Correlation between minimum apparent diffusion coefficient values and the histological grade of breast invasive ductal carcinoma

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Abstract. The present study aimed to investigate the correlation between the minimum apparent diffusion coefficient (ADC_{min}) value and the histological grade of breast invasive ductal carcinoma (IDC). In total, 129 pathologically verified lesions that were subjected to dynamic breast magnetic resonance imaging and diffusion weighted imaging prior to biopsy were included. The ADC_{min} value was calculated and its correlation with the tumor histological grade was investigated. Tumors of lower grades demonstrated significantly higher ADC_{min} values as compared with tumors of higher grades (F=33.49; P<0.01). The mean ADC_{min} values for IDC of grades I, II and III were $(1.14\pm0.11)x10^{-3}$, $(0.99\pm0.12)x10^{-3}$ and $(0.86\pm0.13)x10^{-3}$ mm^2/sec, respectively. Statistically significant differences were detected in the mean ADC_{min} value between tumors of grades II and III (P<0.01), as well as between tumors of grades I and II (P<0.01). In addition, the mean ADC_{min} values for the less aggressive (grades I and II) and more aggressive (grade III) groups were $(1.01\pm0.13)x10^{-3}$ and $(0.86\pm0.13)x10^{-3}$ mm^2/sec, respectively (t=5.76, P<0.01). In conclusion, these data indicated that the ADC_{min} value was correlated with the IDC histological grade, and lower ADC_{min} values were associated with a higher histological grade and more aggressiveness. Thus, the ADC_{min} value may be considered as a promising prognostic parameter in identifying tumor aggressiveness.

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Introduction

Invasive ductal carcinoma (IDC), a heterogeneous disease, is the most common pathological type of breast cancer (1). There are three main prognostic determinants for breast cancer, including the lymph node status, tumor size and histological grade (2). The prognostic value of histological grade is considered to be equivalent to that of the lymph node status (3), whereas it is greater than that of tumor size (4). According to the World Health Organization (5), IDC can be classified into grades I, II and III, depending on the nuclear features, tubular formation and mitotic count. Compared with grades I and II, IDC of grade III is associated with a reduced time to relapse or mortality due to breast cancer (6). Therefore, the accurate determination of the IDC histological grade is particularly important for selection of the appropriate treatment and prediction of the disease prognosis.

Diffusion weighted imaging (DWI) is an advanced functional magnetic resonance imaging (MRI) technique, which is based on the measurement of water molecule diffusion in tissues (7,8). Diffusion is quantified by the apparent diffusion coefficient (ADC), with low ADC values suggesting restricted diffusion (8). DWI has been initially applied for the diagnosis of acute stroke in clinical practice (9). With the rapid development of MRI techniques over the past years, the clinical application of DWI has been greatly extended for the imaging of various tumors (7-10). DWI is particularly helpful in the evaluation of breast masses by providing information on tumor behavior (8).

There have been numerous studies regarding the application of DWI in the diagnosis of breast lesions, and in the differential diagnosis between benign and malignant breast tumors (11,12). The association between DWI and the histological grade of IDC has also been reported, although differential findings have been observed due to the use of a different region of interest (ROI) and measurement methods (13-20). The majority of previous studies have applied the mean ADC value to indicate the pathological characteristics of tumors. However, the minimum ADC (ADC_{min}) value is considered to be able to reflect the most malignant portions of tumors (21). In particular, the ADC_{min} value would be helpful for the selection

of treatment plans if information on the IDC histological grade was also provided.

In the present retrospective study, the aim was to investigate the correlation of the ADC_{min} value with the histological grade and the aggressiveness of breast IDC.

