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MRI-Based Differentiation of Benign and Malignant Breast Lesions Using Multiparametric MRI and Quantitative Apparent Diffusion Coefficient Analysis.

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Abstract

Background: Breast magnetic resonance imaging (MRI) provides high sensitivity for breast cancer detection but may demonstrate limited specificity because benign lesions can exhibit suspicious morphological and enhancement features. Diffusion-weighted imaging (DWI) and quantitative apparent diffusion coefficient (ADC) measurements provide complementary information regarding tissue microstructure and may improve lesion characterization. This study evaluated the diagnostic performance of multiparametric breast MRI and quantitative ADC measurements for differentiating benign from malignant breast lesions. ***Methods***: A prospective diagnostic accuracy study was conducted involving 236 breast lesions in 218 women who underwent breast MRI followed by histopathological evaluation. MRI examinations included T2-weighted imaging, T1-weighted imaging, dynamic contrast-enhanced MRI (DCE-MRI), DWI, and ADC mapping. Two radiologists independently assessed lesion morphology and enhancement characteristics and assigned MRI BI-RADS categories while blinded to histopathological findings and each other's assessments. ADC was measured using a standardized region-of-interest technique. Histopathology was used as the reference standard. Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic performance of ADC, and the optimal ADC threshold was identified using the Youden index. A combined model incorporating BI-RADS assessment and continuous ADC values was subsequently evaluated. ***Results***: Of the 236 lesions, 139 (58.9%) were malignant and 97 (41.1%) were benign. Mean ADC was significantly lower in malignant lesions than in benign lesions ($1.06 \pm 0.27 \times 10^{-3}$ mm^2/s vs. $1.61 \pm 0.41 \times 10^{-3}$ mm^2/s; $P < 0.001$). An ADC threshold of $\leq 1.31 \times 10^{-3}$ mm^2/s yielded an AUC of 0.934 (95% CI, 0.898–0.961), with 91.4% sensitivity, 86.6% specificity, 90.7% positive predictive value (PPV), 88.9% negative predictive value (NPV), and 89.4% diagnostic accuracy. BI-RADS categories 4/5 as the positive threshold demonstrated 97.1% sensitivity, 72.2% specificity, 83.3% PPV, 94.6% NPV, and 86.9% accuracy. The combined BI-RADS and ADC model demonstrated an AUC of 0.958 (95% CI, 0.929–0.978), with 95.0% sensitivity, 91.8% specificity, 94.3% PPV, 92.7% NPV, and 93.6% accuracy. ***Conclusion***: Quantitative ADC analysis demonstrated good diagnostic performance for differentiating benign from malignant breast lesions and provided complementary information to conventional BI-RADS assessment. The combined BI-RADS and ADC model demonstrated high diagnostic discrimination and improved specificity while maintaining high sensitivity. The ADC threshold identified in this study is cohort- and protocol-specific and requires external multicenter prospective validation before routine clinical implementation.

Keywords: breast MRI; diffusion-weighted imaging; apparent diffusion coefficient; breast lesions; breast carcinoma; BI-RADS; dynamic contrast-enhanced MRI; diagnostic accuracy.

INTRODUCTION

Breast cancer remains a major cause of cancer-related morbidity and mortality among women. Imaging plays a central role in detection, characterization, staging, treatment planning, and surveillance. Breast MRI is particularly sensitive for invasive breast cancer and provides information that complements mammography and ultrasonography. Current ACR BI-RADS guidance provides standardized terminology and assessment categories for breast MRI and links imaging assessment to clinical management.1,2

Despite its high sensitivity, breast MRI can produce false-positive findings because benign lesions and benign proliferative processes may demonstrate enhancement patterns that overlap with malignancy.3 This limitation is clinically relevant because suspicious MRI findings may lead to additional imaging or tissue sampling.

Multiparametric MRI addresses this limitation by combining anatomical and functional information. Dynamic contrast-enhanced MRI evaluates lesion vascularity and enhancement kinetics, whereas diffusion-weighted imaging provides information about the movement of water molecules within tissue. Quantitative analysis of DWI produces an ADC value that can be used as an imaging biomarker.4,5

Many malignant breast tumors demonstrate reduced water diffusivity because of increased cellularity and altered extracellular space. However, ADC is not a tumor-specific parameter.6 Benign lesions with high cellularity may demonstrate restricted diffusion, whereas some malignant tumors may show relatively higher ADC because of necrosis, mucin, extracellular matrix, or lower cellular density.

The EUSOBI International Breast DWI working group recommends standardized DWI acquisition and emphasizes the importance of appropriate b-values, fat suppression, spatial resolution, image quality, and reproducible ADC measurement.7 The group also recommends placement of a small ROI in the darkest portion of the lesion on the ADC map while avoiding necrotic, noisy, or non-enhancing regions. Importantly, EUSOBI emphasizes that ADC thresholds require standardization and quality assurance before being applied clinically.

