Quantitative evaluation of intravoxel incoherent motion diffusion-weighted imaging (IVIM) for differential diagnosis and grading prediction of benign and malignant breast lesions

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Abstract

Background: That breast carcinoma is the most common malignant lesion in women. This study aimed to differentiate benign from malignant breast lesions and to predict grading of the latter by comparing the diagnostic value of different parameters in intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI).

Materials and methods: Retrospective analysis was performed utilizing imaging and pathological data from 112 patients with 124 breast lesions that underwent IVIM-DWI examination with 3.0 T MRI. Out of 124, 47 benign and 77 malignant lesions were confirmed by pathological diagnosis. The diagnostic performance of f, D, and D* value to distinguish benign from malignant breast lesions, was evaluated using pathological results as the gold standard. Correlation between D value and Ki-67 index was evaluated to predict grading of malignant breast lesions.

Results: The D value (0.99 ± 0.21) of patients with malignant lesions was significantly lower than that (1.34 ± 0.18) of patients harboring benign lesions ($P = .00$). The D* value (7.60 ± 2.10) in malignant lesion group was higher than that (6.83 ± 2.13) of the benign lesion group ($P = .113$). The f value (8.50 ± 2.13) in malignant lesion group was remarkably higher than that (7.68 ± 1.98) of benign lesion group ($P = .035$). For differential diagnosis of benign from malignant breast lesions, optimal diagnostic threshold of D value and f value were 1.21 and 7.86, respectively. The areas of D and f values under the ROC curve were 0.883 and 0.601, respectively. The sensitivity, specificity, and accuracy of D value were 83.0%, 86.7%, and 85.5%, respectively. Accordingly, those indexes of f value were 64.9%, 57.4%, and 62.1%, respectively. Furthermore, the Ki-67 staining index of malignant lesions was robustly negatively correlated with D value ($r = -0.395$, $P < .01$).

Conclusion: Concrete parameters of IVIM-DWI can help to improve the specificity and accuracy in differential diagnosis of breast benign and malignant lesions. D value is most relevant and valuable in predicting the grading of malignant breast lesions.

Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, EPI = single-shot spin-echo planar sequence, FOV = field of view, IVIM = intravoxel incoherent motion, MRI = magnetic resonance imaging, ROC = region of interest, T1WI = T1-weighted, T2WI = T2-weighted, TE = echo time, TR = repetition time.

Keywords: breast lesions, D value, IVIM-DWI, Ki-67

1. Introduction

It has been reported that morbidity and mortality of breast cancer has increased greatly in China during the past 20 years, especially in metropolis.[1] Early diagnosis and treatment are imperative to improve overall survival of breast cancer patients.

Mammography has been proved to be efficient in distinguishing benign from malignant lesions for fat-type breast, while frequently missing the lesion for dense-type breast, which is vastly popular in Chinese women. The internal composition, boundary, and surrounding tissues of breast lesions can be shown intuitively by ultrasound elastography. However, the grading of elastic coefficient could be easily influenced by the technique of operator, the composition, and location of the lesion.

Dynamic contrast-enhanced MRI has been widely applied in clinic due to its high soft tissue resolution and multidimensional imaging without radiation.[2–4] It has been reported that dynamic contrast-enhanced MRI of breast lesions had high sensitivity (90%–95%) but low specificity (around 46%).[5] The discrimination of breast lesions by dynamic contrast-enhanced MRI is still quite challenging, especially of benign and malignant breast lesions.[6,7] The valuable quantitative parameters (V_e, k_{ep}, and K^{trans}) of physiology can be calculated using the mathematical model but at its initial stage the performances are controversial.[8]

