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ORIGINAL RESEARCH

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Values of magnetic resonance imaging apparent diffusion coefficient for prognostic evaluation and pathological typing of patients with breast cancer

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Abstract

We aimed to explore the values of magnetic resonance imaging (MRI) apparent diffusion coefficient (ADC) for the prognostic evaluation and pathological typing of breast cancer. A total of 136 patients diagnosed as breast cancer were retrospectively collected as an experimental group, and divided into a non-recurrence group (n = 104) and a recurrence group (n = 32) according to the 5-year follow-up results. Another 136 patients pathologically diagnosed as non-malignant tumors after operation in the same period were selected as a control group. The diffusion weighted imaging (DWI) signal intensity distributions and mean ADC values of different pathological types of breast cancer with various *b* values were compared. The predictive value of ADC for pathological type was analyzed using receiver operator characteristic curve. The independent risk factors for postoperative recurrence were determined through Cox analysis. When the *b* values were 1000 s/mm^2 and 2000 s/mm^2, the mean ADC values of invasive carcinomas (invasive ductal carcinoma, invasive lobular carcinoma) were significantly lower than those of non-invasive carcinomas (lobular carcinoma *in situ*, intraductal carcinoma *in situ*). The ADC value was an independent risk factor for postoperative recurrence. Based on the optimal cut-off value (1.046×10^{-3} mm^2/s) of ADC for predicting postoperative recurrence, the 5-year recurrence risk of the high-risk group was significantly higher than that of the low-risk group ($p < 0.05$). DWI has clinical significance for assessing benign/malignant breast cancer. High-signal images are dominant in DWI of patients with breast cancer.

Keywords

Magnetic resonance imaging; Apparent diffusion coefficient; Breast cancer; Prognosis

1. Introduction

Breast cancer, as one of the malignancies seriously threatening female health, has high morbidity and mortality rates [1]. About 1 out of every 8 women suffers from breast cancer in developed countries [2]. In China, the morbidity rate of breast cancer in women also rises annually, with an increase rate 1–2% higher than those of developed countries [3]. Early detection, diagnosis and treatment have been verified effective for reducing the mortality rate and ameliorating the prognosis and quality of life of patients. Breast cancer is a highly heterogeneous disease with different natural courses. The prognosis of patients with breast cancer has been predicted by tumor size, axillary lymph node status, histological grade and expression of human epidermal growth factor receptor 2 (HER2) [4, 5].

Traditional imaging methods for breast cancer, such as ultrasound and mammography, have raised the detection and diagnosis rates of breast cancer. However, they have great limitations in distinguishing benign and malignant lesions, especially those in dense breasts. Asian women have dense breast structures with low fat contents, so they are at a high risk for misdiagnosis and missed diagnosis [6]. Breast cancer is highly specific at the molecular level, with diverse biological behaviors and prognoses according to the pathological type [7]. Magnetic resonance imaging (MRI) has higher resolution for soft tissues than traditional imaging modalities, which has been widely used in clinical practice. MRI has a sensitivity of higher than 90% and a specificity of about 72% in the detection of invasive breast cancer [8]. 3.0T-MRI, in particular, is the world's most advanced ultra-high-resolution MRI technique characterized by clear images, accurate positioning, ability to process ultra-high-resolution image data streams and excellent safety [9]. Diffusion weighted imaging (DWI) can be employed to diagnose breast diseases through detecting the Brownian motion of water molecules in tissues, and to quantify this motion by apparent diffusion coefficient (ADC), thereby distinguishing malignant and benign disorders of the

breasts at the molecular level. Since Englander [10] first applied DWI to the diagnosis of breast lesions, the value of DWI for diagnosing breast lesions and the associations of ADC with prognostic factors such as estrogen receptor (ER) and progesterone receptor (PR) have been extensively studied [11]. In addition, most studies have focused only on DWI-ADC at a single *b* value for the analysis of prognostic factors of breast cancer, and obtained different results [12]. However, the predictive value of ADC for the postoperative recurrence of breast cancer has rarely been studied. The aim of this study was to explore the predictive values of ADC at different *b* values for the pathological type and postoperative recurrence of breast cancer, thereby providing a theoretical basis for clinical practice.