The primary objective was to determine the diagnostic performance of ADC in differentiating malignant from benign breast lesions. Secondary objectives were to compare ADC with conventional BI-RADS assessment, evaluate the performance of a combined BI-RADS-plus-ADC model, assess interobserver agreement, and explore associations between ADC values and histopathological characteristics.

MATERIALS AND METHODS

Study Design and Participants

This was a prospective, single-center diagnostic accuracy study conducted at a tertiary-care academic hospital with a dedicated breast imaging service. The study was conducted from January 2025 through December 2025 and was designed and reported in accordance with the principles of the Standards for Reporting Diagnostic Accuracy Studies (STARD).

Women aged 18 years or older who were referred for breast MRI because of a suspicious or indeterminate breast abnormality identified clinically, on mammography, or on ultrasonography were screened for eligibility. Participants were eligible if the breast lesion was adequately visualized on MRI for morphological and diffusion assessment and subsequently underwent tissue sampling that provided a definitive histopathological diagnosis.

Patients were excluded if they had received neoadjuvant chemotherapy before MRI, previous breast surgery involving the index lesion, previous radiotherapy to the breast, known recurrent breast cancer, contraindications to MRI or gadolinium-based contrast administration, pregnancy in which contrast-enhanced MRI was contraindicated, severe motion or susceptibility artifacts that substantially impaired image interpretation, inadequate diffusion-weighted image quality, incomplete MRI examination, or absence of definitive histopathological confirmation. Lesions measuring less than 6 mm were excluded from quantitative ADC analysis because reliable region-of-interest placement was considered difficult and measurements could be substantially affected by partial-volume effects.

The study protocol was approved by the Institutional Ethics Committee before initiation of the study. Written informed consent was obtained from all participants before enrollment.

Sample Size

The sample size was calculated based on the anticipated sensitivity of ADC-based characterization. Assuming an anticipated sensitivity of approximately 90%, an absolute precision of 5 percentage points, and a two-sided 95% confidence level, approximately 138 malignant lesions were required. Assuming a malignant lesion proportion of approximately 60% and allowing for potential exclusions, approximately 240 lesions were targeted.

During the recruitment period, 251 lesions were initially assessed. Fifteen lesions were subsequently excluded because of inadequate diffusion image quality (n=6), absence of histopathological confirmation (n=4), lesion size below the predefined minimum (n=3), or incomplete MRI examination (n=2). The final analysis included 236 lesions from 218 women.

MRI Acquisition

All breast MRI examinations were performed using a 3.0-T GE HealthCare SIGNA MRI scanner equipped with a dedicated bilateral breast coil. Participants were positioned prone with both breasts placed within the dedicated breast coil. Bilateral breast imaging was performed before and after intravenous administration of a gadolinium-based contrast agent.

The MRI protocol consisted of axial T2-weighted fat-suppressed imaging, axial T1-weighted imaging, diffusion-weighted imaging (DWI) with corresponding apparent diffusion coefficient (ADC) mapping, and dynamic contrast-enhanced (DCE) T1-weighted fat-suppressed three-dimensional imaging.

The T2-weighted sequence was acquired with a repetition time/echo time (TR/TE) of approximately 4200/72 ms and a slice thickness of approximately 3 mm. DWI was acquired using b-values of 0, 50, and 800 s/mm², with an approximately 3-mm reconstructed slice thickness. ADC maps were automatically generated by the MRI system from the acquired diffusion data.

DCE-MRI was performed using a T1-weighted fat-suppressed three-dimensional sequence before and after intravenous administration of a macrocyclic gadolinium-based contrast agent at a dose of 0.1 mmol/kg, followed by a saline flush. Six postcontrast acquisitions were obtained at an approximate temporal resolution of 65 seconds per phase. Subtraction images and maximum-intensity-projection images were generated for lesion assessment.

MRI Interpretation

Two radiologists independently interpreted all MRI examinations. Reader 1 had 11 years of post-training experience, including 7 years of breast imaging experience, whereas Reader 2 had 8 years of post-training experience, including 5 years of breast imaging experience. Both radiologists were blinded to the histopathological findings and to each other's interpretations.

Lesions were evaluated for morphology, enhancement characteristics, distribution, and kinetic behavior using standardized breast MRI terminology. For mass lesions, shape was categorized as oval, round, or irregular, while margins were categorized as circumscribed, irregular, or spiculated. Internal enhancement was categorized as homogeneous, heterogeneous, rim, or other recognized patterns. Non-mass enhancement was assessed according to its distribution and internal enhancement pattern. Enhancement kinetics were categorized according to the temporal enhancement pattern.

Each lesion was assigned a final MRI BI-RADS assessment category according to the BI-RADS system in use during the study period. For the primary binary diagnostic analysis, BI-RADS categories 1–3 were classified as negative and categories 4–5 as positive. Category 6 lesions were excluded from the primary diagnostic analysis because they represent biopsy-proven malignancy rather than an independent pre-biopsy diagnostic assessment.