Materials and methods

Study patients. In total, 281 patients with suspected with breast cancer were examined by breast MRI at the Second Hospital of Shandong University, (Jinan, Shandong, China) between May 2013 and July 2016 were reviewed. Among these cases, 152 cases were excluded due to receiving chemotherapy or radiotherapy (n=25), lack of surgical confirmation (n=26), benign lesions (n=76) or suffering from other types of malignant tumors (n=25). The remaining 129 patients with pathologically-diagnosed invasive ductal carcinoma according to the World Health Organization classification of tumors of the breast (5), who were all females, aged between 27 to 72 years old (median age of 48 years), with a mean age of 47.42±10.26 years, were included into the analysis. Following MRI examination, all lesions were pathologically verified by lumpectomy, mastectomy or biopsy at the Institute of Pathology at the Second Hospital of Shandong University (Jinan, China). In order to avoid misdiagnosis caused by tumor heterogeneity, the biopsy was performed under the guidance of MRI inspection. Prior written informed consent was obtained from each patient, and the study was approved by the ethics committee of the Second Hospital of Shandong University.

MRI examination. All breast MRI examinations were performed on a 3.0-T system (GE Discovery MR750; GE Healthcare, Milwaukee, WI, USA), with an eight-channel dedicated breast coil. Patients were in the prone position, and both breasts were imaged simultaneously. For premenopausal females, imaging was performed between day 7 and day 14 of the menstrual cycle. An MRI plain scan was performed with the axial T2-weighted single-shot fast spin echo sequence using a modified Dixon technique (T_2 IDEAL) for intravoxel fat-water separation, using the following parameters: Repetition time (TR), 2,500 msec; echo time (TE), 53.5 msec; slice thickness, 6 mm; layer spacing, 1.0 mm; field of view, 360x360 mm; matrix size, 320x192 pixels; and number of excitations (NEX), 3. Similarly, the parameters for the axial T1-weighted fast spin-echo were as follows: TR, 569 msec; TE, 15.6 msec; slice thickness, 6 mm; layer spacing, 1.0 mm; field of view, 360x360 mm; matrix size, 256x192; NEX, 4.

In order to obtain dynamic contrast-enhanced (DCE) MRI scans, a dynamic examination was performed using the axial T1-weighted 3D dynamic gradient echo fat sequence. The parameters for this examination were as follows: TR/TE, 3.9/1.7; flip angle, 5˚; field of view, 360x360 mm; matrix size, 348x348; and slice thickness, 1.8 mm. Subsequent to unenhanced acquisition, Gadodiamide (0.2 mmol/kg body weight, GE Healthcare Life Sciences, Little Chalfont, UK) was intravenously injected at the rate of 2 ml/sec, followed by 20 ml saline flush. DCE image acquisition was initiated immediately after the saline injection. The sequence was repeated for seven times without time gaps, and each sequence lasted for 60 sec.

DWI was performed with an axial single-shot fat suppressed echo-planar diffusion weighted sequence (TR, 3,000 msec; TE, 49.5 msec; slice thickness, 6 mm; layer spacing, 1.0 mm; field of view, 360x360 mm; matrix size, 128x96; and NEX, 4). The diffusion-sensitizing gradient was applied along the x, y and z axes, while b-values of 0 and 800 sec/mm^2 were used.

Image analysis. MRI scans were independently reviewed by two experienced radiologists at a workstation (Advantage Windows Workstation 4.6; GE Healthcare) in a blinded manner. For each case, the final decision was made only upon agreement between these two radiologists. ADC measurement was performed in the GE workstation software. A ROI with a mean size of 25.7 mm^2 (ranging between 8.0 and 79.0 mm^2) was placed on the highest-signal focal in the DWI images that corresponded to the lowest-signal area in the ADC maps. Subsequently, the ADC values were automatically calculated on the ADC maps. The ROI was smaller than the lesion size and was placed in the solid part of IDC, avoiding the necrotic and hemorrhagic regions. The ROI size of each lesion was consistent for multiple measurements, in which the lowest of three measurements was accepted as the minimum ADC (ADC_{min}) value.

