurrence, showing 100% sensitivity, 92.9% specificity and 94.7% accuracy, with NPV of 100%, suggesting that malignancy is reliably excluded when restrictions are absent.

Likewise, **Yadav and Chauhan [18]** demonstrated that sensitivity and specificity of breast DWI were 92.6% and 90.6% respectively. Furthermore, **Iima et al., [19]** and **Clauser et al., [20]** emphasized DWI as a valuable noninvasive imaging technique for breast lesion characterization. In addition, **Bickelhaupt et al., [21]** reported that DWI proved successful in avoiding unneeded biopsies in patients who had mammogram results that seemed indicative of cancer, where achieved a very good NPV of 0.92. Similarly, **Rotili et al., [22]** reported high sensitivity (93%) and specificity (88%) for DWI, even lesions were smaller than 10mm. The widely variable DWI image quality and acquisition conditions are to blame for the diagnostic accuracy differences between studies, as noted by **Baltzer et al., [23]**.

The current findings demonstrated that the ADC value was statistically significantly decreased in malignant tumors ($0.809 \times 10^{-3} \text{ mm}^2/\text{s}$) compared to the benign tumors ($1.604 \times 10^{-3} \text{ mm}^2/\text{s}$). In addition, regarding the predictive ability of ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$) in prediction of malignancy, the best cutoff point of ADC to identify the malignant lesions was $< 0.985 \times 10^{-3} \text{ mm}^2/\text{s}$ with 100% sensitivity, 92.9% specificity, PPV of 100%, NPV of 94.4%, and diagnostic accuracy of 96.3%. The AUC was 0.955 and this value showed a statistically significant value ($p < 0.001$).

Accordingly, earlier studies have consistently highlighted the notable difference in ADC values between benign and malignant breast tumors. Compared to benign tumors, malignant tumors had significantly lower ADC values ($0.84 \times 10^{-3} \text{ mm}^2/\text{s}$ versus $1.54 \times 10^{-3} \text{ mm}^2/\text{s}$). These findings aligned with earlier research highlighting lower ADC values in malignant tumors due to restricted diffusion caused by higher tumor cellularity. For examples, **Johnson et al., [16]** and **Rahbar et al., [3]** both demonstrated significantly reduced ADC values in malignant breast tumors compared with benign ones which confirm that ADC as a strong diagnostic biomarker. In addition, **Rahbar et al., [3]** reported that applying ADC cut-off values reduced unnecessary biopsies by 20.9%. Furthermore, this came in accordance with **Khan et al., [24]** who reported that the mean ADC value among malignant was $0.89 \times 10^{-3} \text{ mm}^2/\text{s}$ which was statistically significant lower compared to $1.3 \times 10^{-3} \text{ mm}^2/\text{s}$ in benign. ADC value cutoff for benign and malignant lesion prediction was $1.05 \times 10^{-3} \text{ mm}^2/\text{s}$, with sensitivity of 92.3%, specificity of 93%, PPV of 92.28%, NPV of 93.02%, and diagnostic accuracy of 92.67%. 0.965 was the AUC for the ADC value in prediction of malignancy.

In contrast, **Mohammed et al., [25]** reported slightly higher cutoff values ($< 1.21 \times 10^{-3} \text{ mm}^2/\text{s}$) with an AUC of 0.896. Despite such variations, most studies including our study confirm that ADC measurement is a highly effective quantitative parameter for differentiating benign from malignant breast tumors.

The ADC score is a useful tool for distinguishing between benign and malignant breast tumors because of its strong specificity, sensitivity, and accuracy—even if the cut-off number changes from study to study. Numerous technical factors, such as various MRI units, pulse sequences, or b-values, can have an impact on the ADC measurements [24].

Conclusion

The study demonstrates the great diagnostic accuracy of DWI and ADC measurements in distinguishing benign from malignant breast tumors. Malignant lesions consistently showed limited diffusion and much lower ADC values than benign ones. An ADC threshold $< 0.985 \times 10^{-3} \text{ mm}^2/\text{s}$ is highly sensitive and specific for predicting malignancy. These findings revealed that quantitative ADC measurement can serve as a noninvasive, reliable biomarker complementing MRI-BIRADS assessment, boosting diagnostic confidence and perhaps minimizing needless biopsies.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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