Diffusion-Weighted Imaging and ADC Measurement

ADC measurements were independently performed by both radiologists using the ADC maps generated from the DWI dataset.

For each lesion, the enhancing component was identified on postcontrast subtraction images and spatially matched with the corresponding ADC map. A single small region of interest (ROI) was placed entirely within the lesion in the area demonstrating the greatest visually apparent diffusion restriction. Areas of necrosis, hemorrhage, obvious imaging artifact, marked image distortion, and nonenhancing tissue were avoided.

For lesions with heterogeneous diffusion characteristics, the ROI was placed within the most restricted solid component. The mean ADC value within the selected ROI was recorded in units of $\times 10^{-3}$ mm²/s.

A single ROI was used for each lesion, and the same general ROI placement approach was applied across all lesions to promote consistency and reproducibility. The ADC measurement methodology was based on published recommendations for standardized breast DWI acquisition and interpretation.

Histopathological Reference Standard

Histopathology served as the reference standard for lesion classification. Tissue sampling was performed after MRI according to routine clinical management and included core needle biopsy, vacuum-assisted biopsy, or surgical excision, depending on the lesion characteristics and clinical circumstances.

Benign diagnoses included fibroadenoma, fibrocystic or proliferative changes, papilloma, adenosis, benign phyllodes tumor, hamartoma, and other benign lesions. Malignant diagnoses included invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, mucinous carcinoma, tubular carcinoma, and other invasive breast carcinomas.

Histological subtype, tumor grade, and receptor status were recorded where available.

Data Collection

Clinical and imaging data were prospectively recorded using a standardized data collection format. Variables included age, menopausal status, indication for MRI, lesion laterality, lesion size, lesion location, MRI morphology, margin characteristics, enhancement characteristics, kinetic enhancement pattern, BI-RADS category, DWI characteristics, ADC value, and histopathological diagnosis. Histological subtype, tumor grade, and receptor status were recorded where available.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were assessed for distribution using graphical methods and the Shapiro–Wilk test. Normally distributed continuous variables were summarized as mean ± standard deviation, whereas skewed variables were summarized as median with interquartile range. Categorical variables were summarized as frequencies and percentages.

For comparisons between benign and malignant lesions, the independent-samples t-test was used for normally distributed continuous variables, whereas the Mann–Whitney U test was used when distributional assumptions were not met. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Diagnostic Performance of ADC

The diagnostic performance of ADC for differentiating malignant from benign breast lesions was evaluated using receiver operating characteristic (ROC) curve analysis. ADC was analyzed as a continuous variable, with lower ADC values indicating a greater likelihood of malignancy.

The area under the ROC curve (AUC) was calculated with a 95% confidence interval. The optimal ADC threshold was determined using the Youden index. At the derived threshold, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and positive and negative likelihood ratios were calculated with corresponding 95% confidence intervals.

Because the optimal ADC threshold was derived from the study dataset, the resulting cutoff and associated diagnostic performance estimates were considered internally derived and were not interpreted as an externally validated clinical threshold.

Diagnostic Performance of BI-RADS

For the primary binary diagnostic analysis, BI-RADS categories 1–3 were classified as negative and categories 4–5 as positive. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated with 95% confidence intervals.

Combined BI-RADS and ADC Model

A separate multivariable logistic regression model was constructed to evaluate the incremental diagnostic value of quantitative ADC when combined with conventional MRI assessment.

BI-RADS assessment was coded as a binary predictor, with categories 1–3 coded as negative and categories 4–5 coded as positive. ADC was entered into the model as a continuous variable. The model generated an estimated probability of malignancy for each lesion.

The discriminatory performance of the combined model was evaluated using ROC analysis based on the predicted probabilities of malignancy. The AUC and corresponding 95% confidence interval were calculated. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated at the probability threshold used for classification in the model.

Multivariable Logistic Regression

A separate multivariable logistic regression analysis was performed to identify clinical and imaging characteristics independently associated with malignancy.

Candidate predictors were selected a priori based on clinical relevance and included age, lesion size, irregular morphology, irregular or spiculated margins, washout enhancement, and ADC. All prespecified clinically relevant predictors were entered simultaneously into the multivariable logistic regression model.

For the multivariable model, ADC was dichotomized using the internally derived threshold of $\leq 1.31 \times 10^{-3}$ mm²/s. Adjusted odds ratios (ORs), 95% confidence intervals, and P values were reported.

Interobserver Agreement

Interobserver agreement for BI-RADS assessment between the two radiologists was evaluated using weighted Cohen's kappa with a 95% confidence interval.

Agreement between the two radiologists for continuous ADC measurements was assessed using the intraclass correlation coefficient (ICC) with a 95% confidence interval. The ICC was 0.93 (95% CI, 0.91–0.95), indicating excellent agreement between the readers.

Multiple Lesions per Participant

The primary unit of analysis was the breast lesion. Eighteen women contributed two eligible lesions, whereas the remaining 200 women contributed one lesion each.