2. Materials and methods

2.1 Pathological data

A total of 136 patients diagnosed as breast cancer in our hospital from February 2013 to January 2017 were retrospectively collected as an experimental group. The inclusion criteria were as follows: (1) patients diagnosed as breast cancer by pathological examination and imaging, (2) those with a distance >3 cm between the tumor edge and nipple, (3) those with complete clinical data, (4) those with complete long-term follow-up data, and (5) those whose DWI was obtained before pathological biopsy, with measurable ADC values of lesions. The exclusion criteria were as follows: (1) patients with local recurrence or distant metastasis at the time of diagnosis, (2) those who had received other antitumor therapies, radiotherapy or chemotherapy before operation, (3) those undergoing breast-conserving surgery in other hospitals, (4) those who had low-quality MRI images with serious artifacts, (5) those whose lesions could not be simultaneously detected by T2-weighted imaging (T_2WI), DWI and dynamic contrast enhanced-MRI sequences, or (6) those with more than 2 lesions, and a diameter of a single lesion <1 cm. Another 136 patients pathologically diagnosed as non-malignant tumors after operation in the same period were selected as a control group. This study was approved by the ethics committee of our hospital, and all patients signed the informed consent.

2.2 Collection of general data

The following data of patients were collected: age, marital status, fertility status, menstrual status, family history of tumors, course of disease, T stage (T_1, T_2 and T_3), tumor diameter, pathological type (invasive carcinomas (invasive ductal carcinoma, invasive lobular carcinoma), non-invasive carcinomas (lobular carcinoma *in situ*, intraductal carcinoma *in situ*)), lymph node metastasis, hormone receptors (ER, PR, HER2 and Ki-67) and ADC value.

2.3 MRI examination

Scanning was performed with Discovery 750 3.0 T MRI scanner (GE Healthcare, Chicago, IL, USA) using a breast-specific coil. The patient was placed in a prone position, with the breasts naturally sagging. The relevant sequences were selected to simultaneously scan bilateral breasts in coronal and cross-sectional views, and the corresponding sequences were selected to scan the unilateral breast in sagittal views. The scanning parameters were as follows: T_1WI-spoiled gradient recalled echo sequence (inversion time (TI) = 800 ms, repetition time (TR) = 2000 ms, echo time (TE) = 20 ms), T_2WI-fast spin echo sequence (TE = 80 ms, TR = 4000 ms), T_2WI-spectral attenuated inversion recovery sequence and DWI sequence (TE = 59 ms, TR = 5000 ms, b = 0, 1000 and 2000 s/mm^2). After scanning, the original images were automatically uploaded to the post-processing workstation, automatically corrected and analyzed. The ADC value of lesions was measured using the region of interest (ROI).

2.4 Diagnostic criteria

Image analysis: All MRI images were read and assessed by 2 senior radiologists using the double-blind method. In the case of disagreement, they discussed with each other to determine the diagnostic results. ROI was selected to measure the ADC value during post-processing. DWI: The lesions were located using dynamic enhanced magnetic resonance images. Five ROIs away from bleeding, necrosis, cystic changes, calcified and liquefied lesions were selected, and the solid parts of the lesions were detected. They contained at least 50 pixels, and the mean ADC values at different *b* values were calculated by the workstation.

2.5 Follow-up

The patients were followed up by telephone or outpatient clinic from diagnosis to the death of patients or to January 2022. Re-examinations were performed every 3 months within 2 years after operation, and every 6 months from the 3rd year after operation. According to the postoperative follow-up results, the patients were divided into a non-recurrence group (n = 104, without distant metastasis) and a recurrence group (n = 32, with distant metastasis).

2.6 Statistical analysis

SPSS 22.0 software (IBM Inc., Armonk, NY, USA) was used for statistical analysis. The measurement data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and compared between two groups by the independent-samples *t*-test. The count data were expressed as rate (%), and compared between two groups by the χ^2 test. The influencing factors for postoperative recurrence were explored through Cox analysis. The predictive values of ADC for pathological type and postoperative recurrence risk were analyzed using receiver operator characteristic (ROC) curves. Kaplan-Meier survival curves were plotted, and recurrence within 5 years after operation was compared among the patients with different ADC values. The test level was α = 0.05.

3. Results

3.1 DWI signal intensity of breast cancer

In the experimental group, high signals were displayed in 134 cases, including 89 cases of diffuse high signals, 45 cases of

mixed high signals, 2 cases of equal signals, and no cases of low signals. In the control group, low signals, equal signals and mixed high signals were shown in 72, 60 and 4 cases, respectively. The DWI signal intensity had a significant difference between experimental and control groups ($p < 0.05$). When the b value was 1000 s/mm^2, the ADC value of the control group ($(1.203 \pm 0.542) \times 10^{-3}$ mm^2/s) was significantly higher than that of the experimental group ($(0.637 \pm 0.311) \times 10^{-3}$ mm^2/s) ($t = 10.563$, $p < 0.001$) (Table 1).