Diffusion-weighted imaging (DWI), as a non-enhancing type of MRI, can indicate the tissue physiological and pathological status, thereby improve the specificity of differentiating benign and malignant breast lesions through quantitative characteriza-

tion of in vivo movement water at the molecular level.[9–14] The apparent diffusion coefficient (ADC) is also measured to characterize malignant breast lesions, monitor treatment response, assess axillaries lymph nodes, and predict tumor biological behavior.[15–17] However, the value of ADC is not only influenced by the molecular diffusion of water but also affected by microcirculation, the microscopic blood flow.[18] It could make the ADC value of tissue lower, especially of tissue with rich perfusion, therefore making exact calculation of ADC value challenging.[19,20] Intravoxel incoherent motion (IVIM), which was firstly proposed by Bihan[21] in 1986, can differentiate the ADC value affected by microperfusion or by molecular diffusion on account of vivo water movement. Quantitative parameters include micro vascular volume fraction (f), molecular diffusion coefficient (D), and perfusion-related incoherent microcirculation (D*). Compared to normal ADC, the above 3 parameters could reflect the physiological and pathological change of tissues based on the IVIM model more accurately.

The IVIM measurements have been widely applied and reported in prostate,[18] liver,[22] kidney,[23] and so on. Application of IVIM on breast lesions have also been covered.[7,24,25] Few studies evaluate the value of 3 parameters and predict the relationship between the grading of malignant lesions and parameters. And in this study, we focused on the evaluation of the diagnostic efficacy of IVIM parameters in differentiating benign and malignant breast tumors. We evaluated the relationship between the D value and Ki-67 in malignant lesions, which is an antigen related to cell proliferation, and predicts grading of malignant lesions represented by Ki-67 labeling index.

2. Materials and methods

2.1. Patients

The study was approved by the Ethics Committee of Binzhou Medical University Hospital. Potential side effects of the contrast media were notified, and informed consents were signed by all patients personally or their families included in this study. From January 1, 2014 to June 30, 2016, patients who met the criteria of research were recruited in the study retrospectively. The criteria for patients to join this research were as follows: patients with suspicious breast lesions detected by physical examination, other radiological examinations are examined by IVIM sequence of 3.0 T MRI successfully; the quality of imaging examined by 3.0 T MRI is acceptable with marginal noise; the patients did not undergo needle biopsy, chemotherapy, or any other interventions before they were examined by 3.0 T MRI; the diameter of the breast lesions is bigger than 1 cm; the pathological type of breast lesions is confirmed by operation or biopsy; and relevant data of patients are complete. Finally, 135 patients with suspicious breast lesions were examined by 3.0 T MRI. And 112 patients, who had 124 breast lesions, met the criteria of study (Fig. 1). All of them are women. The ages of patients range from 25 to 78 years old (mean: 45.3 ± 8.7 years).

2.2. Image acquisition

Patients were examined by a 3.0 T MRI with a 4-channel dedicated breast coil (Skyra, Siemens, Munich, Germany). The scanning was performed with the patient prone in the toe-to-heed direction, breasts placed within the coils. First, the sequence of conventional MR was performed. Then, the sequence of IVIM-DWI was performed. Finally, contrast-enhanced MRI was performed.

2.2.1. Conventional MR.
Conventional MR sequence included breasts axia T1WI (TR 170 ms, TE 2.8 ms, 2D SPGR), T2WI (TR
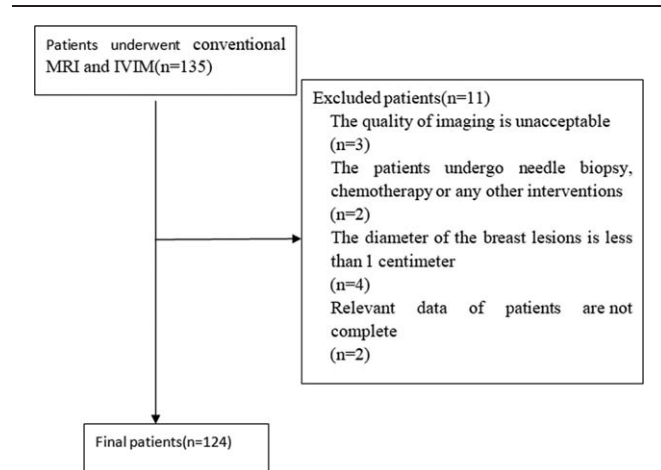

Figure 1. Flow diagram shows the patient selection process with exclusion criteria.