Because a subset of participants contributed more than one lesion, the possibility of within-participant correlation was considered when interpreting lesion-level analyses.

Missing Data

The completeness of clinical, imaging, ADC, and histopathological data was assessed before statistical analysis. Cases with incomplete information required for a particular analysis were excluded from that specific analysis.
A two-sided P value <0.05 was considered statistically significant.

RESULTS

During the recruitment period, 251 lesions were initially assessed for eligibility. Fifteen lesions were excluded, including six because of inadequate diffusion image quality, four because histopathological confirmation was unavailable, three because the lesion measured less than the predefined minimum size, and two because of incomplete MRI examinations. The final analysis therefore included 236 lesions from 218 women.

The mean age of the women was 48.7 ± 12.6 years, with an age range of 21–77 years. Eighty-nine women (40.8%) were premenopausal and 129 (59.2%) were postmenopausal. Eighteen women contributed two eligible lesions, whereas the remaining 200 women contributed one lesion each. Histopathological examination identified 139 malignant lesions (58.9%) and 97 benign lesions (41.1%).

Baseline and Imaging Characteristics

The baseline and imaging characteristics of benign and malignant lesions are presented in Table 1. The mean age was significantly higher among women with malignant lesions than among those with benign lesions (51.2 ± 12.8 vs 45.1 ± 11.7 years, P < 0.001). The mean lesion diameter was also significantly greater among malignant lesions (28.6 ± 14.7 mm) than benign lesions (19.4 ± 10.9 mm, P < 0.001).

The mean ADC value was significantly lower in malignant lesions than in benign lesions (1.06 ± 0.27 vs 1.61 ± 0.41 $\times 10^{-3}$ mm^2/s, P < 0.001). Irregular morphology was observed in 65.5% of malignant lesions compared with 17.5% of benign lesions. Irregular or spiculated margins were present in 62.6% of malignant lesions compared with 11.3% of benign lesions. Washout enhancement was observed in 56.8% of malignant lesions compared with 20.6% of benign lesions. Marked diffusion restriction was observed in 77.7% of malignant lesions compared with 28.9% of benign lesions. Each of these imaging characteristics was significantly more frequent in malignant lesions (P < 0.001 for each comparison).

Table 1. Baseline and imaging characteristics of benign and malignant lesions

Variable	Benign lesions (n=97)	Malignant lesions (n=139)	P value
Age, years	45.1 ± 11.7	51.2 ± 12.8	<0.001
Lesion size, mm	19.4 ± 10.9	28.6 ± 14.7	<0.001
Mean ADC, $\times 10^{-3}$ mm^2/s	1.61 ± 0.41	1.06 ± 0.27	<0.001
Irregular morphology	17 (17.5%)	91 (65.5%)	<0.001
Irregular/spiculated margin	11 (11.3%)	87 (62.6%)	<0.001
Washout enhancement	20 (20.6%)	79 (56.8%)	<0.001
Marked diffusion restriction	28 (28.9%)	108 (77.7%)	<0.001

Histopathological Distribution

Histopathological diagnoses are summarized in Table 2. Among the 139 malignant lesions, invasive ductal carcinoma was the most frequent histological subtype, accounting for 96 lesions (69.1% of malignant lesions and 40.7% of the entire cohort), followed by invasive lobular carcinoma in 13 lesions (9.4% of malignant lesions). Ductal carcinoma in situ was

identified in 9 lesions (6.5%), mucinous carcinoma in 7 (5.0%), tubular carcinoma in 5 (3.6%), and other malignant histological subtypes in 9 (6.5%).

Among the 97 benign lesions, fibroadenoma was the most common diagnosis, accounting for 31 lesions (32.0% of benign lesions and 13.1% of the entire cohort). Fibrocystic or proliferative lesions accounted for 21 lesions (21.6%), papillomas for 13 (13.4%), adenosis for 8 (8.2%), benign phyllodes tumors for 6 (6.2%), hamartomas for 4 (4.1%), and other benign lesions for 14 (14.4%).

Table 2. Histopathological distribution of breast lesions

Histopathological diagnosis	n	% of all lesions
Malignant lesions	139	58.9
Invasive ductal carcinoma	96	40.7
Invasive lobular carcinoma	13	5.5
Ductal carcinoma in situ	9	3.8
Mucinous carcinoma	7	3.0
Tubular carcinoma	5	2.1
Other malignant lesions	9	3.8
Benign lesions	97	41.1
Fibroadenoma	31	13.1
Fibrocystic/proliferative lesions	21	8.9
Papilloma	13	5.5
Adenosis	8	3.4
Benign phyllodes tumor	6	2.5
Hamartoma	4	1.7
Other benign lesions	14	5.9

Diagnostic Performance of ADC

The mean ADC value was significantly lower among malignant lesions than benign lesions (1.06 ± 0.27 vs 1.61 ± 0.41 $\times 10^{-3}$ mm²/s, $P < 0.001$). However, the distributions showed overlap. Several benign lesions demonstrated relatively low ADC values, particularly cellular fibroadenomas and proliferative lesions, whereas some malignant lesions demonstrated relatively higher ADC values, particularly mucin-rich and lower-cellularity tumors.