TABLE 1. DWI signal intensity in breast cancer patients (n (%), n = 136).

Group	Low signal	Equal signal	Mixed high signal	Diffuse high signal
Experimental	0	2	45	89
Control	72	60	4	0
χ^2		58.37		
p		<0.001		

3.2 ADC values of different pathological types of breast cancer

When the b values were 1000 and 2000 s/mm^2, the mean ADC values of invasive carcinomas (invasive ductal carcinoma, invasive lobular carcinoma) were significantly lower than those of non-invasive carcinomas (lobular carcinoma *in situ*, intraductal carcinoma *in situ*) in the experimental group ($p < 0.05$). The ADC value had no significant difference between lobular and intraductal carcinomas *in situ* ($p > 0.05$), or between invasive ductal and lobular carcinomas ($p > 0.05$). For different pathological types of breast cancer, the ADC value was significantly lower when the b value was 2000 s/mm^2 than that when the b value was 1000 s/mm^2 ($p < 0.05$) (Table 2).

3.3 Predictive values of ADC for invasive carcinomas analyzed using ROC curves

The predictive values of ADC for invasive carcinomas were analyzed using ROC curves. The area under the curve (AUC) values of ADC for predicting the pathological type of breast cancer were 0.718 (95% confidence interval (CI): 0.692–0.852, $p < 0.001$) and 0.846 (95% CI: 0.724–0.872, $p < 0.001$) respectively when the b values were 1000 and 2000 s/mm^2 (Table 3 and Fig. 1).

3.4 Predictive value of ADC for postoperative recurrence of breast cancer analyzed using ROC curve

The predictive value of ADC for the postoperative recurrence of breast cancer was analyzed using ROC curve. The results showed that both sensitivity (83.46%) and specificity (76.33%) were high, and AUC was 0.718 when the ADC value was 1.046×10^{-3} mm^2/s (Fig. 2).

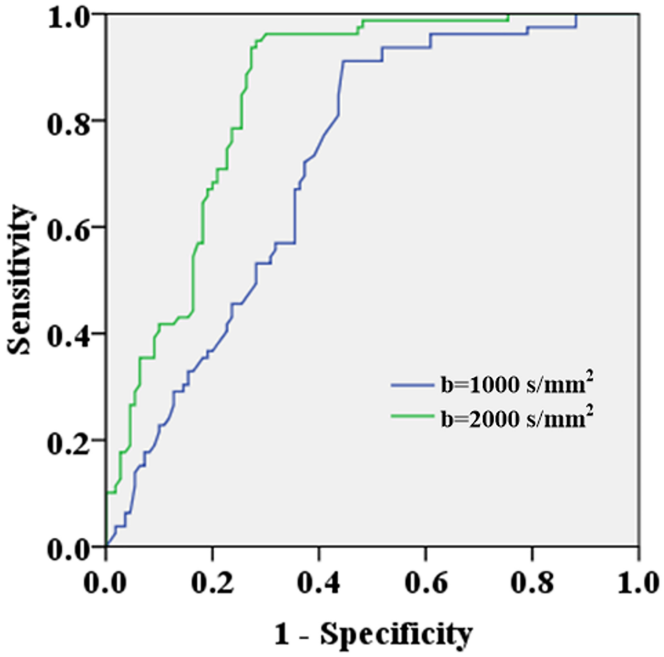

FIGURE 1. Predictive values of ADC for invasive carcinomas analyzed using ROC curves.

3.5 Prognosis analysis results

Based on the optimal cut-off value (1.046×10^{-3} mm^2/s) of ADC for predicting postoperative recurrence, the patients in the experimental group were divided into a high-risk group (n = 38, ADC $\leq 1.046 \times 10^{-3}$ mm^2/s) and a low-risk group (n = 98, ADC $> 1.046 \times 10^{-3}$ mm^2/s). The Kaplan-Meier survival curves were plotted, and the 5-year recurrence status was compared between the two groups. The 5-year recurrence risk of the high-risk group (92.11% (35/38)) was significantly higher than that of the low-risk group (76.53% (75/98)) (Log-Rank $\chi^2 = 8.502$, $p = 0.003$) (Fig. 3).