3500 ms, TE 70 ms, Fast Inversion Recovery), and T2WI with fat suppression (TR 3300 ms, TE 70 ms), thickness 4.0 mm, space 0.4 mm, FOV 340 mm × 340 mm, and matrix 269 × 384.

2.2.2. IVIM-DWI sequence.
IVIM-DWI sequences were obtained using single-shot spin-echo planar sequence (EPI); fat suppression techniques were performed. b values were 0, 50, 100, 150, 200, 250, 300, 400, 600, 800, 1000, and 1200 s/mm^2. Each b-value was acquired for X, Y, Z—3 orthogonal directions—NEX 1,1, 1, 1, 1, 2, 2, 4, 4, 4, 6, and 6, respectively.

Parameters of IVIM-DWI sequences were as follows: TR 6500 ms, TE 65 ms, thickness 5 mm, space 1 mm, FOV 340 mm × 138 mm, matrix 192 × 78.

2.2.3. Contrast-enhanced MRI.
Contrast-enhanced MRI was obtained by VIBE sequences (TR 4.48 ms, TE, 1.65 ms, FOV 340 mm × 340 mm, matrix 352 × 260, thickness 1 mm, space 0.25 mm, flip angle 10°). A total of 8 phases were performed; 1 phase before enhancement, which was a mask, and 7 phases after enhancement. After the first phase, a gadolinium-based agent Gd-DTPA (Germany, Berlin, Schering Co Ltd. (SCHERING)) was intravenously injected at a dose of 0.2 mL/kg of body weight and at a rate of 2.5 mL/s via antecubital vein using pressure injector, which was followed by 20 mL saline flush.

2.3. Image analysis

The contrast-enhanced MRI images and IVIM-DWI images were transmitted to the syngo MMWP VE40B workstation. IVIM-DWI images were reconstructed by post processing software of MITK-Diffusion. The conventional MRI images, enhanced MRI images, and IVIM-DWI images were all evaluated as references to determine the area of lesions on the IVIM-DWI parametric maps, which were called region of interest (ROI) and drawn in the IVIM parametric maps. The principle of choosing the ROI area is as follows: ROI should be placed on the area at the level of maximum transverse diameter of the each lesion; ROI should be drawn as large as possible to contain the breast lesion entity; and large cystic and necrotic areas should be avoided, which could be displayed very well by enhanced MRI images and T2 sequence images.

The ROC of MRI images were drawn by 2 radiologists (XJ and XZ), who had experience in breast MRI diagnosis for 15 and 8 years, respectively, and were blinded to the details of patients and

pathologic data. Disagreement of both radiologists was resolved in consensus. All data were measured for 3 times and the average of 3 times is taken to reduce the bias caused by measurement error.

The D, D*, and f value were calculated by MITK-Diffusion processing software using the equation of bi-exponential model: $Sb/S0 = (1–f) \exp (–bD) + f \exp [–b (D* +D)]$, described first by Le Bihan et al.[26] Sb is the signal intensity in the pixel with diffusion gradient b, S0 is the signal intensity in the pixel without diffusion gradient.[7] D value is the true diffusion of water molecules in the intercellular gap, excluding reflection by microcirculation in the intercellular gap. D* value represents perfusion-related diffusion affected by microcirculation in the intercellular gap. f value represents the proportion of perfusion influenced by microcirculation in blood capillary of tissue.

In this study, ROI was drawn first in D map because of its high quality of image and the value was calculated using a simplified single-exponential model when b value $>170 \, s/mm^2$. Then the intercept (Sint) and the signal intensity at $b=0(S_0)$ were obtained based on the fit curve of the model. The f was calculated using the formula: $f = (S_0 – S_{int})/S0$. Finally D* was calculated using D and f value.