ROC analysis demonstrated good discriminatory performance of ADC, with an AUC of 0.934 (95% CI, 0.898–0.961). The maximum Youden index occurred at an ADC threshold of $\leq 1.31 \times 10^{-3}$ mm²/s.

At this threshold, 127 of 139 malignant lesions were classified as ADC-positive, while 12 were classified as ADC-negative. Among the 97 benign lesions, 13 were classified as ADC-positive and 84 as ADC-negative. The corresponding sensitivity was 91.4%, specificity was 86.6%, PPV was 90.7%, NPV was 88.9%, and diagnostic accuracy was 89.4%. The positive likelihood ratio was 6.82 and the negative likelihood ratio was 0.10.

Table 3. Diagnostic performance of the imaging approaches

Diagnostic approach	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
BI-RADS 4/5	97.1%	72.2%	83.3%	94.6%	86.9%	Not calculated
ADC $\leq 1.31 \times 10^{-3}$ mm²/s	91.4%	86.6%	90.7%	88.9%	89.4%	0.934
Combined BI-RADS + ADC model	95.0%	91.8%	94.3%	92.7%	93.6%	0.958

Diagnostic Performance of BI-RADS

Conventional MRI assessment using BI-RADS categories 4 and 5 as the positive threshold identified 135 of 139 malignant lesions, corresponding to a sensitivity of 97.1%. Seventy of 97 benign lesions were classified as negative, corresponding to a specificity of 72.2%. The PPV was 83.3%, NPV was 94.6%, and overall diagnostic accuracy was 86.9%.

Combined BI-RADS and ADC Model

A combined prediction model incorporating BI-RADS assessment and continuous ADC demonstrated higher apparent diagnostic discrimination than either approach alone. The model yielded an AUC of 0.958 (95% CI, 0.929–0.978). At the probability threshold used for classification, 132 of 139 malignant lesions were classified as positive and 89 of 97 benign lesions were classified as negative.

The combined model demonstrated a sensitivity of 95.0%, specificity of 91.8%, PPV of 94.3%, NPV of 92.7%, and diagnostic accuracy of 93.6%.

Multivariable Logistic Regression

In multivariable logistic regression analysis, lower ADC, irregular or spiculated margins, washout enhancement, and larger lesion size were independently associated with malignancy. An ADC value of ≤1.31 ×10⁻³ mm²/s was associated with an adjusted OR of 7.84 (95% CI, 3.74–16.45; P < 0.001). Irregular or spiculated margins were associated with an adjusted OR of 4.63 (95% CI, 2.32–9.25; P < 0.001), while washout enhancement was associated with an adjusted OR of 2.71 (95% CI, 1.44–5.11; P = 0.002). Lesion size >25 mm demonstrated a weaker but statistically significant independent association with malignancy (adjusted OR, 1.76; 95% CI, 1.01–3.08; P = 0.046). Age >50 years was not independently associated with malignancy (adjusted OR, 1.58; 95% CI, 0.91–2.76; P = 0.104).

Table 4. Multivariable logistic regression analysis of factors associated with malignancy

Variable	Adjusted OR	95% CI	P value
Age >50 years	1.58	0.91–2.76	0.104
Lesion >25 mm	1.76	1.01–3.08	0.046
Irregular/spiculated margin	4.63	2.32–9.25	<0.001
Washout enhancement	2.71	1.44–5.11	0.002
ADC ≤1.31 ×10⁻³ mm²/s	7.84	3.74–16.45	<0.001

Interobserver Agreement

Interobserver agreement for BI-RADS assessment was substantial, with a weighted Cohen's kappa of 0.79 (95% CI, 0.72–0.85). Agreement between the two radiologists for ADC measurements was excellent, with an ICC of 0.93 (95% CI, 0.91–0.95).

ADC Classification and Histopathological Findings

The ADC-based classification results are summarized in Table 5. Using the threshold of ≤1.31 ×10⁻³ mm²/s, 127 malignant lesions were correctly classified as ADC-positive and 12 malignant lesions were classified as ADC-negative. Among benign lesions, 84 were correctly classified as ADC-negative, whereas 13 were classified as ADC-positive.

Table 5. ADC-based classification according to histopathological diagnosis

ADC classification	Histopathologically malignant	Histopathologically benign	Total
ADC positive	127	13	140
ADC negative	12	84	96
Total	139	97	236

False-negative ADC classifications occurred in 12 malignant lesions. These comprised five invasive lobular carcinomas, three mucinous carcinomas, two low-grade invasive ductal carcinomas, and two heterogeneous lesions with substantial necrotic components. False-positive ADC classifications occurred in 13 benign lesions, most commonly cellular fibroadenomas and proliferative lesions.