3.6 Predictive value of ADC for postoperative recurrence of invasive breast cancer analyzed using ROC curve

The predictive value of ADC for the postoperative recurrence of invasive breast cancer was analyzed by ROC curve. When the ADC value was 1.017×10^{-3} mm^2/s, high sensitivity (86.64%) and specificity (79.45%) were obtained. AUC was 0.852 (Fig. 4).

3.7 Clinical data of patients

The general clinical data of recurrence and non-recurrence groups were compared. Significant differences were found in T stage, pathological type, lymph node metastasis, expressions of hormone receptors (ER, PR, HER2 and Ki-67) and ADC value between the two groups ($p < 0.05$) (Table 4).

3.8 Cox analysis results of influencing factors for postoperative recurrence

Cox analysis was conducted by using the clinical variables that had significant differences ($p < 0.05$) between recurrence and non-recurrence groups as independent variables, and presence

TABLE 2. Mean ADC values of different pathological types of breast cancer ($\times 10^{-3}$ mm^2/s, $\bar{x} \pm s$).

Pathological type	n	b = 1000 s/mm^2	b = 2000 s/mm^2	t	p
Intraductal carcinoma *in situ*	32	1.301 ± 0.214	1.100 ± 0.150	4.351	<0.001
Lobular carcinoma *in situ*	4	1.221 ± 0.124	1.001 ± 0.115	2.602	0.035
t		0.727	0.854		
p		0.472	0.399		
Invasive ductal carcinoma	79	1.083 ± 0.163	0.804 ± 0.164	10.725	<0.001
Invasive lobular carcinoma	21	1.081 ± 0.125	0.768 ± 0.138	7.703	<0.001
t		0.052	0.922		
p		0.958	0.359		
ADC_{mean} of non-invasive carcinomas	36	1.261 ± 0.169	1.051 ± 0.133	5.859	<0.001
ADC_{mean} of invasive carcinomas	100	1.082 ± 0.144	0.786 ± 0.151	14.186	<0.001
t		6.102	9.306		
p		<0.001	<0.001		

ADC: apparent diffusion coefficient.

TABLE 3. Predictive values of ADC for invasive carcinomas analyzed using ROC curves.

b value	Cut-off value	AUC (95% CI)	p	Sensitivity (%)	Specificity (%)	Youden Index
1.072 × 10^{-3} mm^2/s	0.718 (0.692~0.852)	<0.001	87.67	88.19	0.759	1.072 × 10^{-3} mm^2/s
0.919 × 10^{-3} mm^2/s	0.846 (0.724~0.872)	<0.001	73.46	78.65	0.521	0.919 × 10^{-3} mm^2/s

AUC: area under the curve; CI: confidence interval.