2.4. Pathological diagnosis

The histologic diagnosis was made by a single pathologist with 15 years of experience in breast histologic evaluation. The immunoreactivity of Ki-67 was graded in accordance with the following procedures. The intensity of cell staining was scored on a scale of 1 to 3, with 1 indicating weak staining, 2 indicating moderate staining, and 3 indicating the strongest staining. The extent of staining was calculated according to the percentage of positive cells as follows: 0, positive immunostaining of $\leq5\%$ of tumor cells; 1, positive immunostaining of 6% to 25% of tumor cells; 2, positive immunostaining of 26% to 50% of tumor cells; 3, positive immunostaining of 51% to 75% of tumor cells; and 4, positive immunostaining of $>75\%$ of tumor cells.

2.5. Statistical analysis

SPSS statistics V19.0 (Statistical Package for Social Sciences, IBM Company, IL) was used for the statistics analysis. D, D*, and f value were presented as mean $\pm$ SD. First, the parameters of IVIM-DWI were tested by normal distribution test. Data (D, D*, and f value) was compared with each other using 2 independent samples t-test when according with normal distribution. Data was compared using Wilcoxon rank sum test when lacking a normal distribution. $P < .05$ was considered statistically significant. Using pathological results of breast lesions as the gold standard, receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic efficacy of D, D*, and f value when differentiating benign and malignant breast lesions. Spearman correlation analysis was used to evaluate the pertinence of D value and Ki-67 expressing index in the malignant breast lesions.

3. Result

3.1. Pathological types of breast lesions recruited in our study

A total of 124 lesions were confirmed by pathological examination after operations. The number of benign lesions (refer to one representation in Fig. 2) was 47 and the number of
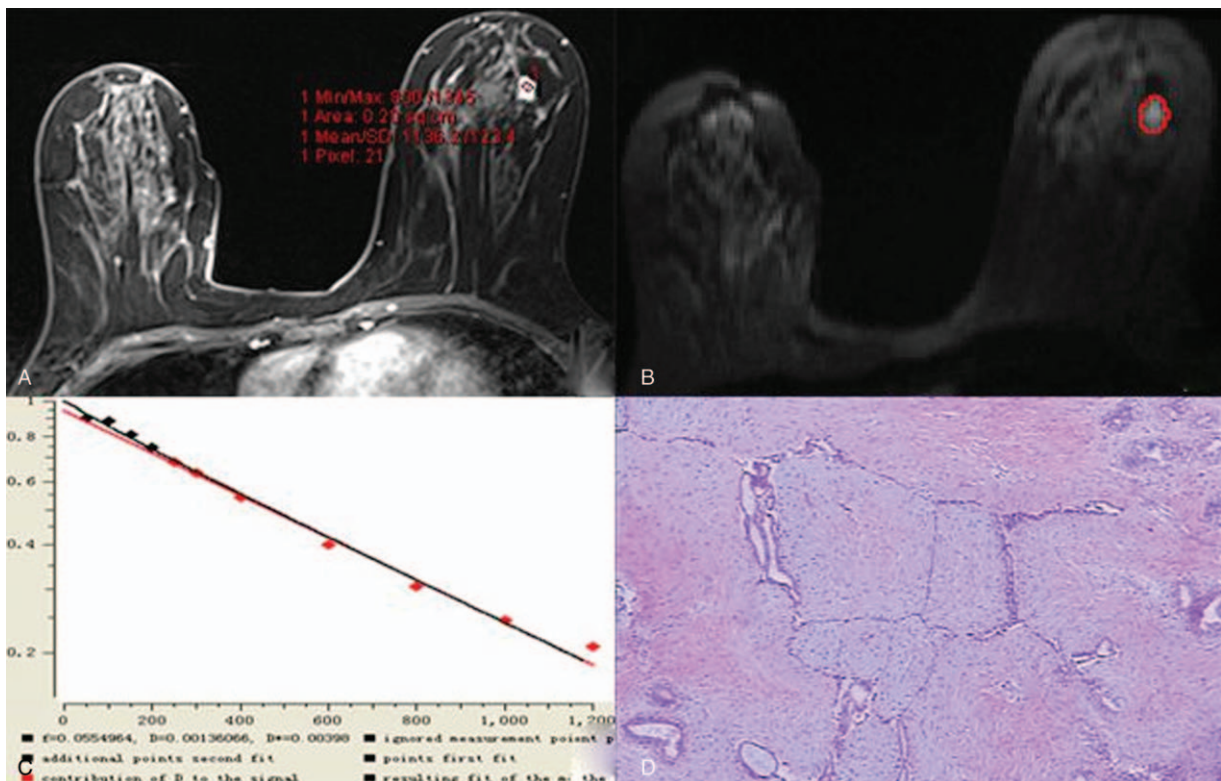