DISCUSSION

The present prospective diagnostic accuracy study evaluated the ability of multiparametric breast MRI and quantitative apparent diffusion coefficient (ADC) analysis to differentiate benign from malignant breast lesions. Among 236 histopathologically confirmed lesions, malignant lesions were significantly larger and more frequently demonstrated irregular morphology, irregular or spiculated margins, washout enhancement, and marked diffusion restriction. Quantitative ADC was significantly lower in malignant than in benign lesions. An ADC threshold of ≤1.31 ×10⁻³ mm²/s yielded an AUC of 0.934, with 91.4% sensitivity and 86.6% specificity. Conventional BI-RADS 4/5 assessment demonstrated higher sensitivity (97.1%) but lower specificity (72.2%), whereas the combined BI-RADS and ADC model demonstrated an AUC of 0.958, with 95.0% sensitivity and 91.8% specificity. These findings support the potential role of quantitative diffusion information as a complementary component of multiparametric breast MRI.

The morphological and kinetic findings observed in our cohort are consistent with established breast MRI literature. Jansen et al., in an analysis of 852 MRI-detected breast lesions, evaluated enhancement kinetics according to lesion morphology and demonstrated that kinetic characteristics differed between malignant and benign lesions across mass, nonmass, and focus enhancement patterns.8 Their findings support the value of interpreting enhancement kinetics together with lesion morphology rather than considering either feature in isolation. In our cohort, irregular or spiculated margins were present in 62.6% of malignant lesions compared with 11.3% of benign lesions and remained independently associated with malignancy (adjusted OR, 4.63; P < 0.001).

The importance of dynamic enhancement kinetics is also supported by the seminal study of Kuhl et al., in which 266 breast lesions were evaluated using dynamic contrast-enhanced MRI.9 The authors classified enhancement according to the time-signal intensity curve and demonstrated that the enhancement time course provided useful information for differentiating benign and malignant lesions. In particular, a type III washout pattern was associated with malignancy. Another study by

Kuhl et al. showed that morphologic information remained diagnostically important when temporal resolution was modified and that enhancement time-course patterns retained high specificity and positive predictive value.10 These findings are consistent with our observation that washout enhancement was significantly more common among malignant lesions and remained independently associated with malignancy (adjusted OR, 2.71; P = 0.002).

The biological and diagnostic significance of ADC findings in our study is strongly supported by the large meta-analysis of Surov et al., which included 123 studies and 13,847 breast lesions.11 They demonstrated substantially lower mean ADC values in malignant lesions than in benign lesions, with pooled mean values of approximately 1.03 $\times 10^{-3}$ mm²/s and 1.50 $\times 10^{-3}$ mm²/s, respectively. Our corresponding values of 1.06 $\times 10^{-3}$ mm²/s for malignant lesions and 1.61 $\times 10^{-3}$ mm²/s for benign lesions are therefore broadly consistent with the published literature.

The diagnostic performance of ADC in our study is also comparable with previous individual and meta-analytic studies. Caivano et al., using 3-T MRI, reported mean ADC values of approximately 1.03 $\times 10^{-3}$ mm²/s for malignant lesions and 2.06 $\times 10^{-3}$ mm²/s for benign lesions and concluded that DWI and ADC measurements could assist in differentiating benign from malignant breast masses.12 The malignant ADC value in that study is very similar to the value of 1.06 $\times 10^{-3}$ mm²/s observed in our cohort.

Similarly, Tan et al. evaluated quantitative DWI at 3 T in 44 breast lesions and reported significant differences between benign and malignant lesions.13 They identified ADC thresholds of approximately 1.21 $\times 10^{-3}$ mm²/s at b = 500 s/mm² and 1.22 $\times 10^{-3}$ mm²/s at b = 1000 s/mm². They also found that combining DWI with DCE-MRI improved specificity while maintaining high sensitivity. The threshold of $\leq$1.31 $\times 10^{-3}$ mm²/s identified in our study is somewhat higher than those reported by Tan et al., emphasizing the dependence of ADC thresholds on acquisition parameters, b-values, lesion spectrum, and measurement methodology.

The variation in reported ADC thresholds is further illustrated by the work of Pereira et al., who evaluated different b-value combinations in 52 breast lesions.14 Although ADC values remained significantly lower in malignant than benign lesions across the tested b-values, the diagnostic characteristics varied according to the diffusion acquisition. Their findings demonstrate why an ADC cutoff derived using one MRI protocol should not automatically be transferred to another scanner or sequence.

The quantitative diffusion findings in our study are also consistent with the whole-lesion analysis reported by Suo et al. Using 3-T MRI and whole-lesion ADC histogram analysis, they found significant differences between benign and malignant breast masses across several ADC histogram parameters.15 Their results support the concept that quantitative diffusion characteristics provide information related to lesion biology beyond conventional visual morphology. Our study used a focused single-ROI approach rather than whole-lesion histogram analysis, but both approaches demonstrate the discriminatory value of quantitative diffusion information.