Histopathological analysis. The histological grade of the tumors was assessed using the Nottingham modification of the Bloom-Richardson system (22), considering the following three parameters: i) Tubular formation (1 point, tubular formation in >75% of the tumor; 2 points, tubular formation in 10-75%; and 3 points, tubular formation in <10%); ii) nuclear pleomorphism (1 point, nuclei with minimal variation in size and shape; 2 points, moderate nuclear variation; and 3 points, marked nuclear variation); and iii) mitotic count (1 point, 0-11 mitotic counts; 2 points, 12-22 mitotic counts; and 3 points, >23 mitotic counts), calculated using a light microscope (BX43; Olympus Corporation, Tokyo, Japan) at magnification of x40 with a field diameter of 0.63 mm and a field area of 0.312 mm^2. The final decision on the histological grade was established only upon agreement of the investigators (two pathologists). Scores of 3-5, 6-7 and 8-9 were considered to indicate histological grades I, II and III, respectively (22).

Statistical analysis. Data are expressed as the mean ± standard deviation. SPSS software (version 18.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Due to the fact that the minimum ADC_{min} or maximum ADC_{min} represented a specific value for each patient, no statistical analysis could be performed on these data. In the present study, the mean ADC_{min} value was calculated by averaging the values of all the patients. The mean ADC_{min} value difference was compared with the histological grade using the one-way analysis of variance and least significant difference test. Independent sample (Student's t-test) and receiver operating characteristic (ROC) curve analysis were used to analyze the diagnostic value of the mean ADC_{min} value in differentiating less and more aggressive IDC cases. The optimal cutoff point of the mean ADC_{min} value, and the corresponding sensitivity and specificity were determined. $P<0.05$ was considered to indicate differences that were statistically significant.

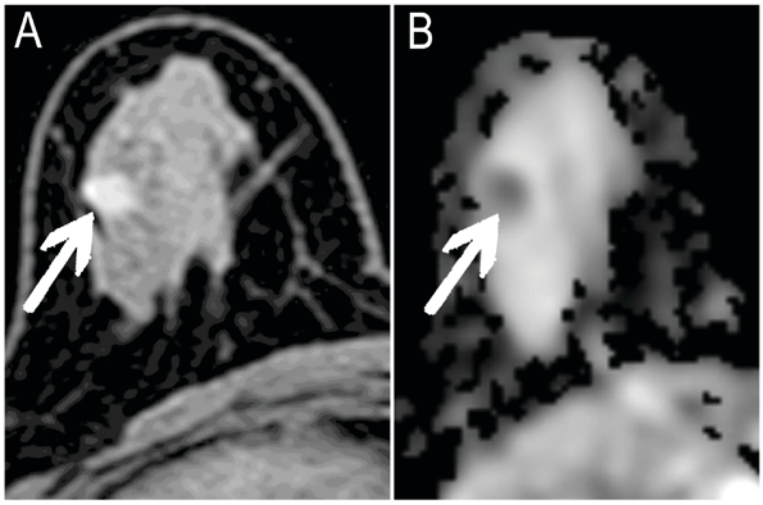

Figure 1. Representative imaging examination of histological grade I breast invasive ductal carcinoma in a 44-year-old female. (A) Axial contrast-enhanced image demonstrating the 1.2-cm round mass with heterogeneous enhancement in the lower-outer quadrant of the right breast (arrow). (B) Axial ADC map of the breast demonstrating a low signal with a low ADC_{min} value ($1.20x10^{-3}$ mm^2/sec) (arrow). ADC_{min}, minimum apparent diffusion coefficient.