Figure 2. A 35-year-old female patient with left breast fibroadenoma. (A) DCE-MRI image of lesion with irregular shape and mass-like enhancement; (B) IVIM-DWI image, high signal; (C) Quantification of IVIM-DWI image, $f=5.71 \times 10^{-2}$, $D=1.42 \times 10^{-3} \, s/mm^2$, $D*=3.98 \times 10^{-3} \, s/mm^2$; (D) HE staining indicated increase of ductal epithelial cells and fibroblasts. Duct epithelial cells were identified with "finger-like protrusions" (HE, $\times200$).
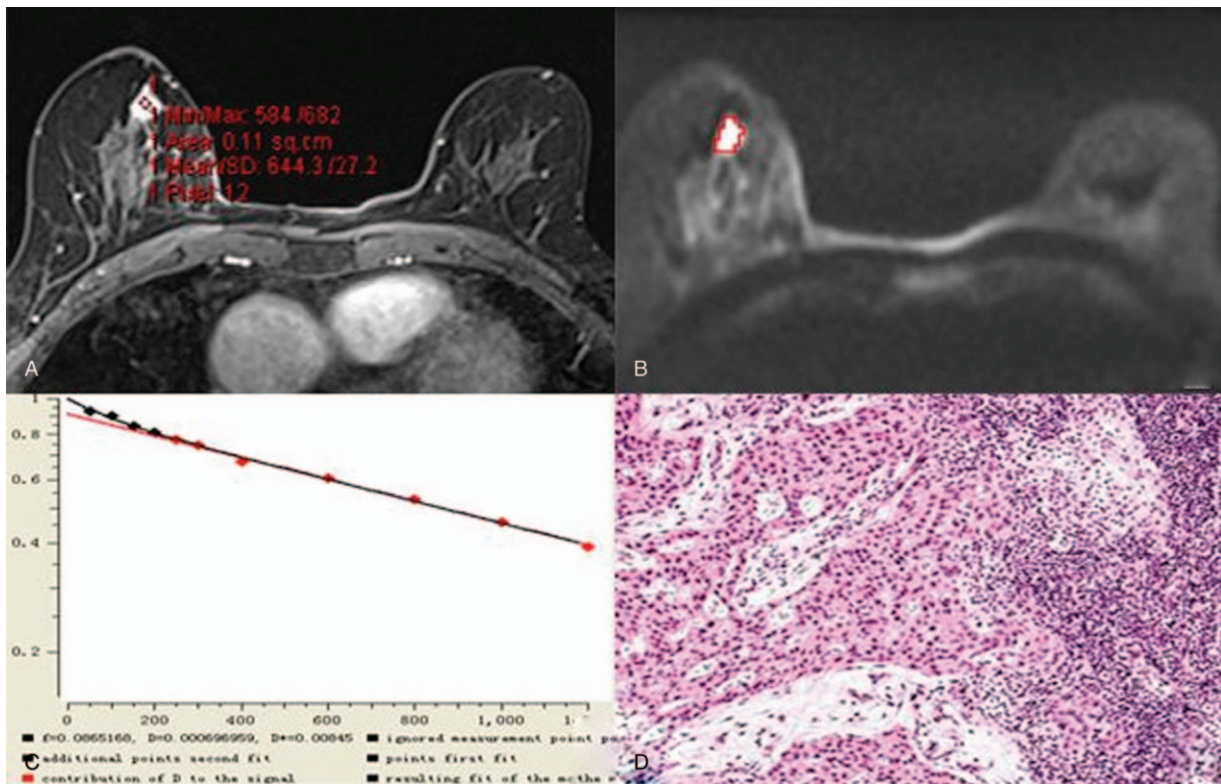
Figure 3. A 53-year-old female patient with invasive ductal carcinoma in the right breast. (A) Breast DCE-MRI image showing a lesion with irregular shape and mass-like enhancement; (B) IVIM-DWI image, high signal; (C) Quantification of IVIM-DWI image, f=8.73×10^{-2}, D=1.07×10^{-3} s/mm^2, D*=6.96×10^{-3} s/mm^2; biexponential model fitting curve; (D) HE staining showing hyperplasia of the glands and interstitial fibrous tissue. Tubules lesions invaded into the adjacent fibrous tissue, with glandular and myoepithelial bilayer structure (×100).