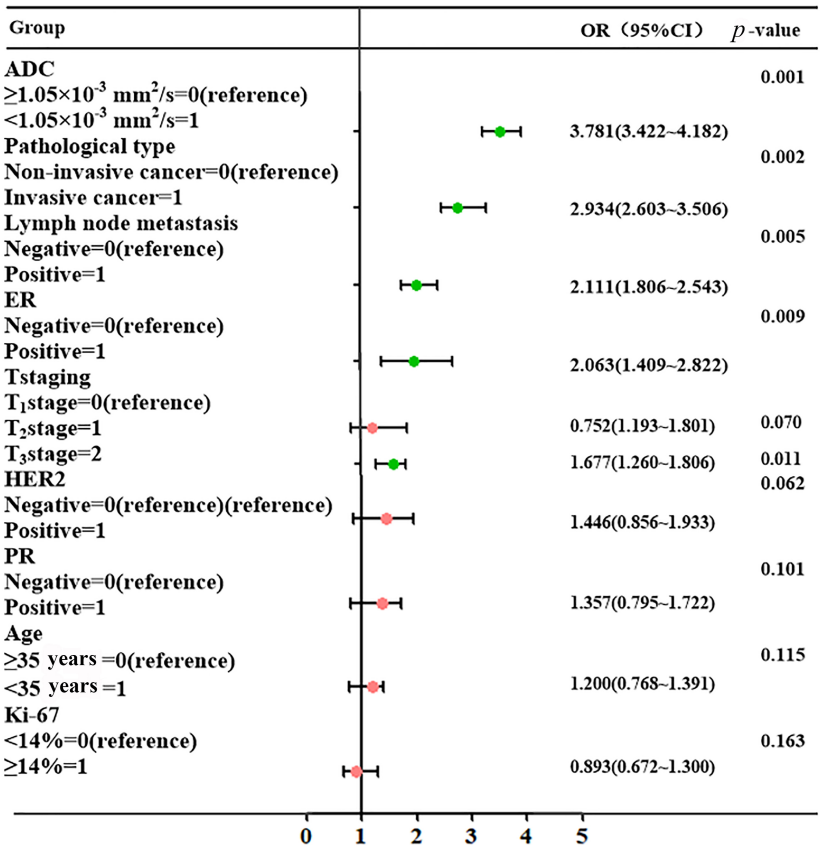

FIGURE 2. Predictive value of ADC for postoperative recurrence of breast cancer analyzed using ROC curve. ADC: apparent diffusion coefficient; ER: estrogen receptor; HER: human epidermal growth factor receptor; OR: odds ratio; PR: progesterone receptor; CI: confidence interval.

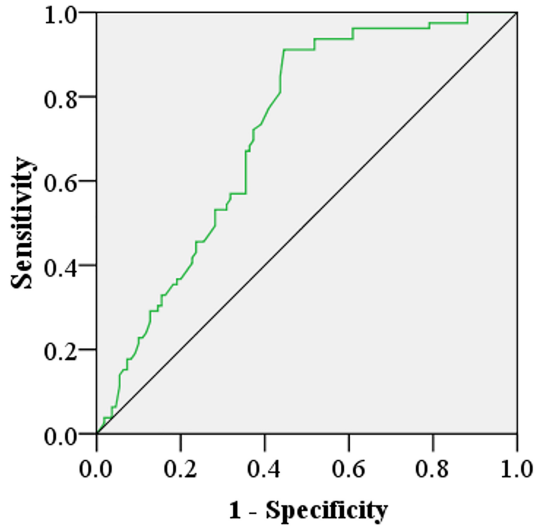

FIGURE 3. Postoperative recurrence of breast cancer analyzed using Kaplan-Meier survival curves.

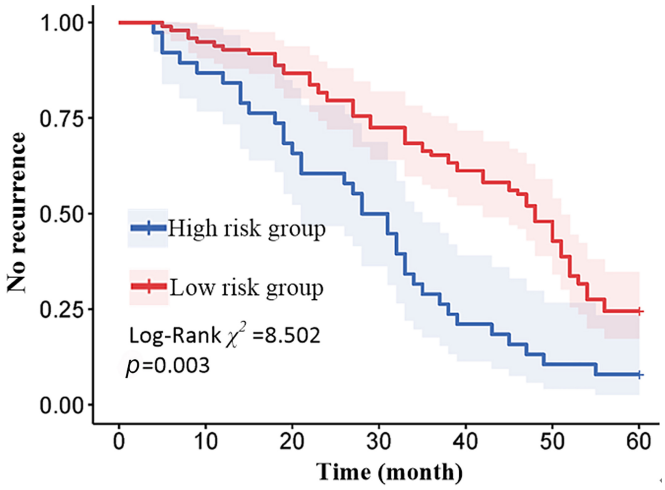

FIGURE 4. Predictive value of ADC for postoperative recurrence of invasive breast cancer analyzed using ROC curve.

or absence of recurrence as the dependent variable. The results revealed that T stage, pathological type, lymph node metastasis, ER and ADC values were all independent risk factors for the postoperative recurrence of breast cancer (Tables 5 and 6).

4. Discussion

Through detecting the intensity change in diffusion-sensitive signals, DWI indirectly reflects the difference in the diffusion motion of water molecules between normal tissues and tissues with lesions [13]. The Brownian motion of water molecules in tissues can be quantitatively analyzed using the ADC value. Due to a higher cell density, smaller intercellular spaces and restricted free motion of water molecules, malignant tumors have higher intensity of signals in DWI than those of benign lesions, and their ADC values are lower [14], being consistent with the findings in this study. As a key quantitative parameter for DWI, the *b* value affects the image quality and ADC value. With the improvement of 3.0T-MRI equipment, the problem of "T_2 penetration effect" in conventional DWI can be effectively solved and the real physiological basis such as facilitated diffusion can also be reflected by a high *b* value, with a highly stable ADC value [15]. It is well-documented that the diagnostic value of ADC value (1.0×10^{-3} mm^2/s) for benign and malignant tumors is higher when the *b* value is $\leq$1000 s/mm^2 [16]. Likewise, all the 136 patients in this study had stable parameters.