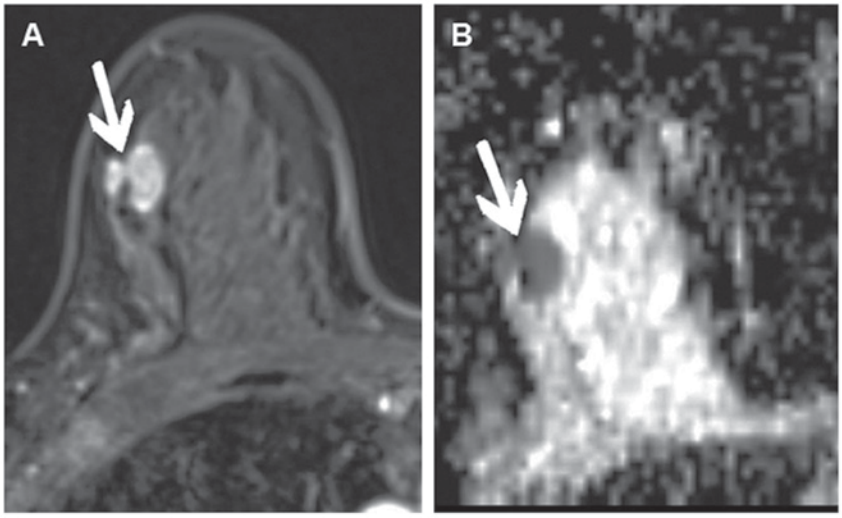

Figure 2. Representative imaging examination of histological grade II breast invasive ductal carcinoma in a 45-year-old female. (A) Axial contrast-enhanced image demonstrating the 1.3-cm irregular mass with heterogeneous enhancement in the upper-outer quadrant of the right breast (arrow). (B) Axial ADC map of the breast demonstrating a low signal with a low ADC_{min} value ($0.96x10^{-3}$ mm^2/sec) (arrow). ADC_{min}, minimum apparent diffusion coefficient.

Results

Histological grade and ADC_{min} values in IDC patients. Among the 129 breast IDC cases included in the present study, pathological analysis revealed that there were 17 (13.18%) cases of histological grade I, 79 (61.24%) cases of histological grade II, and 33 (25.58%) cases of histological grade III (Figs. 1-3). Furthermore, the mean ADC_{min} value of all IDC cases was $(0.97\pm0.15)x10^{-3}$ mm^2/sec. The minimum, maximum and mean ADC_{min} values of IDC obtained by histological grade are presented in Table I.

When considering the different histological grades of the included IDC patients, the mean ADC_{min} values were $(1.14\pm0.11)x10^{-3}$, $(0.99\pm0.12)x10^{-3}$ and $(0.86\pm0.13)x10^{-3}$ mm^2/sec for patients with grade I, II and III disease, respectively. The corresponding ranges of these values were $(0.95\text{-}1.34)x10^{-3}$, $(0.72\text{-}1.30)x10^{-3}$ and $(0.50\text{-}1.10)x10^{-3}$ mm^2/sec, respectively. These measurement results revealed that different ADC_{min} values corresponded to IDC cases with different histological grades. Compared with cases of higher grades, tumors of lower grades exhibited significantly higher ADC values ($F=33.49$; $P<0.01$). In particular, there was a significant difference in the ADC_{min} value between grade II and III tumors ($P<0.01$), as well as between grade I and II tumors ($P<0.01$; Fig. 4). Taken together, these results suggest that, the ADC_{min} value is inversely correlated with the histological grade of IDC.

ADC_{min} value and disease aggressiveness in IDC patients. To evaluate the role of the ADC_{min} value in determining the aggressiveness of IDC, the cases were divided into the less aggressive (grades I and II) and more aggressive (grade III) groups. The results revealed that the mean ADC_{min} values in the less aggressive group was $(1.01\pm0.13)x10^{-3}$ mm^2/sec, while this value was $(0.86\pm0.13)x10^{-3}$ mm^2/sec in the more aggressive