malignant lesions was 77 (Fig. 3 as a representation for HE staining). The histological classification of breast lesions was summarized in Table 1.

3.2. IVIM-DWI parameters for benign and malignant lesions

The D, D*, and f value of IVIM-DWI parameters in malignant lesion group were 0.99±0.21, 7.60±2.10, and 8.50±2.13, respectively. The D, D*, and f value of benign lesions group were 1.34±0.18, 6.83±2.13, and 7.68±1.98, accordingly. The D value in malignant lesions group (0.99±0.21) was lower than that of the benign lesions group (1.34±0.18) ($P<.05$). The D* value in malignant lesions group (7.60±2.10) was higher than that of the benign lesions group (6.83±2.13) ($P>.05$). The f value in malignant lesions group was higher than that of the benign lesions group (8.50±2.13 vs 7.68±1.98) ($P<.05$) (Table 2).

3.3. Diagnostic performance of the f, D value for benign and malignant lesions

Taking pathological results of breast lesions as the gold standard, (ROC) curves of IVIM-DWI parameters were generated. The optimal diagnostic threshold of D value and f value in the differential diagnosis of benign and malignant breast lesions were 1.21 and 7.86, respectively. According to these criteria, breast lesions with D value >1.21 or f value <7.86 were identified to be malignant. The other way around, breast lesions with D value <1.21 or f value >7.86 were classified to be benign. The area of D and f value under the ROC curve was 0.883 (95% CI, 0.822–0.944) and 0.601 (95% CI, 0.498–0.703), respectively (Fig. 4). The sensitivity, specificity, and accuracy of D value to differentiate the benign and malignant breast lesions were 83.0%, 86.7%, and 85.5% respectively. The sensitivity, specificity, and accuracy of f value were respectively 64.9%, 57.4%, and 62.1% (Table 3). According to the results aforementioned, the diagnostic efficacy of D value was higher than that of f value.

Table 1

Pathological types of the 124 confirmed breast lesions.

Benign (N=47)		Malignant (N=77)	
Fibroadenoma	24	Invasive ductal carcinoma	35
Benign phyllodes tumor	8	Ductal carcinoma in situ	12
Intraductal papilloma	4	Invasive lobular carcinoma	11
Galactocele	4	Mucinous carcinoma	8
Granulomatous lobular mastitis	3	Medullary carcinoma	5
Mammary duct ectasia	2	Eczematoid carcinoma	3
Simple cyst	1	Basaloid cell cancer	2
Scleradenitis	1	Adenoid cystic carcinoma	1

Table 2

The f, D, D* values of benign and malignant lesions.