In terms of pathological types, breast cancer is often classified into invasive carcinomas (invasive ductal carcinoma, invasive lobular carcinoma) and non-invasive carcinomas (lobular carcinoma *in situ*, intraductal carcinoma *in situ*), and the formers are more common. Compared with non-invasive carcinomas, invasive carcinomas have more obvious pleomorphism, various sizes and shapes of cancer cells, so water molecules have poor diffusion in the interstitial space and high signals are displayed in DWI, with a lower ADC value [17]. In this study, high signals were dominant in DWI among the 136 patients with breast cancer, and equal signals were observed in only 2 cases. The ADC values are different at different *b* values, *i.e.*, a higher *b* value corresponds to a lower ADC value, and the ADC value has a significant difference between invasive and non-invasive carcinomas [18]. The same results were also obtained in this study. At present, a high *b* value is often used during MRI for image clarity and lesion scope, and the value of 600–1000 s/mm^2 is mostly selected [19]. Invasive breast cancer has a lower ADC value than that of benign breast lesions [20]. Similarly, we herein found that the ADC values of invasive breast cancer were lower than those of non-invasive breast cancer when the b values were 1000 and 2000 s/mm^2. In addition, the ADC value had a higher predictive value for the pathological type of breast cancer, and well distinguished invasive and non-invasive breast cancer when the *b* value was 1000 s/mm^2, with clear lesion images. A high *b* value was thus used for the cases who were hard to be identified.

Ultrasonography can be utilized to assess the shape, orientation, internal structure and borders of mammary glands. Preoperative axillary ultrasonography is of great significance to the staging and management of breast cancer, which can show metastatic foci and reduce the number of biopsies for false-positive lesions. Elastography and contrast-enhanced ultrasound (CEUS) have been increasingly applied in the diagnosis of breast cancer. Elastography can determine whether breast lesions are benign or malignant by measuring the stiffness of tissue. Kang *et al.* [21] included 121 breast cancer cases and found that high shear wave elasticity was associated with triple-negative breast cancer. CEUS can reflect the blood supply and perfusion information of lesions, as a supplement to the color Doppler ultrasonography of tumor neovascularization [22]. CEUS not only allows the qualitative diagnosis of breast cancer, but also provides information regarding the microcirculation and macrocirculation. Vraka *et al.* [23] reported that the blurred border after tumor enhancement was the most important characteristic affecting the prognosis of patients with breast cancer, which was observed in the tumors with negative ER expression (p = 0.01) and high histological grade (p = 0.03). Concentric enhancement and perfusion defects were more common in ER-negative tumors, and perifocal enhancement was positively correlated with Ki-67 [23].

TABLE 4. Clinical data of patients (n (%), $\bar{x} \pm s$).

Clinical data	Non-recurrence group (n = 104)	Recurrence group (n = 32)	t/χ^2	p
Age (yr)				
<35	20	12	4.539	0.033
≥35	84	20		
Marital status				
Married	95	28	0.419	0.518
Single	9	4		
Fertility status				
Already	89	25	1.002	0.317
None	15	7		
Menstrual status				
Non-menopause	80	21	1.634	0.201
Menopause	24	11		
Family history of tumors				
Yes	12	4	0.022	0.883
No	92	28		
Course of disease (mon)	2.79 ± 0.72	3.01 ± 0.78	1.482	0.141
T stage				
T_1	20	7		
T_2	69	14	7.229	0.027
T_3	15	11		
Tumor diameter (cm)	2.10 ± 0.52	2.18 ± 0.67	0.709	0.480
Pathological type				
Non-invasive carcinomas	34	2	8.791	0.003
Invasive carcinomas	70	30		
Lymph node metastasis				
Positive	45	21	4.896	0.027
Negative	59	11		
Hormone receptors				
ER				
Positive	55	27	10.136	0.001
Negative	49	5		
PR				
Positive	62	24	4.188	0.041
Negative	51	8		
HER2				
Positive	44	20	4.005	0.045
Negative	60	12		
Ki-67				
≥14%	62	26	5.015	0.025
<14%	42	6		
ADC value ($\times 10^{-3}$ mm^2/s)	1.16 ± 0.15	0.93 ± 0.15	7.306	<0.001

ER: estrogen receptor; PR: progesterone receptor; HER: human epidermal growth factor receptor; ADC: apparent diffusion coefficient.