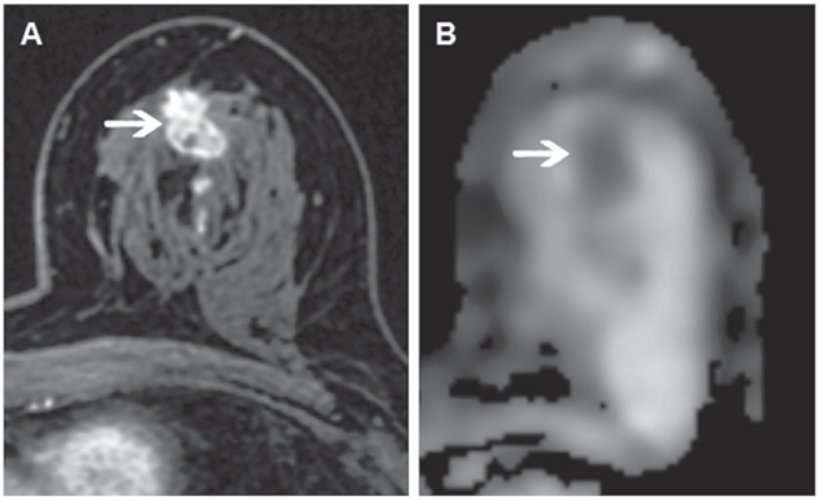

Figure 3. Representative imaging examination of histological grade III breast invasive ductal carcinoma in a 53-year-old female. (A) Axial contrast-enhanced image demonstrating the 1.6-cm irregular mass with heterogeneous enhancement in the central area of the left breast (arrow). (B) Axial ADC map of the breast demonstrating a low signal with a low ADC_{min} value ($0.78x10^{-3}$ mm^2/sec) (arrow). ADC_{min}, minimum apparent diffusion coefficient.

Table I. Range and mean values of ADC_{min} of IDC according to the different histological grades.

Grade	n	ADC_{min} range ($x10^{-3}$ mm^2/sec)	Mean ADC_{min} ($x10^{-3}$ mm^2/sec)	P-value
I	17	0.95-1.34	1.14±0.11	<0.01
II	79	0.72-1.30	0.99±0.12	<0.01
III	33	0.50-1.10	0.86±0.13	<0.01

P-values were obtained from comparison with the mean ADC_{min} groups. ADC_{min}, minimum apparent diffusion coefficient.

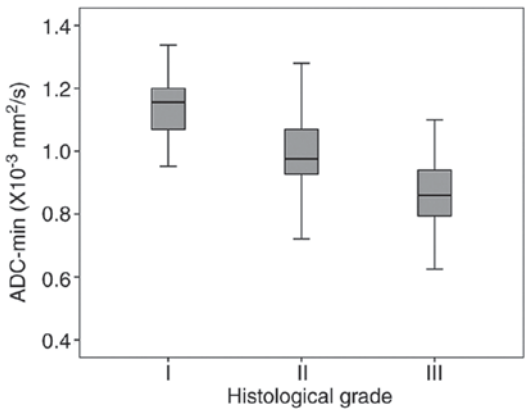

Figure 4. Box plot demonstrating the correlation between the ADC_{min} value and the histological grade of IDC. Mean ADC_{min} values for IDC cases of histological grades I, II and III were $(1.14±0.11)x10^{-3}$, $(0.99±0.12)x10^{-3}$ and $(0.86±0.13)x10^{-3}$ mm^2/sec, respectively (P<0.01). ADC_{min}, minimum apparent diffusion coefficient; IDC, invasive ductal carcinoma.

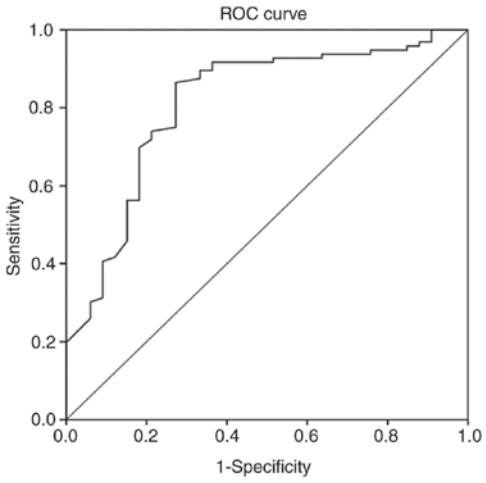

Figure 5. Receiver operating characteristic curve analysis of ADC_{min} values in the diagnosis of IDC. The ADC_{min} value exhibited great significance in the diagnosis of less aggressive IDC cases, with an area under the curve of 0.81. The ADC_{min} threshold value of $0.90x10^{-3}$ mm^2/sec corresponded to a sensitivity of 86.5% and a specificity of 72.7% for the detection of less aggressive tumors. ADC_{min}, minimum apparent diffusion coefficient; IDC, invasive ductal carcinoma.

group (t=5.76, P<0.01). These results suggest that the ADC_{min} value is inversely correlated with the aggressiveness of IDC.