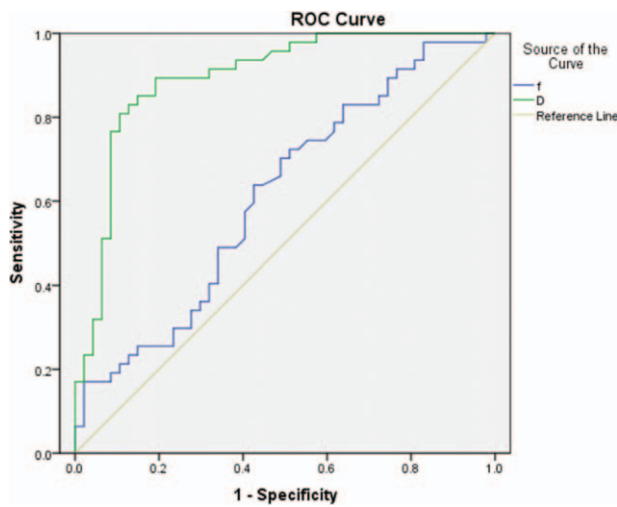| Group	f (%)	D (×10^{-3} s/mm^2)	D*(×10^{-3} s/mm^2)
Benign group	7.68±1.98	1.34±0.18	6.83±2.13
Malignant group	8.50±2.13	0.99±0.21	7.60±2.10
t value	−2.14	9.21	−1.96
P value	.035	.000	.113

Figure 4. ROC curves showing the diagnostic performance of D value and f value. The area of ROC curve for D and f values were 0.883 and 0.601, respectively.

3.4. The relationship between D value and Ki-67 labeling index for malignant lesions

The labeling index of Ki-67 was negatively correlated with D value in cases of malignant lesions ($r = -0.395$, $P < .01$) (Table 4) (Fig. 5).

4. Discussion

In clinical practice, DWI and DCE-MRI are the most widely used radiological examinations for breast lesion diagnosis. TIC curve of DCE-MRI is referable but has limited clinical application due to low specificity.[27] Especially when in mode II, TIC curve can hardly differentiate benign from malignant breast lesions. The ADC value is influenced by water molecule diffusion and capillary microcirculation perfusion in ordinary single exponential model DWI. The measurement of ADC value is sensitively affected by b value, therefore leading to its inaccuracy. The lower the b value is, the more greatly the ADC value is influenced by capillary microcirculation perfusion. However, the signal-to-noise ratio of MRI imaging becomes poor and results in missed diagnosis of small lesions when b value becomes bigger. Hence, the ADC value in ordinary single exponential model of DWI is not sufficient to diagnose breast lesions.

MITK-Diffusion processing of bi-exponential model was first proposed by Le Bihan et al.[26] The D, D*, and f values are calculated using equation of the MITK-Diffusion processing of bi-exponential model, which is named as intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI). It is known that the D value is mainly affected by water molecule diffusion of

Table 3

Diagnostic performance of the f, D value for benign and malignant lesions.

Methods	Sensitivity (%)	Specificity (%)	Accuracy (%)
f value	64.9	57.4	62.1
D value	83.0	86.7	85.5

Table 4

The relationship between D value and Ki-67 labeling index for malignant lesions.

	r value	*P* value
D value	−0.40	<.01
Ki-67 value		

the lesion tissue rather than by microcirculation perfusion. D* value is mainly influenced by capillary microcirculation perfusion. In accordance with previous reports,[7,28] our study showed that the D value in malignant lesions group was lower than that of the benign lesions group ($P < .05$). One possibility that accounts for this is the shrunken extracellular space due to abnormal proliferation of cancer cells and following incremental local cell density in malignant tumor tissues. On the other hand, the intracellular water diffusion is limited because of increased viscosity and decreased permeability of the cellular membrane. This generates more severe diffusion limitation in malignant lesions than in benign lesions. The f value, reflecting the proportion of perfusion of microcirculation in tissue diffusion, is mainly affected by perfusion blood volume of microcirculation perfusion. The f value of malignant lesions is significantly higher than that of benign lesions ($P < .05$) Our findings go in line with the result of Liu[7] and Bokacheva,[24] which concluded that blood volume of microcirculation perfusion of the malignant tumor was higher. Combined with the aforementioned results, we conclude that the lesions are more likely to be malignant when they have lower D value and higher F value. D* value, reflecting the pseudo diffusion coefficient produced by microcirculation perfusion, is mainly influenced by the length of capillaries in the microcirculation perfusion and blood flow velocity. Our data showed that the D* value of the malignant tumor was slightly higher than that of benign lesions, but the difference was not statistically significant. The lack of repeatability of D* measurement as reported by other researchers[22,29] may be responsible for this.