TABLE 5. Variable assignment in logistic regression analysis results of influencing factors for postoperative recurrence.

Variable	Assignment
Age	$\geq$35 yr = 0, <35 yr = 1
T stage	T_1 = 0, T_2 = 1, T_3 = 2
Pathological type	Non-invasive carcinomas = 0, invasive carcinomas = 1
Lymph node metastasis	Negative = 0, Positive = 1
ER	Negative = 0, Positive = 1
PR	Negative = 0, Positive = 1
HER2	Negative = 0, Positive = 1
Ki-67	<14% = 0, $\geq$14% = 1
ADC value	$\geq 1.05 \times 10^{-3}$ mm^2/s = 0, $<1.05 \times 10^{-3}$ mm^2/s = 1

ER: estrogen receptor; PR: progesterone receptor; HER: human epidermal growth factor receptor; ADC: apparent diffusion coefficient.

TABLE 6. Cox analysis results of influencing factors for postoperative recurrence.

Factor	Regression coefficient	Standard error	Wald^2	Hazard ratio	95% CI	*p*
ADC value	1.245	0.245	3.761	2.123	1.952~2.380	0.012
Invasive carcinoma	0.228	0.077	8.763	1.256	1.018~2.134	0.001
Lymph node metastasis	2.069	0.306	5.551	1.709	1.263~2.314	0.004
ER positive	2.068	0.177	5.040	2.775	1.212~4.532	0.024
T stage (T_2–T_3)	2.413	0.241	2.762	2.522	0.649~2.324	0.116
HER2 positive	2.216	0.158	2.632	2.362	0.724~1.521	0.184
Age (<35 yr)	2.168	0.325	2.265	1.251	0.415~4.114	0.085
Ki-67 ($\geq$14%)	2.342	0.126	1.214	2.325	0.514~1.169	0.616

ADC: apparent diffusion coefficient; ER: estrogen receptor; HER: human epidermal growth factor receptor; CI: confidence interval.

Additionally, Caiazzo *et al*. [24] found a positive correlation between intratumoral perfusion defects and Ki-67. In the quantitative analysis of CEUS by Ji *et al*. [25], the peak intensity was negatively correlated with ER and PR, and the peak time of the HER-2 positive group was shorter than that of the negative group. Although these quantitative parameters were correlated with some prognostic factors, their diagnostic efficiencies were relatively low (AUC = 0.5–0.7) [25].

The associations of ADC value with pathological factors and malignancy grade have been widely explored [26], but its correlation with patients' prognosis has rarely been studied. In this study, the association between the ADC value and the prognosis of patients at the first visit was analyzed through long-term follow-up. The mean ADC value at the first visit of the recurrence group was significantly lower than that of the non-recurrence group, and the ADC value was a risk factor for the postoperative recurrence of breast cancer, demonstrating that a low ADC value at the first visit may predict a poor prognosis [27]. Additionally, the results of ROC curve analysis revealed that the risk of 5-year recurrence was higher among the patients with an ADC value $\leq 1.046 \times 10^{-3}$ mm^2/s. According to COX hazards regression analysis, ADC $\leq 1.046 \times 10^{-3}$ mm^2/s was an index effectively predicting the recurrence of breast cancer, and a lower ADC value of lesions indicated a higher recurrence risk. Taken together, a lower ADC value suggests more cancer cells and stronger invasion ability, and it has an association with the prognosis.

5. Conclusions

In conclusion, DWI is of great clinical significance to the assessment of benign/malignant breast cancer. High-signal images are dominant in DWI of patients with breast cancer. The ADC values at different *b* values play a key role in the pathological typing of breast cancer, and can provide a basis for predicting the 5-year postoperative recurrence. Therefore, MRI-ADC value is worthy of popularization in the assessment of preoperative pathological types and recurrence of breast cancer. However, this study still has limitations. In this single-center retrospective study, the sample size was small, probably leading to selection bias. The detection machine and *b* value were different from those in previous studies, resulting in certain deviation. In the future, multi-center studies with large sample sizes are in need to validate the findings herein.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

JTF, QSJ and JFP—designed this study and significant revised the manuscript; CS, LL, QHL and GPT—performed this study and drafted this manuscript. All coauthors have approved the

submission and publication of this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Jinhua Central Hospital (approval No. 2020-234), and all patients signed the informed consent.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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