ROC analysis of ADC_{min} value in IDC diagnosis. ROC analysis demonstrated that the ADC_{min} value was a significant parameter in the diagnosis of less aggressive IDC, with an area under the curve (AUC) of 0.81. The ADC_{min} threshold value of $0.90x10^{-3}$ mm^2/sec corresponded to a sensitivity of 86.5% and a specificity of 72.7% in the detection of less aggressive tumors (Fig. 5). These results suggest the importance of the ADC_{min} value in diagnosing less aggressive IDC.

Discussion

The histological grade represents an important prognostic factor for tumors in clinical practice, which is helpful in evaluating the tumor behavior (2). In addition, DWI is quick examination that does not require the use of a contrast agent and is quantified by the apparent diffusion coefficient. Moreever, the ADC value is quantitative and, therefore, an objective calculation (8,23). Previous studies have examined the association between the ADC value and tumor grade. For instance, certain studies have demonstrated that the ADC value is inversely correlated with the tumor grade (13-15). Cipolla *et al* (16) also revealed that the ADC values were significantly higher in G1 tumors as compared with G3 tumors, while there was no statistically significant difference upon comparison of G1 and G3 tumors with G2 tumors. By contrast, several other studies have indicated that no correlation exists between the ADC value and tumor grade (17-20).

In the present study, the results demonstrated that the mean ADC_{min} values for IDC of grades I, II and III were $(1.14\pm0.11)x10^{-3}$, $(0.99\pm0.12)x10^{-3}$ and $(0.86\pm0.13)x10^{-3}$ mm^2/sec, respectively, with the corresponding ranges of $(0.95\text{-}1.34)x10^{-3}$, $(0.72\text{-}1.30)x10^{-3}$ and $(0.50\text{-}1.10)x10^{-3}$ mm^2/sec. Tumors of lower grades were observed to exhibit significantly higher ADC values compared with tumors of higher grades. In addition, there was significant difference in the ADC_{min} value between tumors of grades II and III, as well as between tumors of grades I and II. This phenomenon may be attributed to the higher cellular density and smaller extracellular space in IDC of higher grades, which results in lower ADC values (24). Additionally, the overlapping of the ADC_{min} for the three grades of IDC is possibly due to tumor heterogeneity (1).

The majority of previous studies (13-20) have used the mean ADC value when investigating its correlation with the tumor grade. However, in the present study, the ADC_{min} values were used instead, and significant differences were observed in these values between different tumor grades. IDC is a heterogeneous tumor consisting of invasive cancer nests, fibrosis and necrosis. In MRI scans, the regions of the maximum ADC (ADC_{max}) values reflect the lowest cellular zone, while the regions of the ADC_{min} values reflect the highest cellular zone composed of stroma (21). Furthermore, the presence of fibrosis and necrosis may affect the ADC values, particularly the ADC_{max} values. Therefore, there will always be differences in the ADC_{max} values in the local measurement and pathological characterization of tumors. In the present study, the ADC_{min} value was used for tumor pathological characterization, which has been suggested to reflect the most malignant portions of tumors (21).