Parameters of IVIM model with statistically significant differences were analyzed using ROC curve. The D value of the area under the curve (AUC) was 0.883, which was higher than
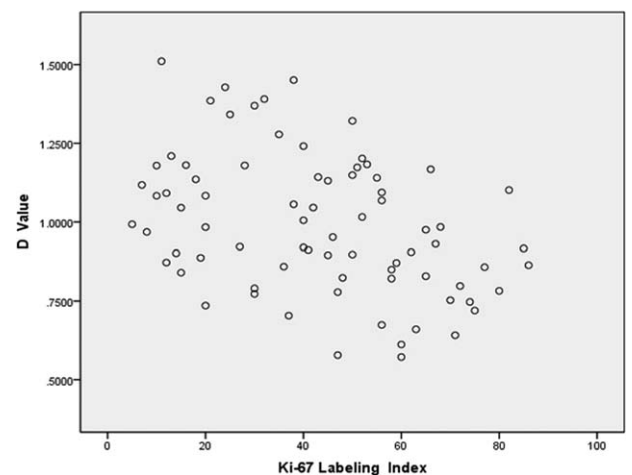

Figure 5. The correlation of D value and Ki67 staining regarding their diagnostic performance of beast malignant lesions.

the f value. In accordance with previous studies,[7,24,30] when the cutoff was set at 1.21×10^{-3} mm^2/s, the optimal sensitivity and specificity of diagnosis can be 83% and 86.7%, accordingly

Our data showed that D value of malignant breast tumors was lower and f value was higher compared with that of benign lesions. It is known that the ADC value of lesions is influenced by the diffusion and perfusion of tissues in 2 opposite directions. Therefore, compared to f value, the D value, which excluded from the influence of microcirculation perfusion, could be more valuable to differentiate benign from malignant breast lesions. Our results suggested that D value is a promising diagnostic index to distinguish benign from malignant breast tumors.

The correlation analysis between D value and Ki-67 labeling index in malignant breast tumors showed that D value was significantly positively correlated with the expression level of Ki-67 ($r = -0.395$, $P < .01$). Choi et al[31] found that the ADC value of Ki-67 high expression group was lower than that of Ki-67 low expression group ($P = .028$). Kim Y et al[32] reported D value was lower in high Ki-67 cancer than in low Ki-67 cancer. Different from this, Sun et al[33] reported that there was no significant difference in the mean value of ADC between the high expression group and low expression group (Ki-67) ($P = .087$). Our result showed that the Ki-67 labeling index in malignant lesions is remarkably correlated with D value. In case of malignant breast tumor, the extracellular diffusion of water molecules is limited due to high local cell density and small extracellular gap. The higher the degree of tumor malignancy, the more conspicuous cell hydrodynamic changes are. Therefore, D value can not only differentiate benign from malignant breast lesions, but also predict the malignant degree of breast tumor, and provide reliable imaging basis for the diagnosis and preoperative staging of breast cancer.

Although with novel findings, there are still some limitations in our study, which we would further improve in the future work. For one thing, the small sample size and simplex pathological types of breast cancer included in this research impose restriction for stratification study. For another, the setting of b value could exert impact on the parameters of the IVIM model especially on F-measure,[34] thus could bring about biased result. So far there is no specific standard about multiple b value of IVIM sequences, therefore the selection of b value needs to be further optimized.

Author contributions

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Writing – review & editing: Jing Du.

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