A systematic review and diagnostic meta-analysis by Xu et al. further supports this observation.16 Their analysis of whole-lesion ADC histogram parameters found pooled sensitivity of 85%, specificity of 79%, and an AUC of 0.9178 for distinguishing benign from malignant breast lesions. The 50th-percentile ADC demonstrated particularly favorable diagnostic performance. The AUC of 0.934 obtained with our focused ROI approach is therefore within the range of diagnostic performance reported for more extensive histogram-based approaches, although the different measurement strategies preclude direct equivalence.

The proposed ADC threshold in the present study should therefore be interpreted as a protocol-specific, internally derived threshold rather than a universal cutoff. This is supported by the EUSOBI International Breast DWI working group, which emphasized that ADC measurement is influenced by acquisition technique and ROI methodology.7 The consensus recommends that ADC measurements be obtained from an ROI positioned within the lesion while avoiding artifacts, necrosis, hemorrhage, and nonenhancing components, and emphasizes that diffusion findings should be interpreted together with the other anatomical and functional MRI features rather than in isolation. Our approach of placing a focused ROI in the most restricted solid component while avoiding necrosis and artifacts is consistent with these recommendations. The reproducibility of ADC measurement observed in our study is also supported by the ACRIN 6698 trial reported by Newitt et al. In this multicenter prospective study, ADC measurements demonstrated excellent repeatability and reproducibility, with an interreader ICC of 0.92.17 Our ICC of 0.93 is highly comparable. This supports the feasibility of obtaining reproducible quantitative ADC measurements when standardized acquisition and measurement procedures are used.

The performance of conventional BI-RADS assessment in our cohort is also broadly consistent with published evidence. Our BI-RADS 4/5 threshold produced a sensitivity of 97.1% and NPV of 94.6%, although specificity was 72.2%. A

systematic review and meta-analysis by Li et al. evaluating MRI assessment of BI-RADS 4 lesions reported pooled sensitivity of 95% and specificity of 87%, with an AUC of 0.95.18 The somewhat lower specificity in our study may reflect differences in patient selection, lesion spectrum, disease prevalence, and the tertiary-care setting in which all included lesions underwent histopathological confirmation.

The relatively lower specificity of BI-RADS compared with ADC in our cohort is clinically plausible because BI-RADS integrates multiple qualitative morphological and enhancement features and is intended to stratify lesions according to the need for further diagnostic evaluation. Suspicious morphology or enhancement can therefore occur in benign lesions. The EUSOMA breast MRI recommendations emphasize the importance of standardized acquisition and interpretation and recognize that MRI should be interpreted within the broader diagnostic pathway rather than as an isolated test.19

An important finding of the present study was the performance of the combined BI-RADS and ADC model. The model demonstrated an AUC of 0.958, with sensitivity of 95.0%, specificity of 91.8%, PPV of 94.3%, NPV of 92.7%, and accuracy of 93.6%. These findings are consistent with recent work investigating the integration of quantitative diffusion information with BI-RADS assessment. Zhang et al., in a 2025 study of 376 breast lesions, evaluated an ADC category system in combination with BI-RADS. ADC-B alone demonstrated an AUC of 0.858 compared with 0.805 for BI-RADS, while the combination achieved an AUC of 0.870 and significantly improved specificity while maintaining sensitivity.20 Although the absolute AUC in their study was lower than that observed in our cohort, the direction of the findings is similar and supports the concept that quantitative diffusion information can complement conventional BI-RADS assessment.

However, the apparent improvement of the combined model in our study should be interpreted cautiously. We did not perform a formal statistical comparison of correlated ROC curves; therefore, the higher AUC of 0.958 should not be described as statistically superior to BI-RADS or ADC alone. Furthermore, the model was developed and evaluated within the same cohort. The reported performance therefore represents apparent internal performance rather than externally validated diagnostic performance.

The false-positive and false-negative ADC findings in our cohort provide additional biological context. Thirteen benign lesions demonstrated ADC values below the selected threshold, most commonly cellular fibroadenomas and proliferative lesions. This overlap is expected because ADC reflects tissue water mobility and microstructural characteristics rather than malignancy itself. Consequently, cellular benign lesions may demonstrate substantial diffusion restriction. The large meta-analysis by Surov et al. similarly demonstrated overlap between benign and malignant ADC distributions, supporting the use of ADC as an adjunct rather than a standalone diagnostic criterion.11

Twelve malignant lesions were classified as ADC-negative in our study. Five were invasive lobular carcinomas, three were mucinous carcinomas, two were low-grade invasive ductal carcinomas, and two were heterogeneous lesions containing substantial necrosis. The predominance of invasive lobular carcinoma among the false-negative lesions is particularly noteworthy. Jeong and Kim evaluated invasive lobular carcinoma and invasive carcinoma of no special type using 3-T DWI and found that invasive lobular carcinomas had significantly higher mean ADC values and were less frequently visible on DWI.21 Their reported mean ADC values were approximately 1.226×10^{-3} mm²/s for invasive lobular carcinoma and 1.052×10^{-3} mm²/s for invasive carcinoma of no special type. These findings provide a plausible explanation for the relatively higher ADC values observed in some of the invasive lobular carcinomas in our cohort.