There have been several studies investigating the application of the ADC_{min} values in differentiating the benign and malignant breast masses (as well as in differentiating breast cancer subtypes), and in detecting the invasive component in ductal carcinoma *in situ* (21,25,26). Byun *et al* (27) have measured the mean ADC and the mean ADC_{min} values in the regions with the highest fluorodeoxyglucose (FDG) uptake using sequential ^{18}F-FDG positron-emission tomography and MRI, and examined the correlation of the corresponding ADC values with the histological grade of IDC. The majority of these aforementioned studies have applied the multiple ROI method in breast MRI, and the ADC_{min} value represented the lowest mean ADC value among multiple small ROIs within the lesion. However, this method is time-consuming, limiting its clinical application (21,25,27). In the present study, the single ROI was smaller in size when compared with the lesion size, and was placed in the solid part of the IDC, avoiding the necrotic and hemorrhagic regions. The ROI size of each lesion was consistent for multiple measurements, and the lowest ADC value among three measurements was determined as the ADC_{min} for each lesion. This method has been previously reported, with considerable feasibility in clinical settings (26). Furthermore, the results of the current study were consistent with previous findings (13-15), with a simpler and more feasible method used, and confirmed that the ADC_{min} value was inversely correlated with the histological grade of breast IDC. Further studies with larger sample sizes are required to evaluate the clinical application of the ADC_{min} value in tumor grading.

Biological evaluation of tumors is important for the selection of treatment options. Different tumor cell densities may indicate different histological structures and biological invasions. The ADC values for IDC lesions were lower as compared with those of other malignant tumors, which may be due to the densely packed tumor cells, restricting effective motion and diffusion of water molecules (28). Costantini *et al* (13) have identified that the mean ADC value for IDC was $1.03x10^{-3}$ mm^2/sec, while the mean ADC value for ductal carcinoma *in situ* was $1.05x10^{-3}$ mm^2/sec. In the present study, the mean ADC_{min} value for IDC was $(0.97\pm0.15)x10^{-3}$ mm^2/sec, while the values for the less aggressive (grades I and II) and more aggressive (grade III) tumor groups were $(1.01\pm0.13)x10^{-3}$ and $(0.86\pm0.13)x10^{-3}$ mm^2/sec, respectively. Thus, a significant difference was observed in the mean ADC_{min} value between the less and more aggressive IDC groups, which was in line with previous observations (13). Furthermore, a cutoff point for the ADC_{min} threshold value of $0.90x10^{-3}$ mm^2/sec was used to detect the less aggressive tumors in the present study, corresponding to a sensitivity of 86.5% and a specificity of 72.7%. The results of the ROC curve analysis further revealed that the ADC_{min} value was important in the diagnosis of less aggressive IDC cases, with an AUC of 0.81.

There are also certain limitations in the present study. Firstly, the sample size was relatively small; therefore, the findings need to be validated in studies using larger sample sizes. In addition, all lesions herein were IDCs, appearing as a mass-like enhancement. Therefore, it was not able to evaluate the ADC_{min} value of other types of breast carcinoma appearing as non mass-like enhancement with respect to the pathological grade. Furthermore, the measurement of ADC_{min} value was relatively subjective, which may lead to observational bias. Another limitation is that the association between the histological grade and the morphological alterations, as well as the enhancement pattern, were not examined in the present study. Routine imaging findings combined with the ADC value would improve the accuracy of the preoperative assessment of the histological grade for IDC, which would assist in the selection of the appropriate treatment options for breast cancer. Additionally, the association between the ADC_{min} values and other pathological characteristics was not investigated herein, which should be considered in further in-depth studies in the

future. According to a previous study (29) and clinical practice, only two b-values (0 and 800 mm^2/sec) were applied in the present study; thus, DWI images with more b values would be required in the future to obtain accurate ADC values. Finally, the present study was a retrospective study, and therefore, the ADC_{min} value was not considered in the clinical decisions.

In conclusion, the results of the current study indicated that the ADC_{min} value was correlated with the histological grade of IDC. Lower ADC_{min} values were associated with higher histological grades. These findings suggest that the ADC_{min} value may be considered as a promising prognostic parameter in identifying tumor aggressiveness.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GS and WG designed the study. SZ, RT, PC, ZL, and FS performed the experiments. SZ analysed the data.

Ethics approval and consent to participate

The present study was approved by the ethics committee of the Second Hospital of Shandong University.

Consent for publication

Prior written informed consent was obtained from each patient.

Competing interests

The authors declare that they have no competing interests.

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