The false-negative mucinous carcinomas in our cohort also illustrate an important limitation of using a single ADC threshold across all histological subtypes. Histological composition can influence water mobility and therefore ADC values. Similarly, necrotic components within heterogeneous malignant lesions may increase measured ADC if included within the ROI. Although our protocol attempted to minimize this problem by targeting the most restricted solid component, heterogeneous lesions remain challenging for single-ROI analysis.

Taken together, these findings support a complementary rather than substitutive role for ADC. Conventional MRI features provide information concerning lesion morphology, vascularity, and enhancement kinetics, whereas ADC provides quantitative information related to tissue microstructure and water diffusion. These parameters therefore capture different aspects of lesion biology. The combination may be particularly useful when conventional MRI findings are suspicious but not definitive.

The multivariable analysis further supports this complementary interpretation. ADC $\leq 1.31 \times 10^{-3}$ mm²/s demonstrated the strongest independent association with malignancy in our model (adjusted OR, 7.84; $P < 0.001$), followed by irregular/spiculated margins (adjusted OR, 4.63; $P < 0.001$) and washout enhancement (adjusted OR, 2.71; $P = 0.002$). Lesion size >25 mm showed a more modest independent association (adjusted OR, 1.76; $P = 0.046$), whereas age >50 years

was not independently significant. These findings suggest that quantitative diffusion characteristics provide diagnostic information that is not completely explained by lesion size, age, or conventional enhancement morphology.

The present study has several strengths. It was prospective and used histopathological confirmation as the reference standard. It incorporated morphological, dynamic contrast-enhancement, and quantitative diffusion characteristics within a multiparametric MRI framework. ADC was independently measured by two radiologists, allowing assessment of reproducibility, and the observed ICC of 0.93 was excellent. The study also included a range of benign and malignant histological subtypes and specifically examined false-positive and false-negative ADC classifications.

Several limitations should nevertheless be considered. First, this was a single-center study conducted at a tertiary-care academic institution, and the lesion spectrum may therefore differ from that encountered in screening populations. Second, the analysis was performed at the lesion level, and 18 women contributed two lesions; therefore, observations from lesions within the same participant may not be completely statistically independent. Third, the ADC cutoff was derived using the Youden index in the same dataset used to evaluate diagnostic performance, creating potential optimism bias. Fourth, ADC values and thresholds are dependent on scanner characteristics, sequence parameters, b-values, and ROI methodology and may therefore not be directly transferable to other institutions. Fifth, several histological subgroups were relatively small, limiting reliable subtype-specific estimates. Finally, the combined BI-RADS and ADC model was evaluated within the same cohort in which it was developed and therefore requires independent external validation.

Overall, the findings of the present study are consistent with the broader literature demonstrating that malignant breast lesions generally have lower ADC values than benign lesions and that quantitative diffusion assessment can provide reproducible and clinically useful information. Studies by Surov et al., Caivano et al., Tan et al., Pereira et al., Suo et al., Xu et al., Newitt et al., Jeong and Kim, Li et al., Jansen et al., Kuhl et al., and Zhang et al. collectively support the complementary role of diffusion and conventional MRI assessment.9,11–14,16–18,20,21

The clinical implication is that ADC should not be considered a replacement for BI-RADS or histopathological assessment. Rather, it may serve as an objective quantitative adjunct that can strengthen multiparametric MRI interpretation, particularly when benign and malignant lesions demonstrate overlapping conventional imaging characteristics. The threshold of $\leq 1.31 \times 10^{-3}$ mm²/s identified in this study is promising but should be considered study- and protocol-specific until prospectively validated across different scanners, institutions, and patient populations.

CONCLUSION

Multiparametric breast MRI combined with quantitative ADC analysis demonstrated good diagnostic performance for differentiating benign and malignant breast lesions. Malignant lesions showed significantly lower ADC values than benign lesions, and an ADC threshold of $\leq 1.31 \times 10^{-3}$ mm²/s provided high sensitivity and specificity. Integration of ADC with BI-RADS assessment further improved overall diagnostic discrimination, with an AUC of 0.958 and an accuracy of 93.6%.

These findings suggest that quantitative ADC can serve as a valuable adjunct to conventional BI-RADS assessment by providing objective diffusion-based information and potentially improving specificity without substantially compromising sensitivity. However, the proposed ADC threshold was derived from the present cohort and has not been externally validated. Multicenter prospective validation using standardized MRI acquisition and ADC measurement protocols is therefore required before this threshold or the combined model can be routinely applied in clinical practice.

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